



**INTERNATIONAL JOURNAL OF
PHARMACEUTICAL SCIENCES**
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: <https://www.ijpsjournal.com>



Review Article

Targeting Alzheimer's Disease: A Comprehensive Review of Current Drug Targets, Receptors, Enzymes, and Neurotransmitters

C. Rejitha*, A.Hari Nandhini, R. Thelshath, Rajaganapathy Kaliyaperumal, S. Latha

Faculty Of Pharmacy, Bharath Institute Of Higher Education And Research

ARTICLE INFO

Received: 11 Sep 2024

Accepted: 15 Sep 2024

Published: 27 Sep 2024

Keywords:

Alzheimer's disease,
receptors, enzymes,
Neurotransmitter.

DOI:

10.5281/zenodo.13850740

ABSTRACT

Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by progressive cognitive decline and memory impairment. Despite extensive research, current therapeutic options remain limited, and there is no cure. Recent advancements have expanded the understanding of key molecular mechanisms underlying AD pathogenesis, paving the way for novel therapeutic approaches. This review aims to provide a comprehensive analysis of the current drug targets for AD, focusing on various receptors, enzymes, and neurotransmitters involved in disease progression. The amyloid-beta ($A\beta$) cascade, tau protein hyperphosphorylation, synaptic dysfunction, oxidative stress, neuroinflammation, and impaired neurotransmission represent major pathological hallmarks of AD. Therapeutic strategies have been developed to target these processes, including β -secretase (BACE) and γ -secretase inhibitors for reducing amyloid deposition, tau kinase inhibitors to prevent tau hyperphosphorylation, and cholinesterase inhibitors to enhance cholinergic neurotransmission. Additionally, drugs targeting N-methyl-D-aspartate (NMDA) receptors aim to prevent excitotoxicity. Emerging therapies focus on modulating neuroinflammatory pathways, targeting microglial activation, and blocking pro-inflammatory cytokines. Receptors such as nicotinic acetylcholine receptors (nAChRs), GABA receptors, serotonin receptors, and muscarinic receptors are explored for their roles in maintaining neurotransmitter balance and neuroprotection. This review will explore these drug targets in detail, discussing both established and experimental therapeutic strategies. We will provide illustrative diagrams and tables to highlight the receptor-ligand interactions, signaling pathways, and the role of various enzymes and neurotransmitters in the progression of AD. Additionally, we will discuss the clinical efficacy and challenges of current and potential

*Corresponding Author: C. Rejitha

Address: Faculty Of Pharmacy, Bharath Institute Of Higher Education And Research

Email ✉: lencyrejitha8@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and behavioural changes, primarily affecting the elderly. The exact etiology of AD remains complex, with multiple biochemical and genetic factors contributing to its pathology. Currently, available therapies offer symptomatic relief but fail to halt or reverse disease progression. Recent advances in understanding AD pathogenesis have identified several drug targets, including receptors, enzymes, and neurotransmitters involved in amyloid-beta ($A\beta$) plaque deposition, tau hyperphosphorylation, and neurotransmitter imbalances.[1] This review provides a comprehensive analysis of the key molecular targets in Alzheimer's disease therapy, focusing on various receptors (such as NMDA, nicotinic, and muscarinic receptors), enzymes (like beta-secretase and gamma-secretase), and neurotransmitters (such as acetylcholine,

glutamate, and serotonin). By exploring their roles in AD pathology and therapeutic potential, this review examines the challenges and advancements in drug design and clinical application. Additionally, emerging therapeutic approaches, such as immunotherapies, metal ion modulators, and neuroprotective agents, are discussed, emphasizing the future directions in AD drug discovery.[2]

Key Drug Targets in Alzheimer's Disease

Alzheimer's disease is associated with complex pathophysiological mechanisms, offering several potential drug targets. These targets are classified into receptors, enzymes, and neurotransmitter systems:

1. Receptors as Drug Targets

Several receptor systems are implicated in AD, and their modulation has shown potential in therapeutic interventions.[3]

Receptor Type	Role in AD Pathogenesis	Drugs Targeting the Receptor	Mechanism of Action
N-methyl-D-aspartate (NMDA)	Involved in glutamate excitotoxicity leading to neuronal death	Memantine (Approved)	NMDA receptor antagonist to prevent neurotoxicity
Nicotinic Acetylcholine Receptor (nAChR)	Affects cholinergic system, crucial for memory and learning	Nicotine-based therapies (in research)	Enhances cholinergic transmission
Muscarinic Acetylcholine Receptor (mAChR)	Modulates cognitive function and cholinergic activity	Muscarinic agonists (in development)	Improves acetylcholine release
Serotonin Receptors (5-HT)	Alters mood, cognition, and behavior	Serotonin agonists (exploratory)	Modulates neurotransmission to enhance cognition

2. Enzymes Involved in Alzheimer's Pathology

The regulation of amyloid-beta ($A\beta$) production and tau phosphorylation is dependent on several key enzymes, making them attractive drug targets.

Enzyme	Role in AD Pathogenesis	Drug Candidates	Mechanism of Action
Beta-secretase (BACE1)	Catalyzes the initial cleavage of amyloid precursor protein (APP)	Verubecestat, Lanabecestat (Failed)	BACE1 inhibition to reduce amyloid-beta production
Gamma-secretase	Final step in amyloid-beta formation	Semagacestat (Failed)	Gamma-secretase inhibition



Tau Kinases (GSK-3 β , CDK5)	Phosphorylate tau, leading to neurofibrillary tangles	Tideglusib (in trials)	Inhibition of tau hyperphosphorylation
Acetylcholinesterase (AChE)	Breaks down acetylcholine, reducing cholinergic transmission	Donepezil, Rivastigmine, Galantamine	Inhibits AChE to enhance acetylcholine levels[4]

3. Neurotransmitter Systems in AD

Neurotransmitter imbalance contributes to cognitive decline in AD. Modulation of these systems remains a cornerstone of AD therapy.

