Review

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Posted Date: 24 March 2025

doi: 10.20944/preprints202503.1671.v1

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A Narrative Review of Alzheimer's Disease and the Available Pharmaceuticals for Management of Its Cognitive Impairment in 2024

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Abstract: Alzheimer's disease is a neurodegenerative disorder characterized mainly by neurobehavioral changes that increase in severity over time. Research about this disease is paramount as the current understanding is that this disease will increase in frequency as the population ages. This narrative review seeks to understand the mechanism of Alzheimer's disease and employ this understanding to discuss the available pharmacological management of cognitive impairment due to Alzheimer's disease. Our methodology began with PubMed searches for systematic literature reviews and randomized clinical trials published between 2010 and 2024 about the pharmacological management of Alzheimer's disease. The data was extracted from these studies and then analyzed to supplement our discussion about the efficacy of the available treatments. Additional measures of clinical significance were then found through Google Scholar searches to enhance our discussion of efficacy. Our findings include those current treatments of Alzheimer's disease resulted in statistically significant improvement of cognitive measures but only meager to moderate clinically significant benefit. Another significant finding is that the available disease-modifying therapies provide little clinically significant benefit but pose an increased risk of severe adverse events. We posit that the inability to develop efficacious treatments for Alzheimer's disease is rooted in the lack of knowledge about Alzheimer's Disease and the lack of effective diagnostics. Thus, there is a need for further research into Alzheimer's disease in order to meet the needs of an aging population. This includes research into the disease's pathophysiological processes, which will inform how to diagnose and treat or manage the disease.

Keywords: Alzheimer's disease; mild cognitive impairment; cholinesterase inhibitors; donepezil; rivastigmine; galantamine; memantine; monoclonal antibodies; anti-amyloid therapy; lecanemab; donanemab; combination therapy

1. Introduction

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder that exists on a continuum and is often seen as a disease of accelerated aging [1–7]. The main characteristics of the disease are insidious onset of impairments to memory, language, executive function, and visuospatial abilities but can also come with other neurobehavioral changes [1–4,7,8]. The average prognosis is eight to ten years but can range from three to twenty years depending on the severity of the impairment as well as the age of onset [2,6]. Interestingly, AD patient deaths are mainly due to debilitating impairments in function and cognition [2]. This paper is a narrative review of the existing literature that seeks to understand AD and explore the efficacy of available pharmaceuticals for managing cognitive impairment in AD in 2024.

 doi:10.20944/preprints202503.1671.v1

1.1. Pathophysiology of AD

AD pathogenesis is a complex process with various contributing factors [2–4,6,9–12]. The main pathophysiological findings of AD include the accumulation of extracellular amyloid β (Aβ) plaques and the formation of intracellular neurofibrillary tangles (NFT) [3,5,9,10]. These findings are associated with cognitive and neurobehavioral changes in addition to changes to oxidative stress biomarkers, neuroinflammation, synaptic impairment, and neuronal loss resulting in neural atrophy [9,11,13]. Other lesser-known factors that contribute to AD pathogenesis include defective calcium regulation, presenilin, unfolded protein response system, Mfn2, and the Wnt/catenin system [3,6]. Defects in these processes result in neural atrophy, decreased acetylcholine levels in the basal forebrain, and glutamate excitotoxicity which contributes to AD pathophysiology and symptomology [6]. AD associated neural atrophy can affect cholinergic and serotonergic systems in the brain, which work together for learning and memory explaining AD's hallmark symptoms [3,12]. For example, neural atrophy of the basal forebrain results in the loss of cholinergic nuclei that project to the cerebral cortex, thalamus, and hippocampus, which results in cognitive decline [12,14].

Atrophy and the reduction of volume in the hippocampus is one of the key pathophysiological markers of MCI and AD but AD related neural atrophy occurs throughout the brain [6]. Additionally, neural atrophy in AD mostly results in the loss of grey matter but white matter lesions in the parietal and frontal lobes may also be present [15]. Other structures involved in AD include the entorhinal cortex, inferior temporal lobe, posterior cingulate cortex, splenium, and cerebellum [16]. AD patients may also present with microstructural damage independent of brain atrophy include structures such as the thalamus, striatum, internal capsule, precentral gyrus, and other structures [16]. Atypical presentations of AD are also caused by neurodegeneration of the medial temporal lobe, pyramidal and extrapyramidal systems, occipitoparietal and occipitotemporal lobes, left posterior perisylvian lobes, left posterior parietal lobe, frontoparietal cortex, posterior frontoparietal, posterior medial parietal, and posterior cingulate areas [2]. Degeneration in these neural systems results in the gradual worsening of a patient's global state rendering them dependent on their caregivers until they succumb to their inability to carry out basic functions [16].

1.1.1. Aβ and Associated Hypotheses

As previously stated, Aβ accumulation is a hallmark of AD. Cleavage of the amyloid precursor protein (APP) by γ secretase and β secretase forms the Aβ42 isoform [10,13,17]. Aβ42 itself harms neurons by generating free radicals or puncturing neuron membranes resulting in calcium influx, excessive neuron excitation, decreased neuron activity, and/or neuron death [9,13,17]. This can result in other pathological findings such as kinase activation, neuroinflammation through microglial activation, defects in axonal transportation, and reduced proteasome ability which creates NFTs, another hallmark of AD [8,9,11]. Additionally, Aβ can accumulate in cerebral vessels causing granulovacuolar degeneration of the hippocampal pyramidal cells which directly results in cognitive impairment as well as less cholinergic transmission [13,17].

The amyloid cascade hypothesis states that aggregation of Aβ in brain tissue due to APP cleavage or difficulty clearing Aβ causes hallmark signs and symptoms of AD [5,8,17], This was one of the most widely accepted hypotheses because Aβ deposits are the earliest pathologically evident lesions [17]. However, other hypotheses are gaining popularity due to the amyloid hypothesis's inability to account for other factors contributing to AD pathology and the failure of anti-amyloid therapies to provide significant clinical benefit [11]. As discussed above, catabolic processes of APP result in specific Aβ isoforms with higher aggregation potential, the ability to produce cytotoxic peptides, and increase the concentration of Aβ [8]. Soluble forms of Aβ also exhibit prion-like self-propagation, which allows the spreading of the disease process to multiple brain areas [8]. All these features of Aβ contribute to the belief in its role as the primary pathogenic cause of AD.

However, there is significant evidence that counters the amyloid hypothesis. Though anti-Aβ therapies reduce Aβ levels on PET, they fail to produce clinically meaningful improvements in cognition and function [18]. Anti-amyloid therapies are also associated with significant reduction in

 doi:10.20944/preprints202503.1671.v1

brain volume, not due to Aβ clearance, and have serious adverse events called amyloid related imaging abnormalities, ARIA [5,18]. Additionally, amyloid levels on PET do not correlate well with cognitive decline but rather just the risk of developing AD [5]. These findings suggest that Aβ is likely to be a sign of AD pathology rather than the pathogenic cause [5].

A separate but related hypothesis focuses on amyloid proteins and cerebral vasculature [13]. The neurovascular hypothesis focuses on neurotoxic Aβ's inability to cross the blood brain barrier (BBB) and the subsequent difficulty clearing it from the brain [13]. This results in a buildup of Aβ and causes aberrant angiogenesis, endothelial senescence, and increased levels of Aβ influx receptors [13]. Aberrant angiogenesis can create neuroinflammation and seeds of Aβ that can form plaques [13]. Additionally, neurovascular accumulations of Aβ amplify proteosome-dependent destruction of Aβ clearance receptors, which results in endothelial senescence [13].

Anti-amyloid therapies have historically not provided sufficient clinical benefit which supports research into other targets for therapeutics or refinement of the specific Aβ target [11,19]. For example, in the past, Aβ therapeutics did not target AβO, which is gaining support as a pathogenic molecule [19]. The oligomer hypothesis posits that Aβ oligomers (AβO) and protofibrils are more toxic than the monomers and contribute more towards the pathophysiology of AD [17,19]. Previously, the belief was that AβO was simply an intermediate of amyloid plaque formation, but recent research reveals it is more pathogenic than the Aβ plaques themselves [19]. Evidence supporting this includes the Osaka genetic mutation, where individuals with severe cognitive impairment have low levels of Aβ plaques and cerebrospinal fluid (CSF) with low overall Aβ levels and high levels of AβO [19]. Animal studies further support the oligomer hypothesis by demonstrating that AβOs are necessary and sufficient to cause AD [19]. Further research is needed to determine which AβO isoform is pathogenic [19].

1.1.2. Tau Proteins and Associated Hypotheses

Normal, neuronal tau proteins stabilize axonal microtubules; however, hyperphosphorylation of these proteins result in the accumulation of cytoplasmic NFTs [13]. NFTs are first found in the hippocampus before spreading to other cortical areas [13]. The tauopathy hypothesis posits that the primary pathogenic process is the formation of NFTs that spread through the brain in six stages [13]. Stages I and II begin in the entorhinal area and then progress into stages III and IV in the limbic region [13]. The final two stages, V and VI, are the presence of NFTs in neocortical regions [13].

NFTs harm neurons by impairing the systems that maintain the integrity of cell transport, cytoskeleton, signaling, and mitochondria [13]. Tau protein oligomers and fibrils also induce activation of microglia and elevate the production of nitrates and interleukin-6 which further supports its role as a pathogenic molecule [11]. However, the failure of anti-tau therapies in clinical trials suggests the lack of therapeutic benefits when targeting tau proteins or that the research has targeted the wrong tau isoform [20]. This lack of success further points to tau proteins as a non-causal factor but rather a loss-of-function or epiphenomenon contributing to disease symptomology [20].

