New therapeutic strategy for Alzheimer's disease

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AD background

AD is a neurodegenerative disease characterized clinically by progressive cognitive decline, memory impairment, emotional disturbance, language dysfunction and an inability to perform daily life tasks as usual.

it is commonly classified into two categories:

early onset AD (EOAD) and late onset AD (LOAD),

EOAD :both familial and sporadic

onset before 65 years of age,

<5% of the entire AD population.

autosomal dominant genetic defects

LOAD is more predominant :

- approximately 90–95% of the total AD.
- typically after the age of 65
- 50–70% of all dementia cases
- is the sixth-leading cause of death in the United States
- It is predicted that 70 to 80 million people would suffer from Alzheimer’s disease-related dementia by 2030,

- The incidence of AD was expected to double every five years after the passing of 65 years,
- with each year an estimation of 1275 affected individuals per 100,000
- giving rise to 30–50% of AD patients by the age of 86

The pathogenesis of AD:

- accumulation of Aβ oligomers,
- Aβ plaques in the extracellular region of brain cells,
- an alteration in synaptic function,
- loss of synapse,
- change in the function of neurotransmitters,
- alteration in proinflammatory or inflammatory responses,
- An hallmark of AD is hyperphosphorylated tau protein
- and neuronal death

Additionally:

- oxidative stress
- mitochondrial dysfunction
- excessive reactive oxygen species production
- lipid peroxidation
- proteasomal dysfunction
- microglial activation

Modifiable risk factor

- Dementia and AD are multifactorial and heterogenous disorders affected by genetic and environmental factors, many of which are potentially modifiable. such as:
- vascular diseases
- Type 2 Diabetes
- traumatic brain injury
- epilepsy
- depression

vascular disease:

- **mechanism** are still not fully understood but cerebral perfusion.

- hypertension, atrial fibrillation, atherosclerosis induce increased level of Aβ due to lack of brain blood perfusion/oxygenation

- cerebral amyloid angiopathy, a condition where Aβ accumulates causes hemorrhages, ischemic lesions and encephalopathies.

Type 2 Diabetes

- There is a strong epidemiological link to AD with >65% risk of dementia development compared to non-diabetic patients .
- **Most common theory** is due to diabetic vascular disease leading to lowered cerebral circulation
- There are also reports of chronic hyperglycemia, prolonged hypoglycemic episodes and altered amyloid metabolism which may contribute to AD

Traumatic brain injury

- Traumatic brain injury is a condition where sudden damage occurs to the brain region resulting in mild concussion to severe permanent damage.
- 24% increased risk of AD seen in individuals with history of traumatic brain injury

Epilepsy

- Epilepsy has also been linked to AD as it usually results in cognitive and neuropathological changes and in severe cases, brain atrophy

- . Multiple studies observed the increased risk for AD in epilepsy patients and is theorized that a parallel link between onset age of seizure correlates with severity of AD .