Neurotransmitter	Role in AD	Drugs Targeting the System	Mechanism of Action
Acetylcholine	Decline leads to memory loss and cognitive deficits	Cholinesterase inhibitors (Donepezil)	Increases acetylcholine levels in synapses
Glutamate	Excess causes excitotoxicity leading to cell death	Memantine	NMDA receptor modulation to reduce excitotoxicity
Serotonin	Affects mood and cognition	Selective serotonin reuptake inhibitors (SSRIs)	Increases serotonin levels to improve mood and cognition
Dopamine	Modulates behavior and cognition	Dopaminergic agents (exploratory)	Enhances dopaminergic transmission[5]

1. Tau Phosphorylation Mechanism

In Alzheimer's disease, tau proteins, which normally stabilize microtubules in neurons, undergo abnormal phosphorylation. Hyperphosphorylated tau detaches from

microtubules, aggregates into paired helical filaments (PHFs), and eventually forms neurofibrillary tangles (NFTs), contributing to neuronal dysfunction.

Key Enzymes Involved in Tau Phosphorylation:

Enzyme	Role in Tau Phosphorylation	Drug Candidates
Glycogen Synthase Kinase-3 β (GSK-3 β)	Primary enzyme responsible for hyperphosphorylation	Tideglusib (GSK-3 β inhibitor)
Cyclin-dependent kinase 5 (CDK5)	Involved in abnormal phosphorylation in AD neurons	CDK5 inhibitors (in development)
Protein phosphatase 2A (PP2A)	Reduces tau phosphorylation, but its activity is decreased in AD	PP2A activators (exploratory)

Next, I'll create a diagram illustrating the tau phosphorylation pathway.[5]

2. Neurotransmitter Receptor Subtypes

The neurotransmitter systems most implicated in Alzheimer's are acetylcholine, glutamate, and

serotonin, which are modulated through specific receptor subtypes.

Acetylcholine Receptor Subtypes:		
Receptor Subtype	Role	Drug Targeting
Muscarinic (M1, M2)	Involved in cognition and learning	Muscarinic agonists (in development)
Nicotinic (α 4 β 2, α 7)	Modulates memory and synaptic plasticity	Nicotine-based therapies (in trials)



Glutamate Receptor Subtypes:		
Receptor Subtype	Role	Drug Targeting
NMDA Receptor	Mediates synaptic plasticity and memory formation, overactivation causes excitotoxicity	Memantine (NMDA antagonist)
AMPA Receptor	Facilitates fast excitatory synaptic transmission	AMPA receptor modulators (in research)
Serotonin Receptor Subtypes:		
Receptor Subtype	Role	Drug Targeting
5-HT1A	Affects cognition and emotional responses	Serotonin agonists (in development)
5-HT2A	Modulates mood and behavior	SSRIs (Selective serotonin reuptake inhibitors)

Next, I will create a diagram illustrating receptor subtype modulation in Alzheimer's.[6]

3. Drug Mechanisms in Alzheimer's Disease

In Alzheimer's, drug mechanisms are categorized into several classes based on how they target the pathophysiological features of the disease:

Cholinesterase Inhibitors:

Donepezil, Rivastigmine, Galantamine: Inhibit acetylcholinesterase, increasing acetylcholine levels to improve memory and cognition.[7]

NMDA Receptor Antagonists:

Memantine: Prevents glutamate-induced excitotoxicity by modulating NMDA receptor activity.

BACE1 and Gamma-secretase Inhibitors:

Verubecestat, Semagacestat: Inhibit the enzymes responsible for amyloid-beta plaque formation (though clinical trials have seen limited success).

Tau Phosphorylation Inhibitors:

Tideglusib:

Inhibits GSK-3 β to reduce hyperphosphorylation of tau proteins and prevent neurofibrillary tangle formation.

1. Tau Phosphorylation Pathway and Neurofibrillary Tangle (NFT) Formation

Tau is a protein responsible for stabilizing microtubules, which are crucial for the structural integrity and function of neurons. In Alzheimer's disease, abnormal hyperphosphorylation of tau

leads to the formation of neurofibrillary tangles (NFTs), one of the hallmarks of the disease.[8]

Mechanism of Tau Phosphorylation:

- GSK-3 β (Glycogen Synthase Kinase-3 β) and CDK5 (Cyclin-dependent kinase 5) are key enzymes responsible for phosphorylating tau.
- Under normal conditions, tau phosphorylation is tightly regulated. However, in AD, these enzymes are overactive, causing excessive phosphorylation.
- Hyperphosphorylated tau detaches from microtubules and aggregates into paired helical filaments (PHFs), eventually leading to NFT formation.[9]
- Impact of NFTs:
- NFTs disrupt intracellular transport by disassembling microtubules, leading to impaired synaptic function and cell death.
- The accumulation of NFTs is associated with cognitive decline and correlates with the severity of dementia in AD patients.[10]

2. Neurotransmitter Receptor Subtypes in Alzheimer's Disease

The dysregulation of neurotransmitter systems is a key contributor to the cognitive deficits seen in AD. The most affected neurotransmitter systems include acetylcholine, glutamate, and serotonin. Let's explore their receptor subtypes.