1.1.3. Neuroimmunomodulation Hypothesis and Oxidative Stress

Cytokines, chemokines, reactive oxygen species (ROS), and secondary messengers formed by endothelial cells, peripherally derived immune cells, and resident glia mediate neuroinflammation [11,13,17]. The neuroimmunomodulation hypothesis started with the discovery of the role of interleukin-6 in phosphorylation of tau proteins resulting in the overactivation of the cdk5/p53 pathway and the subsequent microglial dysfunction seen in AD [11]. Neuroinflammation ultimately results in edema, tissue damage, recruitment of immune cells, and possible apoptosis [11,13,17]. Further evidence supporting this hypothesis includes Aβ and tau proteins resulting in microglial activation that mediates neuroinflammation in a biphasic process [11]. Additionally, genes identified as increasing the risk of developing AD also contribute to immune responses [11]. Investigations that studied AD as an inflammatory disease revealed the onset of pathophysiological changes decades before the onset of severe cognitive delay [1]. There is also evidence that dysregulation of

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inflammatory processes creates a positive feedback loop that prevents adequate response to pathological Aβ and tau proteins in AD patients [1].

1.1.4. Oxidative Stress and Mitochondrial Dysfunction Hypotheses

The oxidative stress hypothesis of AD postulates that the primary pathophysiological mechanism is increased oxidative stress [9,13]. First, Aβ oligomers can chelate with metal ions that are naturally available in brain tissue, which can react with oxygen to create ROS, such as superoxide [9]. Additionally, elevated Aβ levels are associated with increased oxidative byproducts from lipid, protein, and deoxyribonucleic acid (DNA) metabolism [9].

Mitochondrial dysfunction is also intricately linked with the oxidative stress hypothesis. AD patients have reduced mitochondrial function with low expression and/or activity of oxidative enzymes, thus creating more ROS, that can result in increased random mutations in mitochondrial DNA (mtDNA) that decrease the level of mitochondrial proteins involved in mtDNA replication and transcription [13]. Mitochondrial dysfunction and the positive feedback loop it forms result in reduced buffering ability and can influence the calcium channels in the endoplasmic reticulum (ER), thus disrupting calcium homeostasis [13].

1.2. AD Risk Factors

Risk factors of AD include aging, genetics and epigenetic mechanisms, head trauma, lifestyle choices, environmental factors, and other pre-existing conditions that result in elevated oxidative stress [6,9]. Aging is known as the most significant risk factor for AD and is associated with a sustained state of neuroinflammation, thus predisposing individuals to neurodegenerative diseases, such as AD [6,11]. However, a recurring theme in AD research is the effect of ApoE4 on treatment efficacy [21]. ApoE4 is associated with an increased risk of familial or autosomal dominant, late-inset familial, and sporadic AD [3,9,21,22]. It is the autosomal dominant allele of the APOE gene, where ApoE3 is considered the wild--type allele [9,21,22]. Clinical and epidemiological data established the APOE4 allele as a factor in the development of 50% of AD cases in the United States [3,21]. Genetics research has also identified other mutations contributing to late-onset, early-onset, familial, and Down Syndrome associated AD [8,17].

1.3. AD Symptomology

The earliest symptom observed in most patients is selective memory impairment, but this can vary depending on the form of AD [2,3]. Other cardinal symptoms include impaired executive function and judgment or problem-solving, visuospatial impairments, word-finding difficulties, and neuropsychiatric symptoms [2,3].

Memory impairment in AD primarily begins with anterograde long-term episodic amnesia, with the most profound effect on declarative memory, due to altered hippocampal and medial temporal lobe degeneration [2]. Additional memory impairments in early AD include episodic memory of recent events due to degeneration of the entorhinal cortex and the structures mentioned earlier [2]. In late AD, memory impairments progress and affect semantic and procedural memory due to neurodegeneration of neocortical temporal and subcortical structures [2]. Impairments in executive function and judgment are typically present in the early stages and progress during late-stage AD, with the most common feature being anosognosia [2]. Visuospatial impairments and word-finding difficulties begin in early AD [2]. Additional cardinal symptoms include severe language impairment and neuropsychiatric symptoms that are mainly present in the later stages of the disease [2]. AD patients can also have a variety of atypical presentations with symptoms outside of the cardinal symptoms [2]. However, cognitive and functional testing used in research do not typically measure atypical symptoms so we will not discuss them further [2].

 doi:10.20944/preprints202503.1671.v1

1.4. Diagnosis of AD

Clinically, AD's typical presentation is an older adult complaining of insidious-onset and progressive decline in cognitive domains and impaired daily functioning that is not due to medications or other pathologies [2]. In clinical settings, the diagnosis of AD includes determining a patient's level of impairment that cannot be attributed to other etiologies in addition to biomarker testing and imaging before initiating disease-modifying treatments or to determine eligibility in clinical trials [1,23]. Typically, neuroimaging, biomarker and genetic testing, as well as other labs are only used in screening or research setting [23]. The gold standard diagnostic test is histopathological exams, but we will not discuss this further as these are not typically feasible in living patients [2].

A 2023 systematic review summarized clinical practice guidelines for mild cognitive impairment (MCI) and dementia due to AD in multiple countries and revealed screening practices for AD were focused to those at risk of developing it while mass screening was generally not recommended [23]. Patients at risk for AD include those with a history of intellectual disabilities, patients older than 75 years of age complaining of impaired memory or a family history of memory disorders, as well as individuals with suspected cognitive impairment [23].

Recent scholarship has moved from recognizing AD as an amalgamation of clinical symptoms to a biological definition that suggests individuals with pathological markers will develop the disease given a long enough lifespan [1]. The Alzheimer's Association released an updated criteria for diagnosing and staging AD in 2024 which reflects this framework by detailing diagnostic core biomarkers regarding amyloid and tau protein levels [1]. The criteria's core 1 reflects the diagnostic biomarkers amyloid β proteinopathy (biomarker A) as well as secreted and phosphorylated tau proteins (biomarker T) [1]. Current diagnostic testing of these core biomarkers includes amyloid positron emission tomography (PET) and CSF Aβ42/40 ratio, p-tau181/Aβ42 ratio, and t-tau/Aβ42 ratio but there are also accurate plasma assays available for testing amyloid and tau protein levels [1]. A current limitation of the amyloid PET is a lack of sensitivity that can only accurately diagnose moderate or frequent amyloid plaque density, correlating with Braak level III or IV NFT [1]. Symptomatic therapy of AD does not require the presence of these diagnostic criteria, but the initiation of biological therapies requires the confirmation of an AD diagnosis through the criteria [1].

In addition to these diagnostic criteria, the Alzheimer's Association discussed additional biomarkers that may signal the presence of other or additional neuropathologies [1]. The new biomarkers include biomarker N, which represents neuronal injury, dysfunction, or degeneration of the neuropil, which can be seen in AD, as well as traumatic and ischemic brain injuries or other pathologies [1]. The biomarkers I, S, and V were added to the 2024 edition because they aid clinicians in ruling out other pathologies such as neuroimmune and neuroinflammatory pathologies, cerebral amyloid angiopathy (CAA) and other cerebrovascular injuries, as well as Parkinson's Disease and dementia with Lewy bodies [1].

1.4.1. Cognitive and Functional Tests for Diagnosis of AD

Neuropsychological testing, as described above, includes tests of cognition, function, and global state [21,24–27]. The following tests are not an exhaustive list of available neuropsychological measures for AD but they are the most common measures used in the studies we will be discussing in this review. Cognition is mainly measured through the Alzheimer's Disease Assessment Scale (ADAS), specifically the ADAS-Cognition (ADAS-Cog), as well as others [24,25,27]. Tests of function include the Alzheimer's Disease Cooperative Study-Action of Daily Living (ADCS-ADL) among others [27]. Global function and composite tests include the Clinical Dementia Rating (CDR), Alzheimer's Disease Composite Score (ADCOMS), and integrated Alzheimer's Disease Rating Scale (iADRS) [24,25,27]. In addition to these, a popular test for AD is the Mini-Mental State Examination (MMSE) [24,25].

The ADAS measures the severity of cognitive and behavioral function on a scale from 0 to 70 [24]. The ADAS-Cog is a specific test that includes only the cognitive measurements related to memory, praxis, and language from the ADAS [25,27]. The ADAS-Cog is best used in symptomatic

 doi:10.20944/preprints202503.1671.v1

mild to moderate AD patients with cognitive deficits but there are limitations due to ceiling effects [3,27]. Interestingly, there are concerns for repeated ADAS-Cog testing resulting in improved scores regardless of actual cognitive decline [21].

The ADCS-ADL measures the extent of a patient's ability to perform daily activities independently [27]. One version of the test, ADCS-iADL, measures a participant's ability to complete daily basic and instrumental activities on a scale from 0-59 [25]. Lower scores on ADCS-iADL confer greater functional impairment [25].

Neuropsychological testing of global function or are a composite of previously mentioned tests include the CDR, ADCOMS, and iADRS [27]. CDR summarizes the global severity of dementia based on six cognitive domains with higher scores reveal more severe dementia [25]. This test is widely used in clinical trials for MCI due to AD or mild dementia due to AD [27]. There are two forms of the CDR that are used in AD diagnosis with the CDR-Global Score focusing on clinical trial eligibility and disease staging and the CDR-Sum of Boxes (CDR-SB) measuring cognitive and functional measures [27]. Of note, the CDR-SB is the most common primary outcome in phase three clinical studies of MCI and mild dementia due to AD [27]. The ADCOMS is a weighted composite test with elements from ADAS-Cog, MMSE, and CDR tests that measure clinical decline in patients with amnestic MCI and mild dementia due to AD and with more sensitivity than the individual tests included [27]. iADRS detects impaired cognition and daily function by combining items ground on the ADAS-Cog13 and ADCS-iADL [25]. Lower scores on the iADRS indicate worse cognition and function [25]. This test has been validated for clinical measurement of MCI to moderate dementia due to AD [26].

Finally, the MMSE assesses cognitive impairments on a scale from 0 to 30, with scores of 23 or less indicative of dementia [24]. It has been widely used clinically but has been viewed as outdated recently due to a lack of a linear relationship with time course of AD [5].

