CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://zenodo.org/records/10778290

https://www.iajps.com/volumes/volume11-february-2024/24-issue-02-february-24/

Available online at: http://www.iajps.com *Review Article*

# NOVEL DRUG TARGETS IN TREATMENT OF ALZHEIMER DISEASE

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**Abstract:**
*Alzheimer disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss , and impaired daily functioning. With the aging population worldwide, the burden of AD has become a significant public health concern. Despite extensive research, there is currently no cure for AD, and available treatments offer only limited symptomatic relief . However, recent years have witnessed significant progress in the development of novel drugs targeting various aspects of AD pathogenesis. This abstract provides an overview of promising novel drugs that hold potential for the treatment od AD and highlights their mechanisms of action.*
*One class of novel drugs focuses on reducing the accumulation of amyloid beta(Aβ) plaques, a hallmark feature of AD pathology. Monoclonal antibodies, such as aducanumab and lecanemab, have shown promise in clinical trails by selectively targeting and clearing Aβ plaques from the brain. Another approach involves inhibiting beta-secretase enzymes, responsible for the production of Aβ peptides. Solanezumab is thought to act as '' amyloid beta sink'' that is facilitating flux of amyloid beta from a central to peripheral compartment. crenezumab is highly homologous to solanezumab another monoclonal antibody targeting amyloid - β peptides.*

***Keywords:*** *Progressive neurodegenerative disorder, cognitive decline, impaired daily functioning, symptomatic relief, amyloid beta(Aβ) plaques, monoclonal antibodies, lecanemab, Aβ Peptides, Amyloid beta sink.*

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*Please cite this article in press S.Kusuma Kumari et al.,* ***Novel Drug Targets In Treatment Of Alzheimer Disease****, Indo Am. J. P. Sci, 2024; 11 (02).*

## INTRODUCTION:

Alzheimer's disease (AD) is a progressive neuro degenerative disease medical and social problem impacting older people, both in industrialized and developing nations. For this condition, there are symptomatic drugs that can correct the neurotransmitter imbalance. Various drugs, like cholinesterase inhibitors, function to decrease the breakdown of acetylcholine and are used in the treatment of Alzheimer's and dementia symptoms. Alzheimer disease is referred to as "early-onset" (or "younger-onset") when it affects someone under the age of 65. The early-onset variant of Alzheimer's disease affects a relatively small percentage of people. When the illness strikes, many of them are in their forties and fifties.After their symptoms manifest, people survive for an average of eight years. However, the disease can advance quickly in certain patients and slowly in others.

## ETIOLOGY:

The exact etiology of Alzheimer disease is not known and associated with risk factors. But stated that there are several genetical and environmental factors have been explored as potential causes of the Alzheimer disease.

Others factors include:-

1. Advancing age
2. Family history
3. Trauma
4. Education
5. Vascular disease like stroke
6. Genetical etc.

## ALZHEIMERS DISEASE RISK FACTORS :-

Modifiable factors :-

1. Type 2 diabetes
2. Obesity
3. Cardiovascular diseases
4. Stroke
5. Depression

Non modifiable factors:-

1. Age
2. Sex
3. Race
4. Genetic mutations
5. Genetic polymorphism

## PATHOPHYSIOLOGY: -

The amyloid precursor protein is a transmembrane protein that can undergo a series of proteolytic cleavage by secretase enzymes. When it is cleaved by α-secretase in the middle of the β-amyloid domain (Aβ), it is not amyloidogenic. However, when APP is cleaved by β-and γ-secretase enzymes, neurotoxic Aβ peptides are released, which can accumulate into oligomer aggregate. Mutations in the APP gene tend to inhibit cleavage by α-secretase and consequently enable preferential cleavage by β-secretase. Mutations in the presenilin-1 and presenilin-2 genes (PSEN1 and PSEN2), which are components of the γ-secretase complex, increase cleavage by γ-secretase at this site. In both situations, the result is excess Aβ peptide production. The current Aβ hypothesis suggests that the soluble oligomers can impair synaptic function between neurons. Simultaneously, the oligomers may aggregate into insoluble β-sheet amyloid fibrils, which can trigger a local inflammatory response. 22 Over time, the subsequent oxidative stress and biochemical changes ultimately lead to neuronal death and the development of neuritic plaques typical of Alzheimer disease.