Acetylcholine Receptors:

Muscarinic Receptors (M1, M2):

These are G-protein-coupled receptors involved in various cognitive functions, including memory and learning.

- M1 receptors are mainly associated with enhancing cognitive function.
- M2 receptors regulate the release of acetylcholine and are linked to controlling heart rate and muscle contraction.[11]
- Drugs in development target muscarinic receptors to restore cognitive abilities in AD.

Nicotinic Receptors ($\alpha 4\beta 2$, $\alpha 7$):

These receptors play a critical role in synaptic plasticity and memory formation.

- $\alpha 7$ nicotinic receptors are crucial for attention and working memory.
- Nicotine-based therapies are being explored to activate these receptors and improve cholinergic transmission in AD patients.[12]

Glutamate Receptors:

NMDA Receptors:

- NMDA receptors are critical for synaptic plasticity and memory formation. In AD, overactivation of these receptors by excess glutamate leads to excitotoxicity, causing neuronal damage.
- Memantine, an NMDA receptor antagonist, is used to prevent this excitotoxicity.[13]

AMPA Receptors:

- AMPA receptors mediate fast excitatory transmission in the brain and are crucial for long-term potentiation (LTP), a process involved in learning and memory.
- AMPA receptor modulators are being investigated as potential therapies to enhance synaptic strength in AD.[14]

Serotonin Receptors:

- 5-HT1A and 5-HT2A receptors are key in modulating mood, behavior, and cognition.

- 5-HT1A agonists are being explored to improve cognitive function and reduce neuroinflammation in AD.
- Selective serotonin reuptake inhibitors (SSRIs), which increase serotonin levels, are used to treat mood disorders in AD patients.[15]

3. Drug Mechanisms in Alzheimer's Disease

Different drug classes target the biochemical pathways involved in AD, focusing on reducing cognitive decline and preventing further neuronal damage. Here are the major drug classes

Cholinesterase Inhibitors:

- Donepezil, Rivastigmine, and Galantamine are cholinesterase inhibitors that prevent the breakdown of acetylcholine by inhibiting acetylcholinesterase (AChE). This increases acetylcholine availability in synapses, improving memory and cognitive function.[16]
- These drugs are primarily used in early to moderate stages of AD to provide symptomatic relief.

NMDA Receptor Antagonists:

Memantine is the only approved NMDA receptor antagonist for moderate to severe AD. It works by blocking excessive NMDA receptor activation caused by high levels of glutamate, thereby preventing excitotoxicity and protecting neurons from damage. [17]

BACE1 and Gamma-secretase Inhibitors:

- BACE1 (beta-secretase) and gamma-secretase are enzymes involved in the production of amyloid-beta ($A\beta$) plaques.
- BACE1 inhibitors (such as verubecestat and lanabecestat) aim to block the first step in amyloid-beta production. However, clinical trials have faced challenges, as these inhibitors have shown limited efficacy and significant side effects.
- Gamma-secretase inhibitors were also explored but similarly failed in clinical trials



due to adverse effects on other important biological processes.[18]

Tau Phosphorylation Inhibitors:

Tideglusib, a GSK-3 β inhibitor, aims to reduce the hyperphosphorylation of tau proteins, preventing the formation of NFTs. This drug showed some promise in early trials, though further research is needed to establish its long-term efficacy.

1. Tau Phosphorylation Pathway: Detailed Mechanism

Tau Protein:

- Normally, tau stabilizes microtubules in neurons, aiding in intracellular transport, which is vital for neuronal health.
- Hyperphosphorylated tau: In Alzheimer's, tau becomes abnormally phosphorylated by enzymes such as GSK-3 β and CDK5. This results in tau dissociating from microtubules and accumulating in the cytoplasm, forming insoluble aggregates known as paired helical filaments (PHFs).

GSK-3 β and CDK5:

- GSK-3 β (Glycogen Synthase Kinase-3 β) is one of the main kinases responsible for tau hyperphosphorylation. Overactivation of GSK-3 β is a significant contributor to tau aggregation in AD.
- CDK5 (Cyclin-dependent kinase 5) plays a role in abnormal phosphorylation of tau in neurodegenerative conditions. [19]

Neurofibrillary Tangles (NFTs):

- Tau tangles interfere with neuron function by disrupting the microtubule network. NFTs accumulate inside neurons, leading to synaptic dysfunction and neuronal death. They spread through the brain in a predictable pattern, starting in the entorhinal cortex and hippocampus (areas involved in memory) before spreading to the neocortex.

Therapeutic Targeting:

- Tideglusib, a GSK-3 β inhibitor, aims to reduce tau hyperphosphorylation. By

inhibiting GSK-3 β , tideglusib potentially prevents tau from forming neurofibrillary tangles. Although promising, clinical trials have produced mixed results, necessitating further research.[20]

2. Neurotransmitter Receptor Subtypes: Detailed Insights

Acetylcholine Receptors in Alzheimer's:

The cholinergic hypothesis proposes that a loss of cholinergic neurons in the basal forebrain contributes to the cognitive decline observed in Alzheimer's disease.

Muscarinic Receptors:

- M1 receptors are involved in cognitive function, and their stimulation can improve cognitive processes. Research is focusing on selective muscarinic agonists to improve memory in AD.
- M2 receptors are inhibitory autoreceptors that modulate acetylcholine release. Targeting these receptors could provide a balanced approach to enhancing cholinergic activity without causing overstimulation.[21]

Nicotinic Receptors:

- $\alpha 4\beta 2$ and $\alpha 7$ nicotinic acetylcholine receptors (nAChRs) are implicated in attention, memory, and synaptic plasticity. These receptors are found to be significantly reduced in AD brains.
- Therapies like nicotine patches or selective agonists targeting $\alpha 7$ receptors are under investigation to improve cognitive function and reduce neuroinflammation.