2. Methods

This narrative review aims to evaluate the available pharmacologic management of cognitive impairment in AD patients. Secondary goals include evaluating failed pharmacologic therapies to determine future directions of AD research. An initial search for sources was carried out on PubMed using the following search terms (Alzheimer's or Alzheimer's Disease) AND (Pharmaco* or therap* or treat* or management) NOT (Music or physical or diet or exercise). Filters used during this search include clinical trials, meta-analysis, randomized controlled trials, systematic review, and from 2014-2024. Inclusion criteria include pharmaceutical interventions, measurements of cognitive function, and studies focusing on treatment rather than prevention. Exclusion criteria include herbal supplements and ayurvedic medicine, outcomes measured only through imaging or biomarker testing, medical procedures, nutraceuticals, and outcomes measured only through neuropsychiatric symptoms. The eligibility of studies was determined based on one author's review of the abstract and further confirmed by a consensus of two or more authors after reading the full article. Additional sources were then found through PubMed and Google searches to supplement discussion of the clinical efficacy of medications.

3. Available Pharmacotherapies

As with potential treatments or therapies, studies have assessed the efficacy, tolerability, and safety of drugs aimed at treating AD and its symptoms. Available treatments fall into one of three categories: cholinesterase inhibitors (ChEIs), N-methyl-D-aspartate receptor (NMDAR) antagonists, and amyloid-targeting therapies [3,5,6].

3.1. Cholinesterase Inhibitors (ChEIs)

ChEIs are a medication class that increases cholinergic transmission by targeting reduced choline acetyltransferase or inhibiting acetylcholinesterase [5,6,11,28–30]. ChEIs were previously

 doi:10.20944/preprints202503.1671.v1

believed to lack neuroprotective qualities and were only recommended for symptomatic treatment of dementia in AD patients; however, advances in MRI technology revealed that ChEIs may slow down neural atrophy which suggests neuroprotective effects [5,6,28,29,31]. A common adverse event of these second generation ChEIs include GI symptoms such as diarrhea, nausea, emesis, dizziness, anorexia, or headache [3]. Current FDA approved ChEIs include donepezil, rivastigmine, and galantamine with the American Psychiatric Association recommending these medications for management of mild to moderate AD [3,6,28,29]. Of note, this narrative review will not discuss the first generation ChEIs such as tacrine, velnacrine, and physostigmine as they were nonspecific inhibitors that had a notably short duration of action [7]. Interestingly, research has determined that APOE4 status has inconsistent effects on ChEI efficacy; however, there is a possible correlation between large study sizes ruling no effect of APOE4 status on treatment efficacy while smaller study sizes tend to contribute to APOE4 status on treatment efficacy [21].

Table 1. Outcomes of treatment with any acetylcholinesterase inhibitor.

Study	Test	Outcome
Lanctot, Hermann, Yau, et al. (2003) [7]	CIBIC-Plus and CGIC, minimal or greater improvement	9% MD vs placebo
	ADAS-Cog, 4+ point improvement	10% MD vs placebo

Overall, ChEIs have a number needed to treat (NNT) between four to fourteen while the number needed to harm (NNH) is between six to twenty thus, they have a favorable risk to benefit ratio [27]. A separate meta-analysis including RCTs of donepezil, rivastigmine, and galantamine reported the total mean proportion of patients exhibiting a global response to ChEIs was between 8-9% more than their placebo counterparts [7]. The same study reported the cognitive response to ChEIs as 10% more than placebo [7]. This meta-analysis then reported ChEIs have an average NNT of ten for cognitive outcomes, twelve in global outcomes, and four in global outcomes of a single Japanese study [7]. These findings are consistent with the view that ChEIs provide moderate therapeutic benefit [7]. Interestingly, the meta-analysis included a single Japanese study that revealed a higher treatment effect than the other studies which suggests a possible ethnic difference in ChEI response [7]. Additionally, the Ontario Drug Policy Research Network reported ChEIs had statistically, but not clinically, significant improvement in cognition of mild to moderate AD patients [32].

3.1.1. Donepezil

Donepezil, the oldest available and best understood ChEI, inhibits acetylcholinesterase and decreases APP levels thus modulating cholinergic effects and oxidative stress due to AD [7,29,31]. Donepezil is available as a tablet or an oral disintegrating tablet, which is prescribed at a starting dose of five milligrams (mg) per day (QD) and, after four to six weeks, increased to a maintenance dose of ten mg QD [29].

Table 2. Outcomes of treatment with donepezil.

Study	Test	Outcome
Guo, Wang, and Liu (2020) [33]	ADAS-Cog	2.93 MD vs placebo
	SIB	-4.70 MD vs placebo
	CGI	0.34 MD vs placebo
	ADCS-ADL and ADL	3.01 MD vs placebo
Chen, Lai, and Tao (2024) [3]	ADAS-Cog	5 mg QD: -1.95 MD vs placebo, I2 of 24%
		10 mg QD: -2.01 MD vs placebo, I2 of 51%

 doi:10.20944/preprints202503.1671.v1

	CIBIC-Plus	5 mg QD: 1.77 M-H Ratio vs placebo, I2 of 43%
		10 mg QD: 1.68 M-H Ratio vs placebo, I2 of 0%
	ADCS-ADL	10 mg QD: 1.70 MD vs placebo, I2 of 85%
Waring, Tang, Robieson, et al. (2015) [21]	ADAS-Cog, ITT population	APOE4 carrier: -2.34 LSMD vs placebo
		APOE4 carrier: -2.95 change from baseline when treated
		APOE4 non-carrier: -1.71 LSMD vs placebo
		APOE4 non-carrier:-4.09 change from baseline when treated
		APOE4 negative: -1.71 LSMD vs placebo
		APOE4 heterozygote: -2.31 LSMD vs placebo
		APOE4 homozygote: -2.32 LSMD vs placebo
	ADAS-Cog, Completer population	APOE4 carrier: -3.53 LSMD vs placebo
		APOE4 non-carrier: -1.62 LSMD vs placebo, without statistical significance
		APOE4 heterozygote: -3.42 LSMD vs placebo
Dou, Tan, and Tan (2018) [34]	ADAS-Cog	5 mg QD: -0.33 SMD vs placebo
		10 mg QD: -0.40 SMD vs placebo
	SIB and MMSE	23 mg QD: 0.53 SMD vs placebo
	ADCS-ADL and BADLS	10 mg QD: 0.15 SMD vs placebo
	CIBIC-Plus and CGIC	5 mg QD: 1.98 OR vs placebo
		10 mg QD: 2.15 OR vs placebo
		23 mg QD: 1.99 OR vs placebo
Lanctot, Hermann, Yau, et al. (2003) [7]	ADAS-Cog, 4+ point improvement	Study 1: 107/305 respond to ChEI. 27/150 respond to placebo
		Study 2: 76/298 respond to ChEI. 17/152 respond to placebo
		Study 3: 125/544 respond to ChEI. 38/274 respond to placebo
	CIBIC-Plus and CGIC, minimal or greater improvement	13% vs placebo

Multiple systematic analyses and metanalyses of donepezil-treated patients revealed it is generally well-tolerated while exerting statistically significant improvement in cognitive and functional domains of mild to moderate AD patients, compared to placebo [3,33]. The included studies reported statistically significant improvement in ADAS-cog, Severe Impairment Battery (SIB), clinical global impression (CGI), ADCS-ADL, and ADL scores [3,33]. Additionally, it was more

 doi:10.20944/preprints202503.1671.v1

beneficial compared to memantine monotherapy for managing mild-to-moderate AD but was less efficacious than combination therapy with memantine [3,33].

Multiple studies have investigated the role of APOE4 status on donepezil efficacy and results have been inconclusive [21]. To further understand this, a multinational RCT of mild to moderate AD patients treated with donepezil versus placebo revealed no overall interaction between APOE status and treatment efficacy based on ADAS-Cog [21]. Interestingly, the authors concluded that APOE4 carrier status is more associated with a difference in the extent of a patient's response to placebo rather than improvement with donepezil treatment [21]. Authors also remarked that there was less improvement in ADAS-Cog scores and decreased placebo response in heterozygous or homozygous APOE4 patients compared to APOE4 non-carriers [21]. This supports previous evidence of APOE4's effects on brain structure and function as well as its effects on AD progression [21].

A commentary of a double-blind placebo controlled RCT of donepezil in AD patients from 1998 revealed the NNT from the provided data to be six [35]. The author also raised concern for a possible conflict of interest in the existing studies and a lack of studies into donepezil at the time of publication [35]. A 2003 meta-analysis reported donepezil's NNT to be eight based on three studies published in 1998 or 1999 [7]. However, the Ontario Drug Policy Network reported donepezil's NNT as 30 [32]. The study reported statistical and clinical improvement on ADAS-Cog scores but not on the MMSE for AD patients regardless of severity [32].

In a network meta-analysis of 41 randomized controlled trials, ten mg QD donepezil had a moderate effect on cognitive function in patients with AD [34]. The SMD indicated a statistically significant improvement in cognitive performance compared to a placebo. This analysis also stated donepezil had a relatively favorable impact on cognitive outcomes compared to other cholinesterase inhibitors and memantine [34]. These findings suggest that donepezil is effective in enhancing cognitive function in Alzheimer's patients, though the effect size is moderate. [34].

3.1.2. Rivastigmine

Rivastigmine is an FDA-approved ChEI for the treatment of AD that is used less frequently than donepezil due to its higher likelihood of side effects, such as nausea and diarrhea [29]. The medication is a pseudo-irreversible selective inhibitor of acetylcholinesterase and butrylcholinesterase (BChE) in the brain [7,30]. It is available in capsule form and prescribed at a starting dose of 1.5 mg twice per day (BID) then increased in 1.5 mg BID intervals up to the maintenance dose of six mg BID [29]. This medication is also available as a transdermal patch and prescribed at a starting dose of a 4.6 mg QD patch, a minimally therapeutic dose of 9.5 mg QD patch, and 13.3 mg QD patch for maintenance [29].