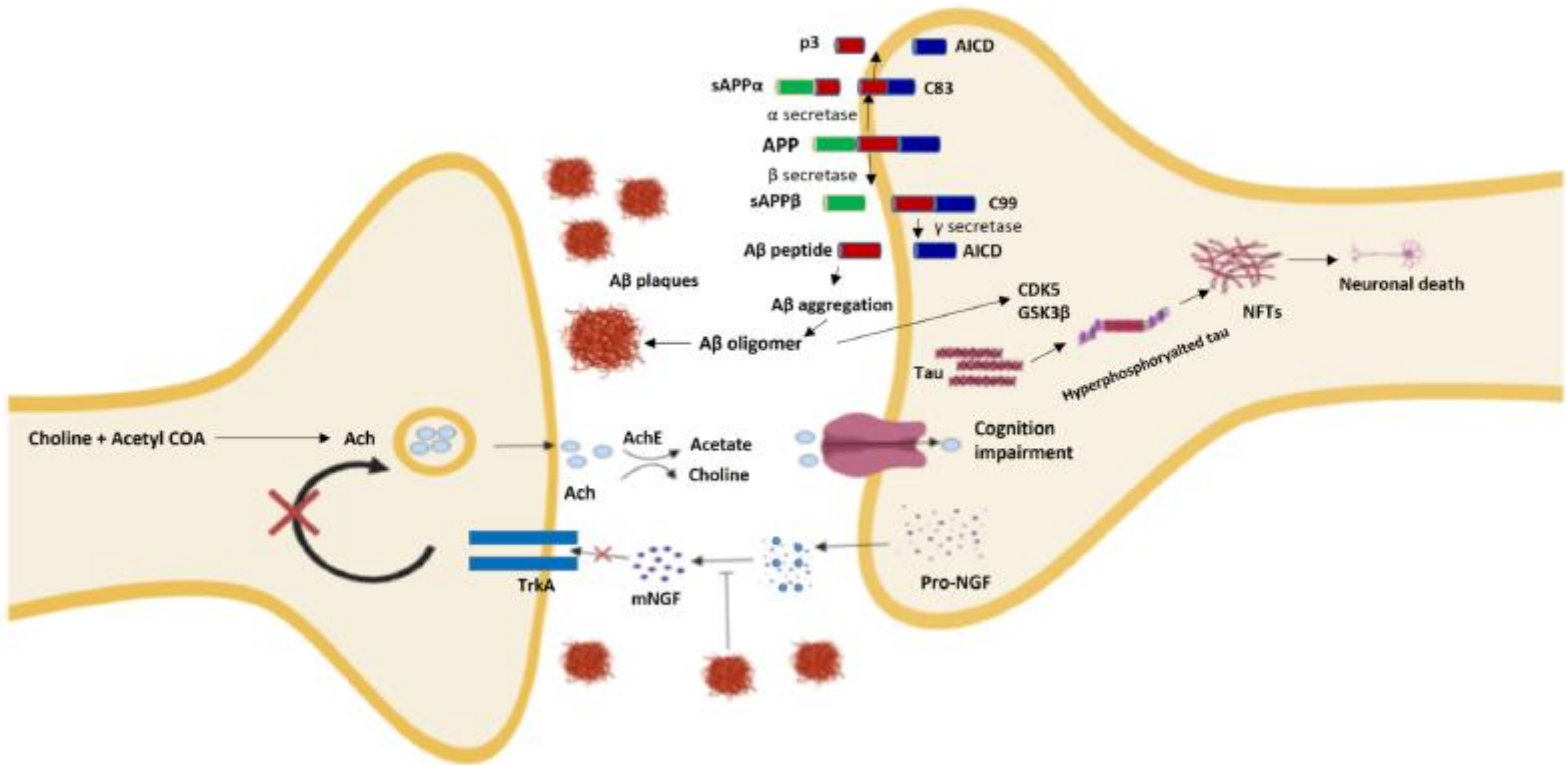
Depression

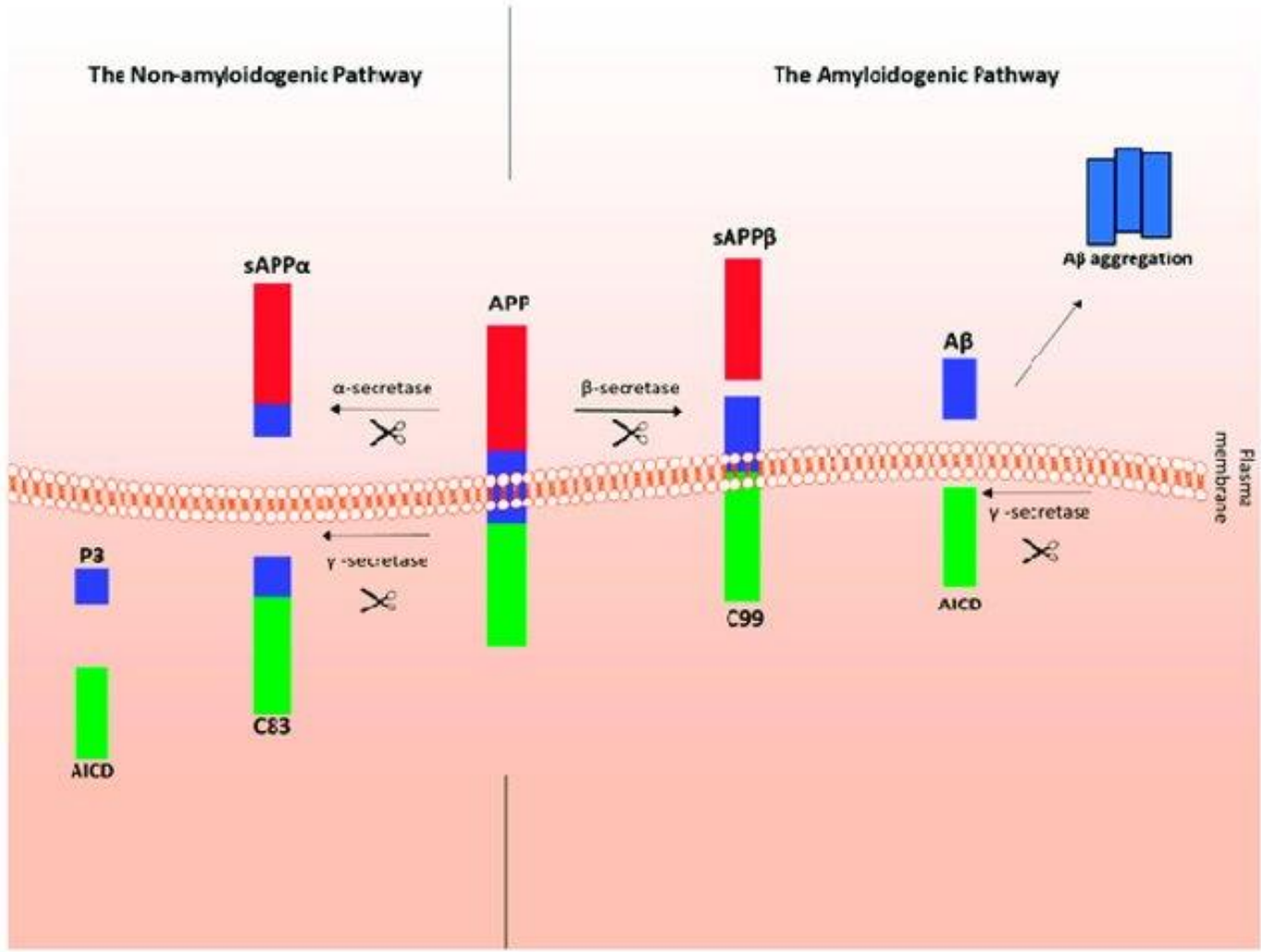
- a recent study reports that patients with major depression showed an increase of Aβ deposition, enhanced formation of amyloid plaques and elevated cortisol level similar to AD patients.
- Currently, there is no study done to prove that managing depression *via* antidepressants can be a preventive therapy for AD