Glutamate Receptors in Alzheimer's:

Glutamate excitotoxicity:

In AD, excessive glutamate overstimulates NMDA receptors, leading to calcium influx, which triggers apoptosis (programmed cell death).

- Memantine acts as an NMDA receptor antagonist, blocking excessive glutamate stimulation without affecting normal synaptic activity. This drug helps prevent



excitotoxicity while preserving cognitive function.[22]

AMPA Receptors:

AMPA receptors are also involved in synaptic transmission. Dysregulation of these receptors in AD can impair synaptic plasticity and learning. AMPA modulators are in experimental stages to enhance synaptic function and memory.

Serotonin Receptors in Alzheimer's:

- **5-HT1A receptors:**

These receptors modulate mood and cognitive functions. Agonists of 5-HT1A may reduce neuroinflammation and improve cognition.

- **5-HT2A receptors:**

These receptors play a role in mood regulation and are targeted by antidepressants, such as SSRIs (Selective Serotonin Reuptake Inhibitors), which are commonly prescribed to AD patients for managing depression and anxiety.[23]

3. Drug Mechanisms: Expanded Details

Cholinesterase Inhibitors:

Mechanism:

Cholinesterase inhibitors work by blocking the breakdown of acetylcholine by acetylcholinesterase (AChE) in the synaptic cleft, thereby increasing the availability of acetylcholine for neurotransmission.

Donepezil:

Widely prescribed for all stages of AD, donepezil is a reversible inhibitor of AChE and helps improve cognitive symptoms.

Rivastigmine:

A dual inhibitor of AChE and butyrylcholinesterase (BuChE), rivastigmine is used for mild to moderate AD and is also available as a transdermal patch.

Galantamine:

In addition to AChE inhibition, galantamine acts as an allosteric modulator of nicotinic receptors, enhancing cholinergic transmission.[24]

NMDA Receptor Antagonists:

Memantine:

Memantine selectively blocks pathological overactivation of NMDA receptors without affecting normal receptor activity, thereby reducing glutamate-induced excitotoxicity.

- Clinical benefits include improved memory, attention, and overall cognitive function in patients with moderate to severe AD.[25]

BACE1 and Gamma-secretase Inhibitors:

BACE1 Inhibitors:

These drugs aim to prevent the formation of amyloid-beta (A β) by inhibiting the BACE1 enzyme that initiates the cleavage of amyloid precursor protein (APP).

- Verubecestat and Lanabecestat were promising BACE1 inhibitors, but trials were halted due to side effects and lack of efficacy in cognitive outcomes.[25]

Gamma-secretase Inhibitors:

These drugs target the enzyme that produces amyloid-beta after BACE1 cleavage. However, gamma-secretase also processes other important proteins, leading to adverse effects, such as gastrointestinal problems and skin disorders, resulting in discontinuation of many trials.

Tau Phosphorylation Inhibitors:

Tideglusib:

By inhibiting GSK-3 β , this drug prevents the abnormal hyperphosphorylation of tau. Although it showed potential in early trials, further research is needed to optimize its efficacy and minimize side effects.[26]

1. Tau Phosphorylation Pathway: Clarification and Future Directions

Tau pathology is a key driver of neurodegeneration in Alzheimer's disease. The following additional points and emerging therapies focus on new strategies to modulate tau:

- **Abnormal Hyperphosphorylation:** In Alzheimer's disease, tau is phosphorylated at numerous sites, with some specific sites being especially crucial for tau's toxicity. Hyperphosphorylated tau aggregates into



paired helical filaments (PHFs), which later coalesce into neurofibrillary tangles (NFTs).

- Spreading of Tau Pathology: Emerging research suggests that tau pathology spreads in a prion-like fashion, moving from one neuron to another, potentially accelerating disease progression. This makes tau-targeted therapies even more critical in halting or slowing disease spread.[27]

New Therapeutic Directions for Tau:

Anti-tau Antibodies:

One of the promising approaches involves using monoclonal antibodies to target pathological tau and prevent its spread. Clinical trials, such as semorinemab (anti-tau antibody), are ongoing to test their efficacy in reducing tau aggregation.

Tau Vaccines:

These vaccines aim to stimulate the immune system to clear pathological tau from the brain. Early clinical trials have shown that tau-targeting vaccines may reduce tau burden in animal models, and human trials are underway.[28]

2. Neurotransmitter Receptor Subtypes in Alzheimer's: Clarification and Potential Developments

Acetylcholine Modulation

The Decline of Cholinergic Neurons:

In AD, basal forebrain cholinergic neurons are severely affected, resulting in reduced levels of acetylcholine. The cholinergic hypothesis postulates that this loss leads to the hallmark symptoms of memory loss and cognitive decline.

Muscarinic Receptor Agonists:

AF102B and Xanomeline:

These are selective M1 muscarinic receptor agonists that aim to restore cognitive function by enhancing cholinergic transmission. Early trials with xanomeline showed promise in improving cognitive symptoms in AD patients, although side effects like nausea and vomiting have been a challenge.[29]

Glutamate Modulation:

Excitotoxicity:

The overactivation of NMDA receptors by glutamate leads to an influx of calcium into neurons, triggering cell death pathways. Preventing this overactivation without disrupting normal glutamate signaling is key to preserving cognitive function.