An early placebo-controlled double-blind RCT investigated rivastigmine's efficacy in treating probable AD patients [30]. Patients who received placebo experienced progressive cognitive worsening while patients who were treated with rivastigmine experienced dose-dependent slower cognitive decline based on ADAS-Cog, progressive deterioration scale, global deterioration scale, and MMSE [30]. Additionally, there was a significantly higher proportion of patients who achieved clinically meaningful improvement, defined as four or more-point improvement, when treated with the higher dose of rivastigmine compared to placebo [30]. These findings were consistent with the findings of a network meta-analysis of rivastigmine [34]. The meta-analysis's SMD indicated a significant improvement of cognitive function compared to a placebo [34]. Of note, the effect size was consistent with other cholinesterase inhibitors [34].

Another meta-analysis of the efficacy and safety of various AD treatments, including rivastigmine, indicated that rivastigmine contributed to improvements in cognitive function in AD patients [3]. While the study did not specifically highlight the effects of rivastigmine alone, it demonstrated that, like other ChEIs, rivastigmine had a positive impact on cognitive performance [3]. The analysis also showed that, although these drugs could slow the progression of AD, their effects on cognitive and behavioral outcomes varied [3]. Furthermore, rivastigmine did not significantly increase the withdrawal rates due to adverse reactions compared to placebo, suggesting its relative safety in long-term use [3].

 doi:10.20944/preprints202503.1671.v1

The optimizing transdermal Exelon in mild to moderate AD (OPTIMA) study was an open label study and concluded that transdermal rivastigmine had significant efficacy in the ADLs of mild to moderate AD patients [14]. This was followed up by the ACTION (ACTivities of daily living and cognitION) study that assessed the efficacy, safety, and tolerability of two rivastigmine patch doses on patients with severe AD [14]. Study results revealed significant improvement in SIB and ADCS-CGIC (Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change) beginning at 16 weeks of treatment with 13.3 mg/24 h rivastigmine patches compared to 4.5 mg/24 h patches [14]. Additionally, there was a significantly higher percentage of patients who experienced clinical improvement when treated with the higher dose of rivastigmine compared to the lower dose [14]. Authors also reported similar AEs between both groups [14]. Overall, severe AD patients treated with the higher dose of rivastigmine patches had a statistically significant improvement in cognitive, functional, and global measures without significant change in AEs from the lower dose [14].

Table 3. Outcomes of treatment with rivastigmine.

Study	Test	Outcome
Chen, Lai, and Tao (2024) [3]	ADAS-Cog	12 mg QD: -2.01 MD vs placebo, I2 of 38%
	CIBIC-Plus	12 mg QD: 1.73 M-H risk ratio vs placebo, I2 of 0%
	ADCS-ADL	12 mg QD: 1.80 MD vs placebo
Rosler, Anand, Cicin-Sain, et al. (1999) [30]	ADAS-Cog, 4+ point improvement in ITT population	10.4 mg QD: 24% vs baseline
		3.7 mg QD: 15% vs baseline
		Placebo: 16% vs baseline
	CGIC, improvement in ITT population	10.4 mg QD: 37% vs baseline
		3.7 mg QD: 30% vs baseline
		Placebo: 20% vs baseline
	PDS, 10%+ improvement in ITT population	10.4 mg QD: 29% vs baseline
		3.7 mg QD: 19% vs baseline
		Placebo: 19% vs baseline
	GDS	10.4 mg QD: -0.06 MD vs baseline
		3.7 mg QD: -0.22 MD vs baseline
		Placebo: -0.26 MD vs baseline
	MMSE	10.4 mg QD: 0.21 MD vs baseline
		3.7 mg QD: -0.62 MD vs baseline
		Placebo: -0.47 MD vs baseline
Farlow, Grossber, Sadowsky, et al. (2013) [14]	SIB	13.3 mg QD patch: 4.9 LSMD vs baseline
	ADCS-ADL-SIV	13.3 mg QD patch: 1.2 LSMD vs baseline
	ADCS-CGIC	13.3 mg QD patch: 24.6% with improvement vs baseline
	NPI-12	13.3 mg QD patch: -1.6 LSMD vs baseline
Dou, Tan, and Tan (2018) [34]	ADAS-Cog	12 mg QD: -0.29 SMD vs placebo
		5 cm2 QD: -0.17 SMD vs placebo, without statistical significance
		10 cm2 QD: -0.25 SMD vs placebo

 doi:10.20944/preprints202503.1671.v1

		15 cm2 QD: -0.35 SMD vs placebo
	ADCS-ADL and BADLS	12 mg QD: 0.21 SMD vs placebo
		5 cm2 QD: 0.28 SMD vs placebo, statistically insignificant
		10 cm2 QD: 0.24 SMD vs placebo
		15 cm2 QD: 0.42 SMD vs placebo
	CIBIC-Plus and CGIC	12 mg QD: 1.80 OR vs placebo
		5 cm2 QD: 1.55 OR vs placebo, without statistical significance
		10 cm2 QD: 1.57 OR vs placebo
		15 cm2 QD: 2.77 OR vs placebo
Lanctot, Hermann, Yau, et al. (2003) [7]	ADAS-Cog, 4+ point improvement	149/167 respond to ChEI. 44/220 respond to placebo
	CIBIC-Plus and CGIC, minimal or greater improvement	12% vs placebo

The Ontario Drug Policy Research Network reported rivastigmine, overall, had an NNT of 58 while its oral formulation's NNT as 22 [32].

3.1.3. Galantamine

Galantamine is another ChEI that is prescribed less frequently than donepezil due to GI side effects as well as its association with an idiopathic rise in death rates within MCI patient populations [6,29]. Galantamine is unique from the aforementioned ChEIs due to its allosteric modulation of nicotinic receptors which may explain its disease-modifying effect [7]. It can be prescribed as an immediate-release tablet or solution starting at 4mg BID and increased by 4 mg BID monthly until reaching the maintenance dose of 12 mg BID [29]. It is also available as an extended-release tablet with a starting dose of 8mg QD then increased by 8mg QD each month until reaching the maintenance dose of 24mg QD [29].

Researchers have determined that galantamine efficaciously improves AD symptoms through modulation of functional brain connectivity [11]. Galantamine enhanced connectivity within brain regions commonly affected by AD such as the default mode network (DMN) in the posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) [11]. Additionally, there was evidence of increased integration between the DMN and the salience network (SN) as well as strengthened the connectivity between the PCC and SN nodes [11]. These structures are involved in memory and self-referential thinking mediated by cholinergic systems thus explaining the mechanism of galantamine's improvement in AD symptomology [11]. This finding indicates a direct connection between galantamine's action and neural activity while establishing galantamine's potential to address network connectivity deficits associated with AD [11].

Another study investigated the efficacy and safety of galantamine in AD patients [3]. The authors reported that galantamine significantly improved cognitive function on cognitive assessment scales compared to the placebo [3]. Additionally, galantamine was generally well-tolerated with adverse events comparable to those observed in the placebo group [3]. These findings support the use of galantamine as an effective and safe treatment option for cognitive symptoms in AD [3]. Galantamine provided moderate improvement in cognitive function for AD patients in another meta-analysis [34]. The SMD suggested a moderately statistically significant improvement in patients compared to a placebo with similar effect size to other ChEIs [34].

 doi:10.20944/preprints202503.1671.v1

Table 4. Outcomes of treatment with galantamine.

Study	Test	Outcome
Chen, Lai, and Tao (2024) [3]	ADAS-Cog	24 mg QD: -3.03 MD vs placebo, I2 of 0%
		32 mg QD: -3.29 MD vs placebo, I2 of 0%
	CIBIC-Plus	24 mg QD: 1.15 M-H risk ratio vs placebo, I2 of 27%
		32 mg QD: 1.34 M-H risk ratio vs placebo, I2 of 0%
	ADCS-ADL	24 mg QD: 1.88 MD vs placebo, I2 of 0%
Dou, Tan, and Tan (2018) [34]	ADAS-Cog	24 mg QD: -0.50 SMD vs placebo
		32 mg QD: -0.51 SMD vs placebo
	ADCS-ADL and BADLS	24 mg QD: 0.21 SMD vs placebo
	CIBIC-Plus and CGIC	24 mg QD: 1.34 OR vs placebo, without statistical significance
		32 mg QD: 1.48 OR vs placebo, without statistical significance
Lanctot, Hermann, Yau, et al. (2003) [7]	ADAS-Cog, 4+ point improvement	Study 1: 64/357 respond to ChEI. 27/196 respond to placebo.
		Study 2: 64/414 respond to ChEI. 33/203 respond to placebo.
		Study 3: 61/240 respond to ChEI. 24/123 respond to placebo.
		Study 4: 59/179 respond to ChEI. 23/83 respond to placebo.
	CIBIC-Plus and CGIC, minimal or greater improvement	5% vs placebo

Galantamine's NNT was reported to be 22 in a 2003 meta-analysis and 23 in a study conducted by the Ontario Drug Policy Research Network [7,32]. The Ontario Drug Policy Research Network also reported galantamine's higher clinically significant effect on global status of AD patients compared to other ChEIs and combination therapy [32].

3.2. NMDA Receptor (NMDAR) Antagonists

Excessive stimulation of NMDARs can lead to neurotoxicity and neuroprotective NMDAR antagonists regulate glutamate activity by blocking their overactivation [3,6,28,33,36]. Due to its mechanism of action, NMDAR antagonists may be viewed as disease-modifying rather than a purely symptomatic treatment; therefore, their effectiveness may only be observed in longer trials [6]. Additionally, a previous study has reported memantine's potential to slow hippocampal atrophy which supports its possible disease-modifying effects [6].