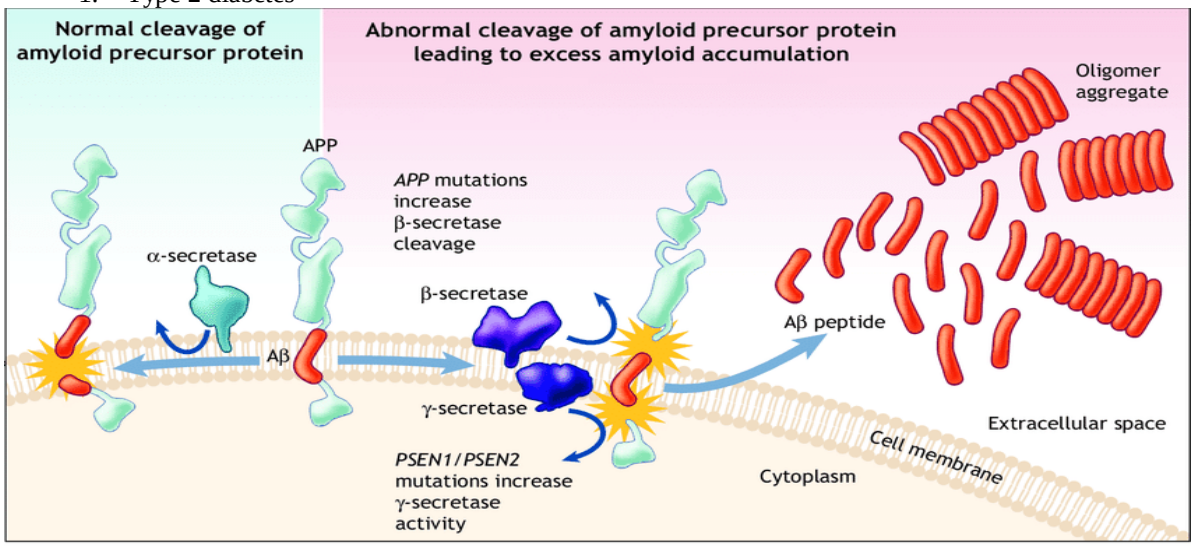


**Fig-1: Pathophysiology of Alzheimer's disease**

- Shortened attention span
- Problems coping with new situations

Changes in sleeping patterns, such as sleeping more during the day and being restless at night

**CLINICAL PRESENTATION: -**

**MILD STAGE SIGNS AND SYMPTOMS OF ALZHEIMERS DISEASE**

In mild Alzheimer's, a person may seem healthy but has more and more trouble making sense of the world around them. The realization that something is wrong often comes gradually to the person and their family. Problems can include:

- Memory loss that disrupts daily life
- Poor judgment, leading to bad decisions
- Loss of spontaneity and sense of initiative
- Losing track of dates or knowing current location
- Taking longer to complete normal daily tasks
- Repeating questions or forgetting recently learned information
- Trouble handling money and paying bills

**MODERATE STAGE SIGNS AND SYMPTOMS OF ALZHEIMER'S DISEASE**

In this stage, more intensive supervision and care become necessary. These changes and increasing needs can be difficult for many spouses and families. Symptoms may include:

- Increased confusion and memory loss, such as forgetting events or personal history
- Withdrawal from social activities
- Inability to learn new things
- Difficulty with language and problems with reading, writing, and working with numbers
- Difficulty organizing thoughts and thinking logically
- Difficulty carrying out familiar, multistep tasks, such as getting dressed
- Repetitive statements or movement, occasional muscle twitches

**SEVERE STAGE SIGNS AND SYMOTOMS OF ALZHEIMERS DISEASE:**

People with severe Alzheimer's cannot communicate and are completely dependent on others for their care. Near the end of life, the person may be in bed most or all of the time as their body shuts down. Symptoms often include:

- Inability to communicate
- No awareness of recent experiences or surroundings
- Weight loss with little interest in eating
- Seizures
- General physical decline, including dental, skin, and foot problems
- Difficulty swallowing