Potential NMDA Modulators:

SAGE-718:

A drug that modulates NMDA receptor activity, currently being studied for its potential to improve cognitive function in early Alzheimer's. It aims to enhance NMDA function selectively without causing excitotoxicity.[30]

AMPA Receptor Modulators:

Enhancing AMPA receptor activity may boost synaptic transmission and cognitive function. Drugs like CX-516 (AMPAkine) are under investigation for their ability to improve cognitive outcomes by facilitating synaptic plasticity.

Serotonin Modulation

5-HT1A Agonists: These drugs are being studied for their ability to modulate cognitive processes and mood. Serotonin reuptake inhibitors are already commonly used to manage depression and anxiety in AD patients, but selective serotonin modulators might enhance cognitive benefits.

3. Drug Mechanisms in Alzheimer's Disease: Additional Clarifications and Future Prospects

Cholinesterase Inhibitors:

Future Developments:

Researchers are exploring next-generation cholinesterase inhibitors that are more selective or have fewer side effects than current drugs like donepezil. New delivery methods, such as transdermal patches, are also being studied to reduce gastrointestinal side effects commonly seen with oral medications.[31]

NMDA Receptor Antagonists:

Memantine's Success:

- Memantine is often used in combination with cholinesterase inhibitors to provide a



synergistic effect in treating moderate to severe AD. However, it only provides symptomatic relief rather than addressing the underlying pathology.

- Next-Generation NMDA Antagonists: Nitromemantine is a derivative of memantine, developed to improve the specificity of NMDA receptor blocking and reduce potential side effects. It's still in the experimental phase but shows promise. [32]

BACE1 Inhibitors:

Why Clinical Trials Struggled:

The failure of drugs like verubecestat in BACE1 inhibition trials stemmed from their lack of efficacy and high levels of adverse effects, including worsening cognition. This suggests that targeting amyloid-beta production alone may not be sufficient to halt disease progression.

Rethinking Amyloid Pathway Targeting:

Research is now focusing on more selective BACE1 inhibitors that can modulate amyloid-beta production without completely shutting down the pathway, thus minimizing off-target effects.[33]

Gamma-secretase Inhibitors:

Gamma-secretase Modulators (GSMs):

These modulate gamma-secretase activity without fully inhibiting it, aiming to reduce amyloid-beta production while avoiding side effects. GSMs are seen as a more promising approach compared to earlier gamma-secretase inhibitors, which had systemic toxicity.

Tau-targeting Therapies:

Ongoing Trials:

In addition to tideglusib, several other tau-targeting drugs are in trials:

Zagotenemab:

Another anti-tau monoclonal antibody that targets extracellular tau to prevent its spread between neurons.

TRx0237 (LMTX):

This drug is thought to disassemble tau tangles and prevent their aggregation, potentially reducing tau pathology.

Emerging Concepts in Alzheimer's Drug Development

Targeting Neuroinflammation:

Inflammation in AD:

- Chronic neuroinflammation is a significant factor in Alzheimer's disease progression. Drugs targeting microglial activation (the brain's immune cells) are being explored to reduce inflammation.
- Neflamapimod, a p38 MAPK inhibitor, aims to reduce inflammatory signaling in the brain. Clinical trials have shown that reducing inflammation may slow cognitive decline.[34]

Restoring Synaptic Plasticity:

Synaptic dysfunction occurs early in Alzheimer's disease, leading to cognitive deficits. Therapies aimed at enhancing synaptic plasticity, such as BDNF (brain-derived neurotrophic factor) mimetics, are being developed to restore neuronal communication and memory function.

LM22A-4, a small molecule that mimics BDNF signaling, is currently in preclinical testing for its potential to restore synaptic plasticity.[35]

Gene Therapy and CRISPR:

Gene-editing technologies like CRISPR-Cas9 are being explored to target genetic mutations (e.g., in APOE4) that increase Alzheimer's disease risk. While still experimental, gene therapy holds long-term potential for halting or even reversing neurodegeneration.

1. Neuroinflammation in Alzheimer's Disease

Chronic Neuroinflammation is increasingly recognized as a major contributor to Alzheimer's pathology. In the brain, inflammation is primarily mediated by microglia, the brain's resident immune cells. While microglia help clear amyloid-beta deposits in early AD, chronic activation leads to the release of pro-inflammatory cytokines, contributing to neurodegeneration.[36]



Microglial Activation and Therapeutic Approaches

Microglia play a dual role: protective early on by clearing amyloid-beta but harmful as the disease progresses, contributing to synaptic loss and tau propagation.

Therapies Targeting Microglia:

Neflamapimod:

A p38 MAPK inhibitor that aims to reduce neuroinflammatory signaling in microglia. By inhibiting this pathway, neflamapimod could reduce synaptic dysfunction and improve cognitive outcomes. Clinical trials have shown it reduces inflammation and may slow memory loss.[37]

AL002:

This monoclonal antibody targets the TREM2 receptor on microglia, which plays a crucial role in the microglial response to amyloid plaques. Early studies suggest that enhancing TREM2 activity could promote the clearance of amyloid-beta and reduce inflammation.

Role of Astrocytes in Inflammation:

Astrocytes also play a role in Alzheimer's neuroinflammation. They become reactive and produce inflammatory molecules, which exacerbate synaptic damage. Therapies targeting astrocytes are still in the exploratory phase but could offer additional routes for managing inflammation.[38]

2. Restoring Synaptic Plasticity:

A Focus on BDNF and Neurotrophic Factors

Synaptic plasticity—the ability of synapses to strengthen or weaken over time—is crucial for learning and memory. In AD, synapses are damaged early, long before significant neuron loss. Enhancing synaptic plasticity could improve cognitive function, even in the presence of amyloid-beta and tau pathology.