3.2.1. Memantine

Memantine is a non-competitive NMDAR antagonist with low to moderate affinity and preferentially binds to calcium NMDAR channels in the open configuration [4]. Its mechanism of action is neuroprotective and is currently approved for treatment of moderate to severe AD patients

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[3,6,28,36]. The tablet form of memantine is prescribed at five mg QD as a starting dose and can be increased weekly to a maximum of 10mg BID [28].

A recent study determined memantine is an effective and safe option for the treatment of cognitive impairment in moderate to severe AD patients [3]. The results indicated that memantine significantly enhanced cognitive function, based on ADAS-Cog scores, and was well tolerated by patients with moderate to severe AD [3].

Table 5. Outcomes of treatment with memantine.

Study	Test	Outcome
Guo, Wang, and Liu (2020) [33]	ADAS-Cog	1.33 MD vs placebo
	SIB	-2.50 MD vs placebo
	CGI	0.30 MD vs placebo
	ADCS-ADL and ADL	-3.89 MD vs placebo
Chen, Lai, and Tao (2024) [3]	ADAS-Cog	20 mg QD: -1.23 MD vs placebo, I2 of 11%
	CIBIC-Plus	20 mg QD: 1.26 M-H risk ratio, I2 of 0%
	ADCS-ADL	20 mg QD: 0.09 MD vs placebo, I2 of 0%, without statistical significance
Wilkinson, Wirth, and Goebel (2014) [37]	Cognitive decline (4+ points on ADAS-Cog, 5+ points on SIB, or 1+ point on BGP-Cog) in memantine vs placebo treated patients	Moderate to severe AD: 0.60 OR in favor of treatment
		Moderate AD: 0.63 OR in favor of treatment
		Severe AD: 0.48 OR in favor of treatment
Matsunaga, Kishi, and Iwata [4]	Overall cognition (SIB, ADAS-Cog, SMMSE/MMSE)	-0.27 SMD vs placebo with I2 of 52%
	ADAS-Cog	-0.17 SMD vs placebo with I2 of 0%
	SMMSE	-0.35 SMD vs placebo
	SIB	-0.31 SMD vs placebo
	ADLs	-0.09 SMD vs placebo
Dou, Tan, and Tan (2018) [34]	ADAS-Cog	20 mg QD: -0.24 SMD vs placebo
	SIB and MMSE	20 mg QD: 0.34 SMD vs placebo
	ADCS-ADL and BADLS	20 mg QD: 0.12 SMD vs placebo
	CIBIC-Plus and CGIC	20 mg QD: 1.24 OR vs placebo, without statistical significance

A meta-analysis evaluated the effectiveness of memantine in patients with moderate to severe AD by analyzing data from nine randomized, double-blind, placebo-controlled trials that involved 2,340 patients [37]. In the publication, practical definitions of clinical worsening were based on meaningful differences in cognitive, functional, and global assessment scales [37]. The findings showed that memantine significantly lowered the incidence of cognitive decline compared to placebo [37]. Furthermore, patients on memantine experienced functional decline less frequently with less severe worsening in their overall status [37]. Overall, memantine reduced the risk of deterioration in cognitive, functional, and global status domains thus emphasizing memantine's significant role in managing symptomatic domains for patients with moderate to severe AD [37].

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Another meta-analysis examined the efficacy and safety of memantine monotherapy in AD by analyzing nine randomized controlled trials with a total of 2,433 participants [4]. Findings demonstrated that memantine provided small statistically significant improvement in cognition, ADLs, global function, and stages of dementia; however, clinical benefit is limited [4]. The authors maintained memantine is a suitable symptomatic treatment of AD because it is well-tolerated and does not exacerbate AD symptoms [4].

Based on two double-blind RCTs of memantine, the NNT was three to six for global improvement, seven for cognitive improvement, and four to eight in improvements in activities of daily living while the number needed to harm was insignificant [38]. The effect size determined by this study was between 0.32 and 0.62 [38]. These results reveal memantine monotherapy is effective with minimal risks and medium range effect size [38]. However, the Ontario Drug Policy Research Network reported memantine's NNT as 56 [32].

3.3. Anti-Amyloid Therapies

Current anti-amyloid therapies are classified as disease modifying treatments that counteract the accumulation of Aβ in AD patients [26,28,39]. FDA approved amyloid-targeted therapies include lecanemab and donanemab but previously included aducanumab [28,40]. These are humanized monoclonal antibodies (mAbs) directed against amyloid beta for treatment of MCI or mild dementia [5,26,28,39]. MAbs have demonstrated their ability to rescue neurons from cell death due to Aβ resulting in improved brain perfusion and neuronal viability [5]. A systematic review of anti-amyloid clinical trials highlighted statistically significant improvement in cognitive assessments which confers decreased or halting the worsening of cognitive decline in AD patients [41]. Their analysis also showed consistent evidence of safety in anti-amyloid antibody use [41].

Anti-amyloid therapies target various binding sites, which explain the statistical success of the FDA approved therapies lecanemab and donanemab compared to other drugs targeting amyloid proteins [42]. However, a major concern against anti-amyloid therapies is the controversy surrounding aducanumab [40]. The FDA previously approved aducanumab despite unclear evidence of its effectiveness in slowing or impeding cognitive decline [40]. Despite initial evidence of promising efficacy, subsequent studies raised concerns that clouded the clinical benefit, such as the unattainable price and lack of clinical efficacy; however, it received accelerated FDA approval despite these concerns [40]. Because of this, Biogen discontinued aducanumab production, citing a move to focus on previously FDA approved and available AD treatments [43].

Anti-amyloid antibodies, including bapineuzumab, solanezumab, gantenerumab, donanemab, lecanemab, aducanumab, and crenezunmab, had statistically significant improvement in ADAS-Cog, MMSE, CDR-SB, ADCS-ADL, ADCS-ADL-MCI, and Disability Assessment for Dementia (DAD) but did not exceed the minimal clinically important difference (MCID), defined by the systematic review [44].

3.3.1. Lecanemab

Lecanemab is an IG 1 humanized mAb that is used as an anti-amyloid therapy targeting soluble Aβ protofibrils [5,39,45–47]. Compared to other anti-AB therapies, lecanemab is more selective for protofibrils than fibrils [5].

Lecanemab achieved superiority compared to placebo with the ten mg/kg bi-weekly dose after eighteen months of treatment during its phase 2 trial for the treatment of early AD [45]. Superiority was determined by a 30% improvement in ADCOMS, 47% improvement in ADAS-Cog, and 26% improvement in CDR-SB scores of lecanemab treated patients [45]. This study supported its accelerated FDA approval then its safety and efficacy was confirmed during its phase three trial [5].

In a network meta-analysis of eight trials, lecanemab showed statistically higher efficacy over placebo in ADAS-Cog and CDR-SB scores [18]. Lecanemab showed a ten times stronger preference for protofibrils, compared to monomer or fibrils, while aducanumab and gantenerumab exhibit stronger binding to amyloid fibrils [18]. By targeting protofibrils, lecanemab reduces the neurotoxic

 doi:10.20944/preprints202503.1671.v1

protein build-up in the brain more efficiently than anti-amyloid therapies that target fibrils or monomeric forms of Aβ [18]. These findings explain lecanemab's efficacy in AD treatment compared to other previous anti-amyloid therapies [18].

Table 6. Outcomes of treatment with lecanemab.

Study	Test	Outcome
Terao and Kodama (2024) [18]	ADAS-Cog	-1.5808 MD vs placebo
	CDR-SB	-0.4350 MD vs placebo
Qiao, Chi, Zhang, et al. (2023) [5]	CDR-SB	-0.45 MD vs placebo with 0% I2
	ADCOMS	-0.05 MD vs placebo with 0% I2
	ADAS-Cog	-1.11 MD vs placebo with 97% I2
Ebell, Barry, Baduni, et al. (2024) [44]	ADAS-Cog	-1.8 MD over placebo
	CDR-SB	-0.43 MD over placebo
	Functional score	0.19 MD over placebo

Another meta-analysis analyzed the safety and effectiveness of lecanemab revealed improvement in CDR-SB, ADCOMS, and ADAS-Cog scores [5]. Study findings provided evidence for lecanemab's therapeutic potential in patients with MCI or early AD; however, there was little data supporting the efficacy in patients with moderate to severe AD [5]. Ultimately, the authors concluded that lecanemab has potential to slow cognitive decline but has little curative effect on clinical symptomology [5]. Unfortunately, as with other anti-amyloid therapies, the incidence of amyloid related imaging abnormalities (ARIA) is significantly higher in the treatment group compared to the placebo group [5]. Additionally, APOE4 patients are less likely to experience therapeutic benefit from lecanemab and have a higher risk for ARIA [5]. This suggests the need to develop treatments avoiding ARIA or preventing ARIA-associated complications. [5].

A systematic analysis of placebo-controlled RCTs of anti-amyloid therapies reported a lack of clinically significant improvement in lecanemab [44]. The study reported statistically significant improvement in ADAS-Cog-14 and CDR-SB scored of those treated with lecanemab; however, this did not exceed the MCID determined by the systematic analysis [44].

An editorial for Medpage Today reported the NNT for lecanemab as fifteen based on its CLARITY AD trials [48]. Another study reported the NNT to be thirteen for CDR-SB, fifteen for ADAS-Cog, and twelve for ADCS-MCI-ADL [47].

3.3.2. Donanemab

Donanemab is an anti-amyloid therapy targeting a specific type of insoluble Aβ found only in brain amyloid plaques [18,26,47].