lifestyle interventions

- physical activity,
- diet,
- smoking
- alcohol consumption.
- The causal link between lifestyle interventions and AD are not yet fully understood but generally it involves neurotoxic, inflammatory, vascular, oxidative stress, and psychosocial processes.

- Physical activity are recommended as it helps to lower stress, metabolic and vascular risk, aide in amyloid clearance, increase brain volume and neurotrophic factor.
- Dietary factors maintaining vascular health, lowering inflammation, relief oxidative stress, upregulate neurotrophic factor and also aids in neuronal membrane maintenance.
- Evidence suggest Mediterranean diet may help reduce risk of dementia


p3
AICD
sAPPα
C83
α secretase
APP
β secretase
sAPPβ
C99
γ secretase
Aβ peptide
AICD
Aβ plaques
Aβ aggregation
CDK5
GSK3β
Aβ oligomer
Tau
Hyperphosphorylated tau
NFTs
Neuronal death
Choline + Acetyl COA
Ach
AchE
Acetate
Choline
Ach
Cognition
impairment
TrkA
mNGF
Pro-NGF


The Non-amyloidogenic Pathway
The Amyloidogenic Pathway
sAPPα
APP
sAPPβ
Aβ aggregation
Aβ
α-secretase
β-secretase
Plasma membrane
γ -secretase
γ -secretase
P3
C83
C99
AICD
AICD

Strategies to prevent Alzheimer's disease progression

- Amyloid precursor protein (APP) is an important player in neural development and neurogenesis.
- In the non-amyloidogenic pathway, APP is cleaved by α-secretase and forms C-terminal 83-residue (C83) fragments which are further processed by γ-secretase into soluble amyloid precursor protein intracellular domain 50 (AICD50).
- In the pathological amyloidogenic pathway, β-secretase cleave transmembrane APP to fragment C-terminal 99 residues (C99)
- γ-secretase, further cleave C99 fragments into the intracellular AICD peptide and extracellular Aβ peptides with 37 to 42 amino acids.
- Aβ42, prominently, has been reported to oligomerize and further the formation of Aβ plaques

- Recent research suggests that soluble oligomeric prefibrillar forms of Aβ may represent the neurotoxic entity and cause synaptic dysfunction rather than highly aggregated Aβ species.