**STAGES OF ALZHEIMER DISEASE :-**

- STAGE-1 - Normal
- STAGE-2 - Normal age forgetfulness
- STAGE-3 - Mild cognitive impairment
- STAGE-4 - Mild Alzheimer
- STAGE-5 - Moderate Alzheimer disease
- STAGE-6 - Moderately severe Alzheimer disease
- STAGE-7 - Severe Alzheimer disease

**DIAGNOSIS:**

- **Psychiatric assessments.**
  - Mental status examination and neuro psychological assessments
  - laboratory tests
  - brain imaging
    - CT Scan
    - MRI
    - PET
    - SPECT
  - CSF Examination
  - Electro -encephalogram
  - Electromyogram

**PET SCAN**:- Of the brain of a person with Alzheimer disease showing a loss of function in the temporal lobe.

**MANAGEMENT AND TREATMENT FOR ALZHEIMER DISEASE:-**

There no cure for Alzheimer disease, but certain medications can temporarily slow the worsening of dementia symptoms. Medications and other interventions can also help with behavioral symptoms. The food and drug administration has approved two types of drugs to treat the symptoms of Alzheimer disease:-

- Cholinesterase inhibitors
- NMDA antagonists

**Cholinesterase inhibitors: -**

The following cholinesterase inhibitors can help treat the symptoms of mild to moderate Alzheimer disease

- **Donepezil:**

This is also FDA approved to treat moderate to severe Alzheimer disease

**Dosage:** Starting dose :5 mg qd

Maintaince dose:5-10mg qd

Time between dose adjustment:4- 6 weeks

- **Rivastigmine**

**Dosage :** Starting dose: 1.5mg bid
Maintaince dose: 3-6 mg bid
Time between dose adjustment: 2 weeks

- **Galantamine**

**Dosage:** Starting dose: 4 mg bid
Maintance dose: 8-16mg bid
Time between dose adjustment: 4 weeks

These drugs work by blocking the action of acetyl cholinesterase, the enzyme responsible for destroying acetylcholine. Acetylcholine is one of the chemicals that help nerve cells communicate. Researchers believe that reduced levels of acetylcholine cause some of the symptoms of Alzheimer disease.

**ADVERSE DRUG REACTIONS:**

- Nausea
- Diarrhea
- Vomiting
- Decreased appetite
- Dyspepsia
- Anorexia
- Asthenia( lack of energy).

**NMDA antagonists:-**

Memantine is Food and drug administration approved for treating moderate to severe Alzheimer disease. It helps keep certain brain cells healthier.
Studies have shown that people with Alzheimer who take memantine perform better in common activities of daily living such as eating, walking, toileting, bathing, and dressing.
Certain medications may help in some people, including:-

- Antidepressants:-These drugs can treat anxiety, restlessness, aggression and depression.
- Anti- anxiety drugs:- these medications can treat agitation.
- Anticonvulsant drugs:- these medications can sometimes treat aggression
- Antipsychotics (neuroleptics):-these drugs can treat paranoia, hallucinations and agitation.

**NOVEL DRUGS APPROVED FOR THE TREATMENT OF ALZHEIMER DISAESE IN THE YEAR 2023 :-**

**LEQEMBI :-**

LEQEMBI is used for Alzheimer disease to show disease progression in patients who are in stage of mild cognitive impairment and also develop of amyloid beta plaques in brain.

LEQEMBI helps control of Alzheimer disease but does not cure it.

**LEQEMBI class:-** monoclonal antibodies.
**LEQEMBI approved date:-** 6 January 2023.
**Indication:-** Mild cognitive impairment.

**MECHANISM OF ACTION**:-

LEQEMBI is an anti amyloid beta protofibril antibody and has been shown to reduce brain amyloid and mostly slow cognitive decline in adult patients.
It is thought to slow down the progression of Alzheimer by neutralizing and eliminating the toxic amyloid beta aggregates found in brain.