The TRAILBLAZER-ALZ 2 study is a phase 3 randomized clinical trial (RCT) assessing the efficacy and safety of donanemab in individuals with early symptomatic AD [26]. Clinical significance was defined as a change of five or more points in AD patients with MCI or nine or more points in AD patients with mild dementia [26]. The highlighted findings concluded that donanemab had clinically meaningful benefit as 52% of the treated low/medium tau patients reached clinically significant improvement in iADRS and CDR-SB scores, as defined by the study [26]. Additionally, analysis concluded a 38.6% reduced risk of disease progression based on CDR-G and the time saved with eighteen months of treatment in the low/medium tau population treated with donanemab [26]. Interestingly, benefits did not translate over to the high tau population which suggests efficacy only when treatment is initiated in the early stages of AD [26]. The study reported expected adverse effects of anti-amyloid therapies, such as ARIA [26]. Additionally, volumetric MRI results also revealed the treatment group had less brain volume, larger ventricles volume, and less decrease in hippocampus

 doi:10.20944/preprints202503.1671.v1

volume which is consistent with hydrocephalus [26]. Long-term monitoring of this adverse effect should be an urgent priority of future research.

Table 7. Outcomes of treatment with donanemab.

Study	Test	Outcome
Terao and Kodama (2024) [18]	ADAS-Cog	-1.4353 MD vs placebo
	CDR-SB	-0.5859 MD vs placebo
Sims, Zimmer, Evans, et al. (2023) [26]	iADRS	Low/Medium Tau Population: 3.25 LSM over placebo
		Combined Population: 2.92 LSM over placebo
	CDR-SB	Low/Medium Tau Population: -0.67 LSM over placebo
		Combined Population: -0.70 LSM over placebo
	ADCS-iADL	Low/Medium Tau Population: 1.83 LSM over placebo
		Combined Population: 1.70 LSM over placebo
	ADAS-Cog	Low/Medium Tau Population: -1.52 LSM over placebo
		Combined Population: -1.33 LSM over placebo
Ebell, Barry, Baduni, et al. (2024) [44]	ADAS-Cog	-1.41 MD over placebo
	MMSE	0.49 MD over placebo
	CDR-SB	-0.59 MD over placebo

A systematic analysis of placebo-controlled RCTs of anti-amyloid therapies reported a lack of clinically significant improvement in donanemab [44]. The study reported statistically significant improvement in ADAS-Cog-14, MMSE, and CDR-SB scored of those treated with donanemab; however, this did not exceed the MCID determined by the systematic analysis [44].

An editorial for Medpage Today revealed donanemab's NNT to be fourteen based on it's TRAILBLAZER-ALZ trials [48]. Another study, based on data from the TRAILBLAZER trials, revealed an NNT of six based on data from the CDR-SB, nine based on the ADAS-Cog, and twelve based on the MMSE [47]. Additionally, when considering high tau populations, the NNT for ADAS-Cog scores was 28 and the CDR-SB was eight [47].

3.4. Combination Therapies

Combination therapy in AD involves using two or more drugs with complementary mechanisms to enhance treatment efficacy [33]. As previously discussed, AD pathogenesis is associated with neural atrophy secondary to neuronal apoptosis from decreased acetylcholine and glutamate excitotoxicity in various areas of the brain [6]. Thus, combination therapies target both defective, cholinergic and glutamatergic, pathways to improve AD symptomatology with higher efficacy than monotherapy [6]. Currently, the only FDA approved combination therapy for AD is donepezil and memantine which provide temporary cognitive improvement; however, researchers are also evaluating the efficacy of other ChEI and memantine combination therapies [6,11].

 doi:10.20944/preprints202503.1671.v1

Table 8. Outcomes of combination therapy with donepezil and memantine.

Study	Test	Outcome
Guo, Wang, and Liu (2020) [33]	ADAS-Cog	5.01 MD vs placebo
	SIB	-9.61 MD vs placebo
	CGI	2.88 MD vs placebo
	ADCS-ADL and ADL	-13.06 MD vs placebo
Dou, Tan, and Tan (2018) [34]	SIB and MMSE	0.76 SMD vs placebo
	ADCS-ADL and BADLS	0.32 SMD vs placebo

A meta-analysis of RCTs from Asia, North America, and Europe revealed that combination therapy of memantine and donepezil was superior to monotherapy of either medication and placebo based on cognition, ADLs, and global clinical outcomes [33]. These findings support the use of combination therapy for treatment of mild to severe dementia due to AD [33]. However, combination therapy is costly, and patients found it less acceptable than monotherapy or placebo [33]. Therefore, the choice between combination therapy or monotherapy should be made between the patient and their provider according to their individuals needs and abilities [33]. For example, patients with more severe AD and tolerate memantine better than combination therapy may benefit more from memantine monotherapy [33]. Alternatively, patients with mild to moderate AD and tolerate donepezil the best may benefit more from donepezil monotherapy 33]. Some limitations to bear in mind when considering these findings is the inclusion of low-quality studies, possible publication bias, reliance on an imprecise ranking system, and the focus on cost-effectiveness rather than slowing of clinical progression [33].

A meta-analysis of ChEIs and memantine compared their efficacy and tolerability in other studies that investigated combination therapy or monotherapy compared to placebo [34]. Patients with moderate to severe AD treated with twenty mg memantine and ten mg donepezil QD had improved ADAS-Cog and SIB scores based on the standard mean difference (SMD) of multiple studies [34]. This superior performance outpaced results for donepezil alone thus exhibiting efficacy of combination therapy [34].

Additionally, a systematic review of combination therapies conducted through human clinical trials found the efficacy of combination therapy with memantine and donepezil to be ambiguous in the treatment of moderate to severe AD [6]. Three of the included trials reported slightly more benefit from a combination of ChEI and memantine therapy compared to monotherapy with ChEIs or placebo; however, the results were not replicated in another four trials [6]. One of the trials with statistically significant findings in favor of combination therapy was not double-blinded, had a low sample size, and focused more on NIRS blood flow rather than cognition so their findings should be used with caution [6]. The other trial that reported statistically significant results revealed improvement in SIB, ADCS-ADL19, and CIBIC-Plus when moderate to severe AD patients were treated with combination therapy, compared to donepezil monotherapy [6]. One of the included studies was 52 weeks in duration, compared to 24 weeks in the other included trials, and found no statistically significant improvement in sMMSE and BADLS with combination therapy compared to donepezil monotherapy [6]. The study reported significant improvement at the halfway mark but none at the end point which raises concerns for long term efficacy of the studied medications [6]. Ultimately, the authors concluded that using an appropriate ChEI monotherapy will not result in missed cognitive benefits compared to using a combination therapy [6]. The study reported the need for longer studies to clarify the true effect of combination therapy compared to monotherapy [6].

The same systematic review also evaluated the efficacy of the following combination therapies: galantamine and memantine, rivastigmine transdermal patches and memantine, and patient choice of ChEI and memantine [6]. Regarding galantamine and memantine trials, there was numerical improvement in ADAS-Cog or ADCS-ADL scores with combination therapy, compared to

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galantamine monotherapy, but this was not statistically significant [6]. However, one of the studies was interrupted due to concerns for safety issues associated with galantamine while the other study ruled combination therapy to be safe and well tolerated in MCI patients [6]. The study about rivastigmine and memantine combination therapy found combination therapy had no statistically significant effect on ADAS-Cog, K-MMSE, FAB, CGA-NPI-12, CMAIK, ADCS-CDL, and CDR-SB compared to rivastigmine monotherapy [6]. Finally, the two studies of patient's choice of ChEI and memantine had conflicting results [6]. One study in mild to moderate AD treated patients with twenty mg QD of memantine in addition to patient's choice of ChEI and there was no statistically significant difference compared to placebo [6]. The other study dd report statistically significant improvement in SIB when moderate to severe AD patients were treated with a higher dose (28 mg QD) of memantine and choice ChEI; however, there was no significant difference in ADCS-ADL scores [6].

A study using data from a previous double-blind placebo-controlled RCT of memantine therapy added to patients on a stable donepezil regimen determined the NNT of combination therapy to be between eight to ten [49]. This confers clinically significant benefits in moderate-to-severe AD based on their ADCS-ADL19, SIB, and CIBIC-Plus scores [49].

4. Discussion

Based on our discussion above about the multiple hypotheses of AD pathogenesis, it can be surmised that future research needs to determine the actual pathogenic mechanism of AD. This will allow for targeted therapy and the development of accurate diagnostic measures. Currently, many CSF and plasma tests can determine the levels of Aβ and tau proteins, but they have not been considered accurate enough for diagnosis [1]. We have also discussed amyloid PET's inability to detect low levels of amyloid plaques thus making it challenging to confirm AD diagnoses in the early stages [1]. This presents a conundrum where initiation of anti-Aβ therapy requires confirmation of AD through amyloid PET, likely when the disease process has progressed past the early stages; however, pharmacological management through ChEIs, NMDAR antagonists, or anti-amyloid therapies are more efficacious in early AD [1,3,26,45]. This is further complicated by the fact that the presence of MCI or pathogenic molecules does not guarantee the development of AD but it does increase the risk of developing AD given enough time [3]. Additionally, available biomarker testing is not necessarily diagnostic for AD because they can also be present in other pathologies. For example, levels of p-tau can diagnose AD, but they can also be elevated in patients with recent acute injuries such as head trauma or cardiorespiratory arrest [1]. Finally, current diagnostic biomarkers are also influenced by specific medications, dynamic disorders of the CSF, impaired renal function, as well as other pathologies [1].

Current therapies for AD have produced meager clinical benefits. Symptomatic treatments, such as ChEIs and NMDAR antagonists, do not significantly modulate the disease pathology but, rather, slow patients' cognitive and functional decline [3,11,14,21,28–31,33]. Overall, ChEIs have an NNT between 4-14 but some sources have cited NNTs 22-58 depending on the medication [7,27,32,35]. Depending on the source, the ChEI with the lowest NNT appears to be donepezil [32,35]. However, the Ontario Drug Policy Research Network calculated much higher NNTs than other sources with the lowest NNT for rivastigmine's oral formulation [32]. The problem with this is that rivastigmine tends to be less tolerable than the patch formulation because of significant GI adverse events [32]. On the other hand, memantine had NNTs between three to eight and effect sizes of 0.32 to 0.62 which confers moderate benefit [38]. However, the Ontario Drug Policy Research Network reported memantine's NNT to be 56 [32]. Possible factors contributing to the significant difference between the reported NNTs include calculations from data reported by studies with conflicts of interest or high amounts of publication bias.