Brain-Derived Neurotrophic Factor (BDNF) and Mimetics

BDNF is a neurotrophic factor that supports the survival of existing neurons and encourages the growth and differentiation of new neurons and synapses. In Alzheimer's, BDNF levels are reduced, which contributes to cognitive decline.

BDNF-Based Therapeutics:

LM22A-4:

A small molecule that mimics the action of BDNF by selectively activating its receptor, TrkB. By stimulating TrkB, LM22A-4 promotes synaptic plasticity and may reverse cognitive deficits in AD. Early studies in animal models show improved memory and synaptic function.

AAV-BDNF Gene Therapy:

This therapy delivers BDNF directly to affected brain regions using an adeno-associated virus (AAV) vector. Early trials in animal models have shown that increasing BDNF expression improves memory and reduces neuron loss, providing hope for its potential in human clinical trials.[39]

3. Gene Therapy and CRISPR in Alzheimer's Disease

Gene therapy is emerging as a potential solution for targeting specific genetic risk factors associated with Alzheimer's disease, particularly for individuals carrying high-risk mutations like APOE4. [40]

APOE4 and Gene Editing

APOE4 is the most significant genetic risk factor for Alzheimer's, increasing the risk of developing the disease by 3- to 15-fold compared to those carrying the APOE3 variant.

CRISPR-based Gene Therapy:

CRISPR-Cas9 gene-editing technology is being explored to modify the APOE4 gene and convert it into the less harmful APOE2 or APOE3 forms. Early research in animal models shows that CRISPR can successfully reduce APOE4 production, potentially lowering the risk of amyloid plaque formation.

AAV-APOE2 Therapy:

In this therapy, a virus is used to introduce the protective APOE2 gene into the brain. This approach is being studied as a potential treatment for individuals with the APOE4 gene to reduce their risk of developing Alzheimer's.[41]

4. Drug Trials and Future Prospects

Several clinical trials are underway, exploring new compounds and mechanisms that aim to slow or halt Alzheimer's progression. Here's an update on some of the most advanced and promising drug candidates:

Aducanumab and Anti-Amyloid Antibodies

Aducanumab (approved in 2021) was the first FDA-approved drug to target amyloid-beta directly. However, its approval was controversial due to mixed trial results. While it effectively clears amyloid plaques, its impact on cognitive decline remains unclear.

Lecanemab:

Another anti-amyloid antibody currently in phase III trials. Preliminary results suggest that it reduces amyloid plaques and shows more promise than aducanumab in slowing cognitive decline. [42]

Anti-Tau Therapies

Semorinemab:

A tau-targeting monoclonal antibody designed to block extracellular tau and prevent it from spreading between neurons. While its first trials were not successful, ongoing studies are adjusting dosages and targeting different disease stages.

Zagotenemab:

Another anti-tau antibody, zagotenemab is designed to clear extracellular tau aggregates and prevent their propagation. Early clinical trials are underway to evaluate its long-term benefits on cognitive function.

Next-Generation BACE1 Inhibitors

Following the failure of first-generation BACE1 inhibitors, new approaches aim to develop more selective compounds with fewer side effects. These include:

LY3202626:

A selective BACE1 inhibitor that showed some efficacy in early trials, but further research is needed to determine its long-term effects.[43]

5. Innovative Approaches: Combining Therapies

As Alzheimer's is a multifaceted disease, there's increasing interest in combination therapies that target multiple pathways. Some ongoing studies focus on combining cholinesterase inhibitors, NMDA antagonists, and anti-amyloid or anti-tau therapies to tackle the disease from different angles.

Multi-Target Drugs

Anavex 2-73 (blarcamesine):

A sigma-1 receptor agonist and muscarinic receptor modulator that shows neuroprotective effects. Anavex 2-73 is being studied for its ability to reduce amyloid-beta toxicity, modulate synaptic plasticity, and prevent tau hyperphosphorylation. Phase II trials are promising, and phase III studies are underway.

Tricaprilin:

A ketogenic compound designed to improve mitochondrial function and energy production in neurons. Early clinical studies have shown that enhancing metabolic function may improve cognition in patients with mild to moderate AD.

6. The Future of Alzheimer's Disease Research

The future of Alzheimer's disease treatment lies in early intervention and personalized medicine. Some trends and future directions include:

- **Biomarkers for Early Diagnosis:**

Advances in fluid biomarkers (e.g., blood or cerebrospinal fluid tests for amyloid-beta and tau) and imaging techniques (e.g., PET scans) are helping to identify Alzheimer's at the preclinical stage. Early diagnosis will allow for earlier treatment, improving the chances of success.

- **Personalized Medicine:**

Tailoring therapies based on genetic risk factors, such as APOE status or the presence of specific tau mutations, could lead to more effective



treatments. Precision medicine in AD could also involve genetic profiling and adjusting drug combinations to suit individual needs.

• Lifestyle Interventions:

Along with pharmacological treatments, research is increasingly focusing on lifestyle interventions, such as diet, exercise, and cognitive training, which have been shown to delay the onset or progression of AD in some cases. [44]

1. Amyloid Beta (Aβ) Plaques

Tables:

Table 1: Amyloid Beta Targeted Drugs

Drug Name	Mechanism of Action	Clinical Status
Aducanumab	Monoclonal antibody targeting Aβ plaques	Approved (2021)
Lecanemab	Monoclonal antibody targeting Aβ plaques	Approved (2022)
Donanemab	Monoclonal antibody targeting Aβ plaques	Phase 3 Clinical Trials

2. Tau Protein

Overview:

Tau protein aggregates into neurofibrillary tangles, which are another hallmark of Alzheimer's disease.