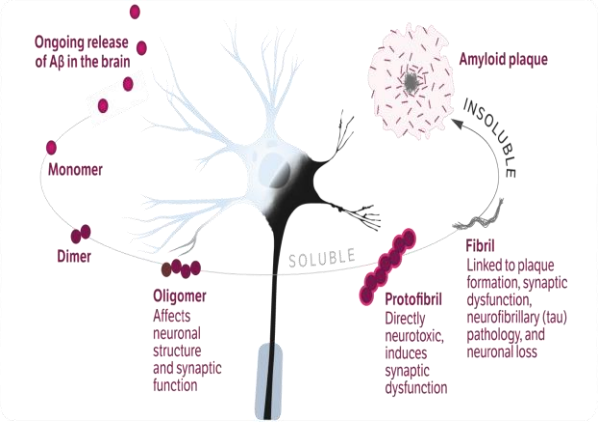


**Fig-2 : Mechanism of action of Leqembi**

**DOSING INFORMATION:-**

Usually LEQEMBI adult dose for Alzheimer disease:- 100mg/kg which must be diluted and administer as intravenous infusion.
One hour once every two weeks.

**LEQEMBI available as:-**

- Injection 500mg /5ml in a single dose unit.
- Injection 200mg/2ml in a single dose vial.

**METABOLISM: -**

Degraded by proteolytic enzymes.
**Half life :-**
The terminal half life is 5 to 7 days.

**PHARMACODYNAMICS**: -

LEQEMBI reduces amyloid beta plaques in a dose and time dependent manner.
In clinical trails , LEQEMBI also reduced plasma p-tau 181.

**WHO CAN USE LEQEMBI:-**

- Mild cognitive impairment
- Presence of amyloid beta pathology.

**LEQEMBI side effects:-**

- ❖ Headache
- ❖ Infusion related reactions
- ❖ Swelling in areas of brain

**LEQEMBI can cause serious side effects .**

Amyloid related imaging abnormalities or ARIA.

The doctor may perform MRI of your brain before and during your treatment with LEQEMBI . Ask doctor about your risk. If you have symptoms like dizziness, headache, difficulty walking, nausea, seizers immediately call health care provider.

**Before receiving LEQEMBI:-**

**PREGNANCY :-**

Tell your health care provider if your pregnant, or plan to become pregnant. It is not known if LEQEMBI will harm your unborn baby.

**BREASTFEEDING** :-

If you are breastfeeding. It is not known LEQEMBI passes into your breast milk. Discuss with your health provider best way to feed your body while receiving medicine.

**HOW WILL LEQEMBI IS RECEIVED**:-

- ➢ LEQEMBI is a solution that is given through a needle placed in a vein in your arm.
- ➢ You usually have an infusion every 2 weeks with each infusion lasting about 1 hour.
- ➢ This medicine may cause a severe reaction while having the infusion oe slowly after infusion.

**Uses:-**

Used to treat Alzheimer disease.

**Interactions** :-

Drug interactions may change how your medications work or increase your risk for serious side effects .Do not start, stop or change dosage of any medicines without your doctors approval.

**Overdose**:-

Overdosed and has serious symptoms such as passing out or trouble breathing.

**Storage**:-

- This medication given in hospital or clinic and will not be stored at home .
- Do not freeze or shake.
- Store in refrigerator at 2’ c to 8’c.

**METFORMIN**

METFORMIN treatment was shown to inhibit neuronal loss, the direct cause of cognitive deficits in Alzheimer disease by promoting neurogenesis and inhibiting pathological neuronal apoptosis in hippocampus of amyloid precursor.

**Study of metformin:-**

This study will test the effects of metformin an Food and drug administration approved medication an other indicators of Alzheimer disease and have mild cognitive impairment but do not have diabetes.

Qualify to participate in this study:-

**Minimum age** :- 55 years

**Maximum age** :- 90 years.

**MUST HAVE**:-

- ➢ No known history of diabetes
- ➢ vision and hearing sufficient to complete test procedures
- ➢ Diagnosis of amnestic Mild cognitive impairment.

**MUST NOT HAVE :-**

- ➢ Current use of metformin
- ➢ history of intolerance to metformin
- ➢ body mass index <20
- ➢ alcohol or substance abuse within past 6 months
- ➢ uncontrolled high blood pressure
- ➢ known history of diabetes

**THE INVESTIGATION DRUGS FOR ALZEIMERS DISEASE IN THE YEAR 2023:-**

**AMYLOID-β PROTEIN TARGETING AGENTS:**

**Amyloid β directed MAbs:**

MAbs are the principle immunotherapies for Alzheimers disease in clinical trails and the most common approach to targeting Aβ in the Alzheimers disease drug development pipeline.the table 1 summarizes the 11Aβ directed MAbs being assessed.