Meanwhile, the only disease-modifying treatments available, anti-amyloid therapies, provide moderate clinical benefits at the cost of an increased risk of serious adverse events [5,26,28,39–44]. The NNT of lecanemab ranged between thirteen to fifteen depending on the neuropsychological test

 doi:10.20944/preprints202503.1671.v1

used [47,48] Donanemab's NNT ranged between six to 28 with the highest NNT for high tau populations and different NNTs based on the neuropsychological testing used [47,49]. This confers moderate improvement at best with little benefit for high tau populations. These findings support further research into therapeutics of alternative targets, a better understanding of AD's pathogenic mechanisms, and the development of targeted therapy against key players in pathogenesis. Other directions for future research also include determining the clinical efficacy of existing medications for AD as well as inclusion of more diverse populations of both age and racial or ethnic identity.

Due to the failure of anti-amyloid therapies to provide clinically significant results, there is reason to suspect other isoforms of amyloid proteins or other pathogenic molecules are the cause of AD [19]. Evidence against the amyloid hypothesis includes the lack of correlation between clinical symptomology and amyloid levels [11]. Rather, tau protein levels correlate better with the progression of AD symptoms [11]. For example, non-steroidal anti-inflammatory drugs (NSAIDs) showed promising but inconclusive results for the treatment of AD, but further well-designed studies need to confirm their efficacy [11].

Lithium, another promising therapeutic, showed possible disease-modifying benefit in a previous meta-analysis [3,18]. Lithium modulates various processes that play a role in AD pathogenesis such as neuroinflammation, oxidative stress, mitochondrial function, neurotransmission, and other factors [18]. In the study, lithium consistently showed higher efficacy on cognitive assessments over a placebo and performed statistically better against donanemab and lecanemab in tolerability and acceptability analyses [3,18]. However, further studies are needed to confirm lithium's therapeutic benefit for AD [18].

Recently, more investigations have evaluated the link between Diabetes Mellitus (DM) and AD. In the normal brain, insulin functions in synapsis, neuroglial metabolism, neuroglial trophism, and neuroinflammation which mediate memory and other cognitive functions [40]. Further evidence supporting this link includes the fact that brain insulin resistance and impaired glucose metabolism precede the onset of AD symptoms in addition to correlating with the severity of a patient's cognitive impairment [22,40]. Furthermore, Type 2 DM is also a known risk factor for both cognitive impairment and dementia [40]. Finally, insulin resistance increases Aβ deposition and tau phosphorylation [40]. Interestingly, the studies about DM and AD demonstrated different medication efficacy based on APOE status [22]. A study of thiazolidinediones, a treatment for DM, showed improvement in cognitive outcomes within ApoE4-negative patients treated with the medication in addition to proving ApoE-4 negative individuals present with higher sensitivity to insulin in the brain than ApoE-4 positive patients [22]. Overall, this relationship has not shown to be causative currently; however, there is increasing research into the topic as well as the possibility of using anti-diabetic medications in the management of AD [22,40].

Finally, many studies that confirmed the efficacy of the currently FDA-approved treatments of AD lacked diversity in racial or ethnic identity and age of their participants [18,26,51]. A study that estimated the population of individuals with clinical AD and MCI within the United States reported an adjusted prevalence based on the 2020 census [52]. The publication reported the adjusted prevalence of AD to be 11.3% of the population while it was 10% in non-Hispanic Whites, 14% in Hispanics, and 18.6% in non-Hispanic African Americans [52]. The prevalence is also projected to increase as the "baby boom" generation ages [52]. This study highlights AD research mainly studying white non-Hispanic populations despite AD disproportionately affecting minority groups thus strengthening the argument for more diversity in research populations [26,52]. Additionally, a systematic review of RCTs published before 2015 studied donepezil, rivastigmine, and galantamine reported that participants were significantly younger than the AD population in real life [51]. The lack of representative study populations means the results are less generalizable. This is concerning, as the phase III trials for the most recently approved anti-amyloid therapy, donanemab, were conducted on mainly non-Hispanic white individuals and were found to be most efficacious in individuals younger than 65 [26].

 doi:10.20944/preprints202503.1671.v1

Abbreviations

Aβ	Amyloid β
AβO	Aβ oligomers
ACTION Study	Activities of Daily Living and Cognition Study
AD	Alzheimer's Disease
ADAS	Alzheimer's Disease Assessment Scale
ADAS-Cog	Alzheimer's Disease Assessment Scale - Cognitive Subscale
ADCOMS	Alzheimer's Disease Composite Score
ADCS-ADL	Alzheimer's Disease Cooperative Study - Activities of Daily Living
ADCS-CGIC	ADCS Clinical Global Impression of Change
ADL	Activities of Daily Living
APP	Amyloid Precursor Protein
ARIA	Amyloid Related Imaging Abnormalities
BADLS	Bristol Activities of Daily Living Scale
BBB	Blood Brain Barrier
BID	Twice per day
CAA	Cerebral Amyloid Angiopathy
CDR	Clinical Dementia Rating
CDR-SB	CDR-Sum of Boxes
CGI	Clinical Global Impression
CGIC	Clinical Global Impression of Change
ChEIs	Cholinesterase Inhibitors
CIBIC+	Clinicians Interview Based Impression of Change Plus Caregiver Input
CSF	Cerebrospinal Fluid
DM	Diabetes Mellitus
DNA	Deoxyribonucleic Acid
DMN	Default Mode Network
ER	Endoplasmic Reticulum
GI	gastrointestinal
IDCS-iADL	Alzheimer's Disease Cooperative Study Instrumental Activities of Daily Living Scale
iADRS	Integrated Alzheimer's Disease Rating Scale
MCI	Mild Cognitive Impairment
MD	Mean Difference
MMSE	Mini Mental State Examination
mPFC	Medial Prefrontal Cortex
mtDNA	Mitochondrial DNA
NFT	Neurofibrillary Tangle
NMDAR	NMDA Receptor
NNH	Number Needed To Harm
NNT	Number Needed To Treat
NSAIDs	Non-steroidal Anti-inflammatory Drugs
OR	Odds Ratio
PCC	Posterior Cingulate Cortex
PET	Positron Emission Tomography
QD	Per day
RCT	Randomized Clinical Trial
ROS	Reactive Oxygen Species
SIB	Severe Impairment Battery
SMD	Standardized Mean Difference
SN	Salience Network
VMRI	Volumetric MRI

References

1. Jack CR Jr, Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association workgroup. *Alzheimers Dement*. 2024;20(8):5143-5169

 doi:10.20944/preprints202503.1671.v1

2. Wolk DA, Dickerson BC. Clinical features and diagnosis of Alzheimer disease [Internet]. Wolters Kluwer: UpToDate; 2024. [cited 2024 Nov 19] available from https://www.uptodate.com/contents/clinical-features-and-diagnosis-of-alzheimer-disease?search=alzheimer%27s%20disease&topicRef=5073&source=see_link#H29
3. Chen Y, Lai M, Tao M. Evaluating the efficacy and safety of Alzheimer's disease drugs: A meta-analysis and systematic review. *Medicine (Baltimore)*. 2024; 103(16): e37799
4. Matsunaga S, Kishi T, Iwata N. Memantine monotherapy for Alzheimer's disease: A systematic review and meta-analysis. *PloS One*. 2015; 10(4):e0123289
5. Qiao Y, Chi Y, Zhang Q, Ma Y. Safety and efficacy of lecanemab for Alzheimer's disease: A systematic review and meta-analysis of randomized clinical trials. *Front Aging Neurosci*. 2023; 15(1169499): 1169499
6. Knorz AL, Quante A. Alzheimer's disease: Efficacy of mono-and combination therapy. A systematic review. *J Geriatr Psychiatry Neurol*. 2022; 35(4):475-486
7. Lanctôt KL, Herrmann N, Yau KK, Khan LR, Liu BA, LouLou MM, et al. Efficacy and safety of cholinesterase inhibitors in Alzheimer's disease: A meta-analysis. *CMAJ*. 2003; 169(6): 557-564
8. Jeremic D, Jiménez-Díaz L, Navarro-López JD. Past, present and future of therapeutic strategies against amyloid-β peptides in Alzheimer's disease: A systematic review. *Ageing Res Rev*. 2021; 72(101496):101496
9. Zeliger HI. Oxidative stress: Its impact on human health and disease onset. Academic Press; 2022. 291-297p
10. Wu W, Ji Y, Wang Z, Wu X, Li J, Gu F, et al. The FDA-approved anti-amyloid-β monoclonal antibodies for the treatment of Alzheimer's disease: A systematic review and meta-analysis of randomized controlled trials. *Eur J Med Res*. 2023; 28(1): 544
11. Wong-Guerra M, Calfio C, Maccioni RB, Rojo LE. Revisiting the neuroinflammation hypothesis in Alzheimer's disease: A focus on the druggability of current targets. *Front Pharmacol*. 2023; 14(1161850):1161850
12. Klaassens BL, van Gerven JMA, Klaassen ES, van der Grond J, Rombouts SARB. Cholinergic and serotonergic modulation of resting state functional brain connectivity in Alzheimer's disease. *Neuroimage*. 2019;199:143-152
13. Adhikary K, Sarkar R, Chowdhury SR, Banerjee P. A review of diverse neurological disorders: Pathophysiology, molecular mechanisms, and therapeutics. Academic Press; 2024. 235-247p
14. Farlow MR, Grossberg GT, Sadowsky CH, Meng X, Somogyi M. A 24-week, randomized, controlled trial of rivastigmine patch 13.3 mg/24 h versus 4.6 mg/24 h in severe Alzheimer's dementia. *CNS Neurosci Ther*. 2013; 19(10): 745-752
15. McAleese KE, Miah M, Graham S, Hadfield GM, Walker L, Johnson M, et al. Frontal white matter lesions in Alzheimer's disease are associated with both small vessel disease and AD-associated cortical pathology. *Acta neuropathol*. 2021; 142: 937-950
16. Canu E, McLaren DG, Fitzgerald ME, Bendlin BB, Zoccatelli G, Alessandrini F, et al. Mapping the structural brain changes in Alzheimer's disease: The independent contribution of two imaging modalities. *J Alzheimers Dis*. 2011; 26(s3): 263-274
17. Hamano T, Mutoh T, editors. Autophagy dysfunction in Alzheimer's disease and dementia. Academic Press; 2022. 73-89p
18. Terao I, Kodama W. Comparative efficacy, tolerability and acceptability of donanemab, lecanemab, aducanumab and lithium on cognitive function in mild cognitive impairment and Alzheimer's disease: A systematic review and network meta-analysis. *Ageing Res Rev*. 2024; 94(102203): 102203
19. Cline EN, Bicca MA, Viola KL, Klein WL. The amyloid-β oligomer hypothesis: Beginning of the third decade. *J Alzheimers Dis*. 2018; 64(s1): S567-S610
20. Younes K, Sha SJ. The most valuable player or the tombstone: Is Tau the correct target to treat Alzheimer's disease? *Brain*. 2023; 146(6): 2211-2213
21. Waring JF, Tang Q, Robieson WZ, King DP, Das U, Dubow J, et al. APOE-ε4 carrier status and donepezil response in patients with Alzheimer's disease. *J Alzheimers Dis*. 2015; 47(1): 137-148
22. Iketani R, Ohno K, Kawasaki Y, Matsumoto K, Yamada H, Kishino S. Apolipoprotein E gene polymorphisms affect the efficacy of thiazolidinediones for Alzheimer's disease: A systematic review and meta-analysis. *Biol Pharm Bull*. 2018; 41(7): 1017-1023