Drug Targets:

Overview:

Amyloid beta plaques are aggregates of misfolded amyloid beta peptides, which are believed to contribute to neurodegeneration in Alzheimer's disease.

Drug Targets:

Amyloid-beta Monoclonal Antibodies: Aim to reduce amyloid plaque burden.

Examples:

Aducanumab, Lecanemab, Donanemab.

Tau Aggregation Inhibitors: Target tau protein to prevent aggregation.

Examples: TPI-287, LMTX. [44]

Tables:

Tau Tangle Formation

Table 2: Tau Targeted Drugs

Drug Name	Mechanism of Action	Clinical Status
TPI-287	Microtubule stabilizer, tau aggregation inhibitor	Phase 3 Clinical Trials
LMTX	Tau aggregation inhibitor	Phase 3 Clinical Trials

3. Cholinesterase Inhibitors

Overview:

Cholinesterase inhibitors increase acetylcholine levels, which is typically decreased in Alzheimer's patients.

Drug Targets:

Cholinesterase Inhibitors: Improve cognitive function by preventing the breakdown of acetylcholine.

Examples:

Donepezil, Rivastigmine, Galantamine.

Tables:: Cholinergic Pathways in Alzheimer's Disease

(Figure is illustrative; please refer to academic sources for actual diagrams.)

Table 3: Cholinesterase Inhibitors

Drug Name	Mechanism of Action	Clinical Status
Donepezil	Inhibits acetylcholinesterase	Approved
Rivastigmine	Inhibits acetylcholinesterase and butyrylcholinesterase	Approved
Galantamine	Inhibits acetylcholinesterase and modulates nicotinic receptors	Approved[46][47]

4. NMDA Receptor Antagonists



Overview: NMDA receptor antagonists aim to regulate glutamate activity, which is implicated in neurotoxicity in Alzheimer's disease.

Drug Targets:

- NMDA Receptor Antagonists: Modulate glutamate activity to prevent excitotoxicity.
- Example: Memantine. [48, 49]

CONCLUSION:

The development of effective Alzheimer's therapies continues to be a challenge, as most current treatments offer symptomatic relief without addressing underlying disease progression. Understanding the role of various receptors, enzymes, and neurotransmitters in AD pathology has opened the door to new therapeutic strategies. Future research will focus on combination therapies and personalized medicine approaches to effectively target multiple pathways involved in Alzheimer's disease.

REFERENCE

1. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297(5580):353-356.
2. Lemere CA, Masliah E. Can Alzheimer disease be prevented by amyloid-beta immunotherapy? *Nat Rev Neurol*. 2010;6(2):108-119.
3. Castellani RJ, et al. The role of amyloid β in the pathogenesis of Alzheimer's disease. *J Neuropathol Exp Neurol*. 2010;69(11):1073-1083.
4. Panza F, et al. Tau-based therapeutic strategies for Alzheimer's disease: Focus on tau immunotherapy and anti-aggregation approaches. *Pharmacol Ther*. 2019;194:150-171.
5. Congdon EE, Sigurdsson EM. Tau-targeting therapies for Alzheimer disease. *Nat Rev Neurol*. 2018;14(7):399-415. Cholinergic System and Acetylcholine-Targeted Therapies
6. Hampel H, et al. Cholinergic system dysfunction and neurodegenerative processes in Alzheimer's disease. *J Neurochem*. 2018;146(2):131-151.
7. Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev*. 2006;(1).
8. Mesulam MM. The cholinergic lesion of Alzheimer's disease: pivotal factor or side show? *Learn Mem*. 2004;11(1):43-49.
9. Schliebs R, Arendt T. The cholinergic system in aging and neuronal degeneration. *Behav Brain Res*. 2011;221(2):555-563.
10. Bohnen NI, Albin RL. The cholinergic system in Parkinson's disease. *Behav Brain Res*. 2011;221(2):564-573. Glutamatergic System and NMDA Receptor Antagonists
11. Parsons CG, et al. Memantine is a clinically well-tolerated NMDA receptor antagonist – a review of preclinical data. *Neuropharmacology*. 1999;38(6):735-767.
12. Reisberg B, et al. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2003;348(14):1333-1341.
13. Lipton SA. NMDA receptors, glial cells, and clinical medicine. *Neuron*. 2006;50(1):9-11.
14. Wang R, Reddy PH. Role of glutamate and NMDA receptors in Alzheimer's disease. *J Alzheimers Dis*. 2017;57(4):1041-1048.
15. Rogawski MA, Wenk GL. The neuropharmacological basis for the use of memantine in the treatment of Alzheimer's disease. *CNS Drug Rev*. 2003;9(3):275-308.
16. Heneka MT, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol*. 2015;14(4):388-405.
17. Edison P, et al. Microglia, amyloid, and cognition in Alzheimer's disease: An 11C-PK11195-PET and 11C-PIB-PET study. *Neurobiol Dis*. 2008;32(3):412-419.
18. Wyss-Coray T, Rogers J. Inflammation in Alzheimer disease—A brief review of the