- ✓ In phase 1, phase2, phase3 clinical trails. Aducanumab had a promising phase 1b trail , after which 2 phase 3 trails were begun but terminated after futility analysis suggested no benefit of treatment.
- ✓ Longer term observations and accrual of additional data , however , indicated 1 of the trails met the primary objective , and the second showed a response among those treated with higher doses for longer periods of time , suggesting that the therapeutic response is time and dependent.

| TABLE 1. AMYLOID-β MONOCLONAL ANTIBODIES IN CLINICAL TRIALS FOR ALZHEIMER DISEASE | | | | |
|---|---|---|---|---|
| **Drug** | **Sponsor** | **Phase** | **Target** | **Population** |
| Aducanumab | Biogen | 3 | Plaque and oligomeric Aβ | Early AD |
| Gantenerumab | Roche | 3 | Plaque and oligomeric Aβ | Early AD |
| Lecanemab (BAN2401) | Eisai | 3 | Protofibrils and plaque Aβ | Early AD |
| Solanezumab | Lilly | 3 | Aβ monomers | Preclinical AD |
| Crenezumab | Genentech | 3 | Monomeric and oligomeric Aβ | Preclinical autosomal dominant AD |
| Donanemab | Lilly | 2 | Pyroglutamated plaque Aβ | Early AD (MMSE score 20-28) |
| RO7126209 | Roche | 2 | Plaque and oligomeric Aβ | Mild-to-moderate AD |
| BIIB092 | Biogen | 2 | Aβ (species undisclosed) | Early AD |
| LY3372993 | Lilly | 1 | Aβ (species undisclosed) | MCI due to AD and mild-moderate AD |
| Abbreviations: Aβ, amyloid β; AD, Alzheimer disease; MCI, mild cognitive impairment, MMSE, Mini-Mental State Examination. | | | | |

**Table-1: amyloid-β monoclonal antibodies in clinical trails for Alzheimer disease**

- ✓ These agents will make unprecedented demands on health care systems for safe delivery of treatment.
- ✓ Ensuring available appropriate treatment will require collaboration among multiple stakeholders including pharmaceutical companies , clinicians, health care system leaders , advocacy groups , patients and care partners and policy makers.

**Amyloid directed small molecules:**

- ✓ Tramiprosate is a pro drug for homotaurine , a modified amino acid previously tested in clinical trails.
- ✓ The prodrug formulation has a longer half-life and less variability in blood levels than seen with the parent compound.
- ✓ ALZ-801 and its metabolites inhibit formation of toxic Aβ oligomers.

**TAU PROTEIN TARGETING AGENTS:**

**Tau directed MAbs:**

- ✓ NFTs compossed of hyperphosphorylated tau are another pathologic hallmark of alzheimers disease and tau is a target for MAb therapies.
- ✓ Table 2 shows 7 tau targeted MAbs in clinical trails. Tau is thought to spread from neuron to neuron in established brain networks and some MAbs target extracellular tau as it passes between neurons.
- ✓ Other MAbs are directed at intracellular tau targets requiring that they penetrate both the blood brain barrier and cell membranes.

| TABLE 2. TAU MONOCLONAL ANTIBODIES IN CLINICAL TRIALS FOR ALZHEIMER DEMENTIA | | | | |
|---|---|---|---|---|
| **Drug** | **Sponsor** | **Phase** | **Target** | **Population** |
| Tilavonemab (ABBV-8E12) | AbbVie | 2 | Aggregated extracellular tau | MCI or mild AD dementia |
| ACI-35 | Janssen | 2 | Phosphorylated tau | Undisclosed |
| IONIS-MAPTRx (BIIB080) | Biogen; Ionis | 2 | Tau RNA to inhibit translation of tau protein | Mild AD |
| JNJ-63733657 | Janssen | 2 | Tau microtubule binding region | Early AD |
| Semorinemab (RO7105705) | Roche | 2 | Extracellular tau | Moderate AD |
| Zagotenemab (LY3303560) | Lilly | 2 | Soluble tau aggregates | 6-month gradual memory decline |
| LuAF7908 | Lundbeck | 1 | Hyperphosphorylated tau aggregates | AD dementia |
| Abbreviations: AD, Alzheimer disease; MCI, mild cognitive impairment. | | | | |

**Table-2: Tau monoclonal antibodies in clinical trails for Alzheimer disease**

Tau abnormalitiies correlate more strongly with cognition than Aβ suggesting successful therapy directed at tau may interrupt cognitive decline.