 doi:10.20944/preprints202503.1671.v1

23. Tahami Monfared AA, Phan NN, Pearson I, Mauskopf J, Cho M, Zhang Q, et al. A systematic review of clinical practice guidelines for Alzheimer's disease and strategies for future advancements. *Neurol Ther*. 2023; 12(4): 1257-1284
24. Harvey PD, Mohs RC. Functional neurobiology of aging. Academic Press; 2001. 53-63
25. Eli Lilly. A study of donanemab (LY3002813) in participants with early Alzheimer's disease (TRAILBLAZER-ALZ 2) [Internet]. ClinicalTrials.gov ; 2024. [cited 2024 Nov 18]. Available from https://clinicaltrials.gov/study/NCT04437511?intr=donanemab&locStr=United%20States&country=United%20States&rank=5
26. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in early symptomatic Alzheimer disease: The TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023; 330(6): 512-527
27. Assunção SS, Sperling RA, Ritchie C, Kerwin DR, Aisen PS, Lansdall C, et al. Meaningful benefits: A framework to assess disease-modifying therapies in preclinical and early Alzheimer's disease. *Alzheimers Res Ther*. 2022; 14(1): 54
28. Press D, Buss SS. Treatment of Alzheimer disease [Internet]. Wolters Kluwer: UpToDate; 2024. [cited 2024 Nov 18]. Available from https://www.uptodate.com/contents/treatment-of-alzheimer-disease?search=alzheimers&topicRef=5071&source=see_link
29. Press D, Alexander M. Cholinesterase inhibitors in the treatment of dementia [Internet]. Wolters Kluwer: UpToDate; 2024. [cited 2024 Nov 18]. Available from https://www.uptodate.com/contents/cholinesterase-inhibitors-in-the-treatment-of-dementia?sectionName=Duration+of+therapy&search=alzheimers&topicRef=5073&anchor=H691890260&source=see_link#H691890260
30. Rosler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, et al. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: International randomised controlled trial. *BMJ*. 1999; 318(7184): 633-638
31. Marucci G, Buccioni M, Dal Ben D, Lambertucci C, Volpini R, Amenta F. Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease. *Neuropharmacology*. 2021; 190(108352): 108352
32. Juurlink D, Mamdani M, Gomes T. Cognitive enhanvers for the treatment of Alzheimer's disease [Internet]. Ontario Drug Policy Research Network (ODPRN); 2015. [cited 2025 Jan 5]. Available from https://odprn.ca/wp-content/uploads/2016/02/cognitive-enhancers-consolidated-final_Updated_Feb-29-2016.pdf
33. Guo J, Wang Z, Liu R, Huang Y, Zhang N, Zhang R. Memantine, donepezil, or combination therapy - What is the best therapy for Alzheimer's disease? A network meta-analysis. *Brain behav*. 2020 Nov; 10(11): e01831
34. Dou KX, Tan MS, Tan CC, Cao XP, Hou XH, Guo QH, et al. Comparative safety and effectiveness of cholinesterase inhibitors and memantine for Alzheimer's disease: A network meta-analysis of 41 randomized controlled trials. *Alzheimers Res Ther*. 2018; 10(1): 126
35. Rogers SL, Doody RS, Mohs RC, Friedhoff LT, Donepezil Study Group. Donepezil improves cognition and global function in Alzheimer disease: A 15-week, double-blind, placebo-controlled study. *Arch Intern Med*. 1998; 158(9): 1021-1031
36. Olivares D, Deshpande VK, Shi Y, Lahiri DK, Greig NH, Rogers JT, et al. N-methyl D-aspartate (NMDA) receptor antagonists and memantine treatment for Alzheimer's disease, vascular dementia and Parkinson's disease. *Curr Alzheimer Res*. 2012; 9(6): 746-758
37. Wilkinson D, Wirth Y, Goebel C. Memantine in patients with moderate to severe Alzheimer's disease: Meta-analyses using realistic definitions of response. *Dement Geriatr Cogn Disord*. 2014; 37(1-2): 71-85
38. Livingston G, Katona C. The place of memantine in the treatment of Alzheimer's disease: A number needed to treat analysis. *Int J Geriatr Psychiatry*. 2004; 19(10): 919-925
39. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023; 388(1): 9-21.
40. Brockmann R, Nixon J, Love BL, Yunusa I. Impacts of FDA approval and Medicare restriction on antiamyloid therapies for Alzheimer's disease: Patient outcomes, healthcare costs, and drug development. *Lancet Reg Health Am*. 2023; 20(100467): 100467

 doi:10.20944/preprints202503.1671.v1

41. Avgerinos KI, Manolopoulos A, Ferrucci L, Kapogiannis D. Critical assessment of anti-amyloid-β monoclonal antibodies effects in Alzheimer's disease: A systematic review and meta-analysis highlighting target engagement and clinical meaningfulness. *Sci Rep*. 2024;14(1):25741
42. Beshir SA, Hussain N, Menon VB, Al Haddad AH, Al Zeer RA, Elnour AA. Advancements and challenges in antiamyloid therapy for Alzheimer's disease: A comprehensive review. *Int J Alzheimers Dis*. 2024; 2024(1): 2052142
43. Padda IS, Parmar M. Aducanumab [Internet]. StatPearls Publishing: StatPearls; 2024 [cited 2024 Nov 21]. Available from https://www.ncbi.nlm.nih.gov/books/NBK573062/
44. Ebell MH, Barry HC, Baduni K, Grasso G. Clinically important benefits and harms of monoclonal antibodies targeting amyloid for the treatment of Alzheimer disease: A systematic review and meta-analysis. *Ann Fam Med*. 2024; 22(1): 50-62
45. Dhadda S, Kanekiyo M, Li D, Swanson CJ, Irizarry M, Berry S, et al. Consistency of efficacy results across various clinical measures and statistical methods in the lecanemab phase 2 trial of early Alzheimer's disease. *Alzheimers Res Ther*. 2022; 14(1): 182
46. Swanson CJ, Zhang Y, Dhadda S, Wang J, Kaplow J, Lai RY, et al. A randomized, double-blind, phase 2b proof-of-concept clinical trial in early Alzheimer's disease with lecanemab, an anti-Aβ protofibril antibody. *Alzheimers Res Ther*. 2021; 13: 1-4
47. Jeremic D, Navarro-Lopez JD, Jimenez-Diaz L. Donanemab outperformed Aducanumab and Lecanemab on cognitive, but not on biomarker and safety outcomes: Systematic review, frequentist and Bayesian network meta-analyses. *medRxiv*. 2024: 2024-03
48. George, J. Alzheimer's drug trials should report effect sizes, researchers say - How effective are anti-amyloid treatments? [Internet]. MedPage Today; 2023 [cited 2025 Jan 5]. Available from https://www.medpagetoday.com/neurology/alzheimersdisease/107522
49. van Dyck CH, Schmitt FA, Olin JT, Memantine MEM-MD-02 Study Group. A responder analysis of memantine treatment in patients with Alzheimer disease maintained on donepezil. *Am J Geriatr Psychiatry*. 2006; 14(5):428-437
50. Muñoz-Jiménez M, Zaarkti A, García-Arnés JA, García-Casares N. Antidiabetic drugs in Alzheimer's disease and mild cognitive impairment: A systematic review. *Dement Geriatr Cogn Disord*. 2021; 49(5): 423-434
51. Leinonen A, Koponen M, Hartikainen S. Systematic review: Representativeness of participants in RCTs of acetylcholinesterase inhibitors. *PloS One*. 2015; 10(5): e0124500
52. Rajan KB, Weuve J, Barnes LL, McAninch EA, Wilson RS, Evans DA. Population estimate of people with clinical Alzheimer's disease and mild cognitive impairment in the United States (2020–2060). *Alzheimers Dement*. 2021; 17(12): 1966-1975