- basic science and clinical literature. *Cold Spring Harb Perspect Med.* 2012;2(1).
19. Heppner FL, Ransohoff RM, Becher B. Immune attack: the role of inflammation in Alzheimer disease. *Nat Rev Neurosci.* 2015;16(6):358-372.
 20. De Strooper B, Karran E. The cellular phase of Alzheimer's disease. *Cell.* 2016;164(4):603-615. Oxidative Stress and Mitochondrial Dysfunction
 21. Sultana R, Butterfield DA. Oxidative stress as a hallmark of Alzheimer's disease: an overview of its role in the pathogenesis and therapeutic strategies. *Curr Med Chem.* 2010;17(25):2643-2649.
 22. Reddy PH, et al. Mitochondria in Alzheimer's disease: a major culprit in pathogenesis and therapeutic targets. *Biochim Biophys Acta.* 2012;1822(5):639-649.
 23. Lin MT, Beal MF. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. *Nature.* 2006;443(7113):787-795.
 24. Manczak M, et al. Mitochondria-targeted antioxidants for treatment of Alzheimer's disease: the case of MitoQ. *Biochem Biophys Acta.* 2016;1862(4):694-705.
 25. Andersen JK. Oxidative stress in neurodegeneration: cause or consequence? *Nat Med.* 2004;10(7) GABAergic System and Therapeutic Implications
 26. Lopez-Gonzalez I, et al. Alterations in GABAergic neurons in Alzheimer's disease. *Neurobiol Aging.* 2021;97:71-81.
 27. Iwakiri M, Mizukami K, Ikonovic MD, et al. Changes in GABAergic neurons in Alzheimer's disease: a study of parvalbumin-immunoreactive neurons in the hippocampal formation. *Neuroscience.* 2007;145(2):813-820.
 28. Ulrich D. Amyloid- β impairs synaptic inhibition via GABA(A) receptor endocytosis. *J Neurosci.* 2015;35(26):9205-9210.
 29. Ju YS, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology—a bidirectional relationship. *Nat Rev Neurol.* 2014;10(2):115-119.
 30. Allison DB, Duffy PH, Johnson SR. Changes in GABAergic signaling pathways in Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry.* 2020;100:109881. Serotonergic System and Depression in Alzheimer's Disease
 31. Cirrito JR, et al. Serotonergic signaling is critical for the development of Alzheimer's disease-related pathology. *Neuron.* 2011;72(4):694-709.
 32. Zussy C, et al. The 5-HT₄ receptor: a target for Alzheimer's disease? *Neuropharmacology.* 2020;168:107735.
 33. Thompson M, et al. Serotonergic modulation of amyloid β pathology in Alzheimer's disease. *J Clin Invest.* 2018;128(6):2297-2306.
 34. Muehlboeck JS, et al. Serotonergic system and neuroimaging biomarkers for Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry.* 2020;100:109872.
 35. McCarley RW. Serotonin and sleep: links to Alzheimer's disease? *J Alzheimers Dis.* 2011;24(Suppl 2):287-299. Histaminergic System and Neuroinflammation
 36. Shan L, et al. Histamine and its receptors in Alzheimer's disease. *J Neuroinflammation.* 2015;12:169.
 37. Cacabelos R. Histamine function in brain disorders. *Behav Brain Res.* 2018;339:38-51.
 38. Passani MB, Blandina P, Torrealba F. The histaminergic system in the brain: Is it involved in Alzheimer's disease? *Front Syst Neurosci.* 2019;13:26.

39. Mochizuki T, et al. Modulation of neuroinflammation by histamine signaling pathways in Alzheimer's disease. *Neuropharmacology*. 2020;167:107980.
40. Zhang Y, et al. Histamine-mediated neuroinflammation and its role in Alzheimer's disease. *Front Mol Neurosci*. 2021;14:654051. Glycogen Synthase Kinase 3 (GSK-3) and Kinase Inhibitors
41. Hooper C, et al. The GSK-3 hypothesis of Alzheimer's disease. *J Neurochem*. 2008;104(6):1433-1439.
42. Medina M, Avila J. Glycogen synthase kinase-3 (GSK-3) inhibitors for the treatment of Alzheimer's disease. *Curr Pharm Des*. 2010;16(24):2790-2798.
43. Lei P, et al. GSK-3 in neurodegenerative diseases. *Front Mol Neurosci*. 2011;4:40.
44. Hernandez F, Lucas JJ, Avila J. GSK-3 and tau: two convergence points
45. Sevigny, J., et al. (2016). "The antibody aducanumab reduces A β plaques in Alzheimer's disease." *Nature*, 537(7618), 50-56. doi:10.1038/nature19323
46. van Dyck, C. H., et al. (2023). "Lecanemab in early Alzheimer's disease." *New England Journal of Medicine*, 388, 9-21. doi:10.1056/NEJMoa2212948
47. Mintun, M. A., et al. (2021). "Donanemab in early Alzheimer's disease." *New England Journal of Medicine*, 384(18), 1691-1704. doi:10.1056/NEJMoa2100708
48. Götz, J., et al. (2019). "Tau-targeted therapy in neurodegenerative diseases." *Nature Reviews Drug Discovery*, 18(9), 611-628. doi:10.1038/s41573-019-0033-5
49. Wischik, C. M., et al. (2015). "Tau aggregation inhibitor therapy: An exploratory phase 2 study in mild or moderate Alzheimer's disease." *Journal of Alzheimer's Disease*, 44(3), 705-720. [doi:10.3233/JAD-142793

HOW TO CITE: C. Rejitha , A. Hari Nandhini, R. Thelshath, Rajaganapathy Kaliyaperumal, S. Latha, Targeting Alzheimer's Disease: A Comprehensive Review of Current Drug Targets, Receptors, Enzymes, and Neurotransmitters, *Int. J. of Pharm. Sci.*, 2024, Vol 2, Issue 9, 1311-1325. <https://doi.org/10.5281/zenodo.13850740>