- ✓ Low tau levels might be required for trails attempting prevention of cognitive decline in individuals with pre clinical alzheimers disease.
- ✓ Whereas higher levels of tau might be required for trails that the target disease progression in people who are mildly symptomatic.

**Tau directed small molecules:**

- ✓ PU-Alzheimers disease has effects on multiple proteins characteristic of neuro degenerate disorders, it is an epichaperome inhibitor of heat shock proteins that promote neuro degeneration in animal models.
- ✓ PU-Alzheimers disease has effects in animal models of alzheimer disease , parkinson disease, amyotropic lateral sclerosis, frontotemporal dementia and huntington disease.
- ✓ PU-Alzheimers disease has been through phase 1 ascending dose studies; a phase 2 trail involving participants with alzheimer disease is anticipated.

**ADUCANUMAB:**

Aducanumab sold under the brand name aduhelm is a medication designed to treat alzheimers disease .

It is a monoclonal antibody. That targets aggregated forms of amyloid beta (Aβ) found in the brains of people with alzheimers disease to reduce its buildup.

**Type -** whole antibody
**Source -**human
**Target-** amyloid beta
**Route of administration -** intravenous
**Mechanism of action:**

APP is cleaved by β-secretase and γ-secretase to form Aβ42 monomers, oligomers, and eventually senile plaques ; these are targets for clearance by aducanumab resulting in reduced amyloid burden.

**GANTENERUMAB:**

Gantenerumab is a monoclonal antibody for the treatment of alzheimers disease.

**Type-** whole antibody
**Source-** human
**Target-** beta - amyloid

**MECHANISM OF ACTION:**

The mechanism of action of gantenerumab is though glial recruitment and phagocytosis of the plaque resulting in its final burden into the brain. In pre clinical studies carried onto the transgenic mice, the results demonstrated the binding of MAb to the cerebral Aβ and significant reduction in the cerebral plaques.

**SOLANEZUMAB:**

Solanezumab is a monoclonal antibody being investigated by Eli lilly as a neuroprotector for patients with alzheimers disease .

**Type -** whole antibody
**Source-**humanized
**Target-**beta amyloid

**MECHANISM OF ACTION:**

Solanezumab is thought to act as ‘’ amyloid beta sink’’ that is facilitating flux of amyloid beta from a central to peripheral compartment.

This increases the peripheral elimination of both amyloid beta and the antibody. Amyloid beta plaques mostly consist of amyloid beta 42.

**CRENEZUMAB:**

Crenezumab is a fully humanized monoclonal antibody against human 1-40 and 1-42 beta amyloid which is being investigated as a treatment of alzheimers disease . crenezumab is highly homologous to solanezumab another monoclonal antibody targeting amyloid - β peptides.

**Type-** whole antibody
**Source-** humanized
**Target-**1- 40 β amyliod

It was engineered to clear excess Aβ while exerting reduced subsequent effector function on microglia; the rationale is to stimulate amyloid phagocytosis while limiting release of inflammatory cytokines as a way to avoid side effects such as vasogenic edema.

**TAU MONOCLONAL ANTIBODIES IN CLINICAL TRAILS FOR ALZHEIMERS DISEASE:**

**TILAVONEMAB:**

Tilavonemab is an immunoglobulin G4 (IgG4) monoclonal antibody that binds to the N- terminates of human tau and targets soluble extracellular tau in the brain.

- ❖ This mechanism may block extracellular tau from propagating between cells and decrease the spread of tau pathology in brains with tauopathies.

**Therapy type-** immunotherapy
**Target type-**tau
**Condition-**progression supranuclear palsy, alzheimers disease.

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