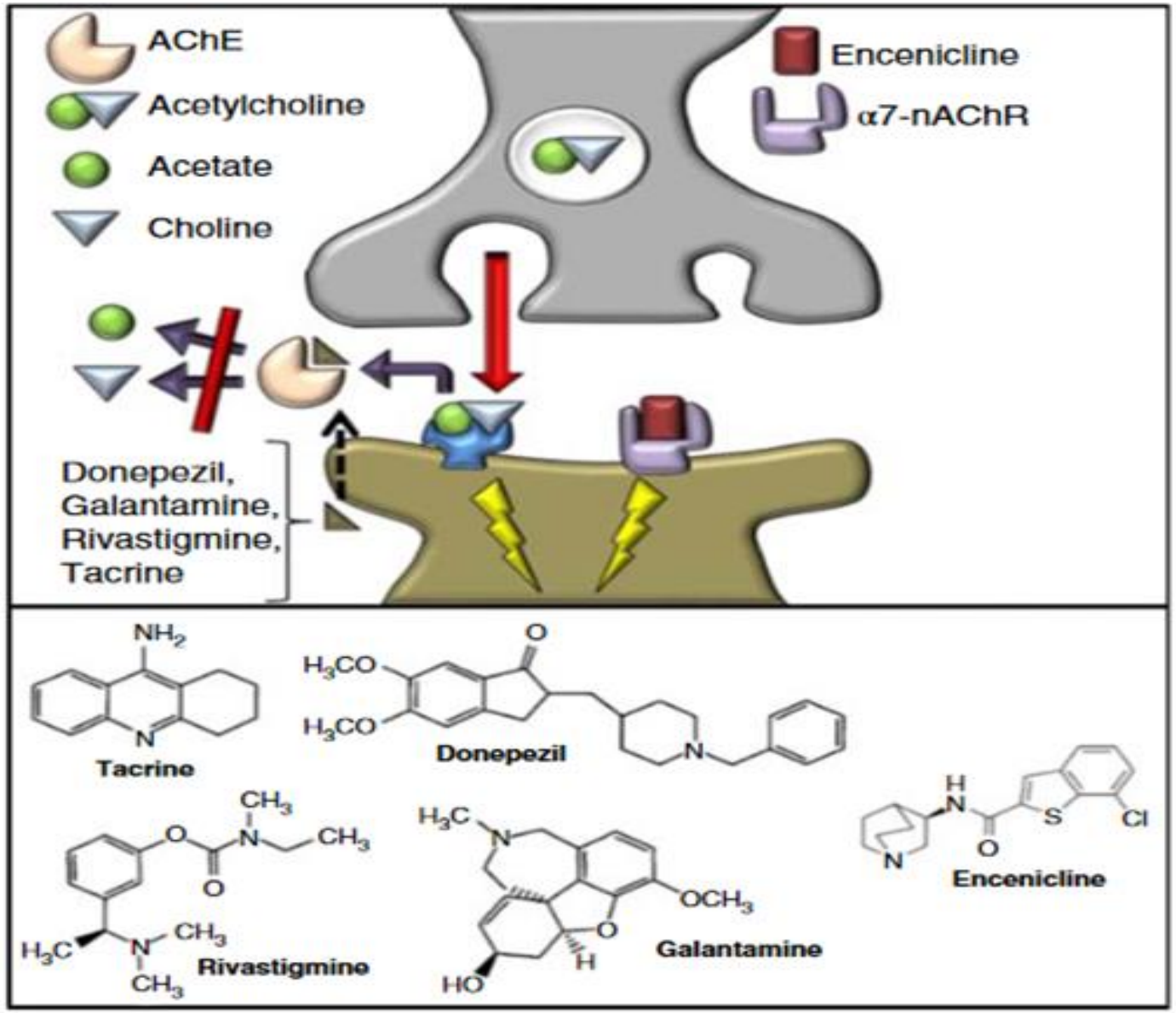
- These peptides are deposited as Aβ plaques outside the neuron. Moreover, the imbalance between production and clearance of Aβ peptides has also been reported to deposition of extracellular Aβ plaques.
- Therefore, either overproduction or impaired clearance of Aβ or a combination of both processes play a central role in AD pathology

- Moreover, the influences of Aβ-related peptides on the function and survival of central cholinergic neurons have also been demonstrated

- Excessive Aβ plaques have been exhibited to hamper cholinergic innervation to the cortex and hippocampal regions of the brain and leading to impaired cognition

Current and Prospective Treatments for Alzheimer’s Disease

Current Medical Treatments


AChE
Acetylcholine
Acetate
Choline
Encenicline
α7-nAChR
Donepezil,
Galantamine,
Rivastigmine,
Tacrine
Tacrine
Donepezil
Rivastigmine
Galantamine
Encenicline

Currently marketed drugs for AD

- Rivastigmine, donepezil, and galantamine belong to the AChEI group
- memantine is an NMDAR antagonist

Donepezil (Aricept)

is an inhibitor of acetylcholinesterase
In the cholinergic synapses, acetylcholinesterase degrades the neurotransmitter acetylcholine after its release from the presynapses into the synaptic space. By inhibiting its degradation, donepezil increases the availability of the neurotransmitter, enhancing cholinergic transmission. Although this drug does not affect the underlying causes of AD, it does delay cognitive impairment in patients affected by the disease.
The most common side effects involve the gastrointestinal system including diarrhoea, nausea, and vomiting, in addition to dizziness, fatigue, and urinary incontinence. These relatively common effects usually occur at the beginning of treatment.

- In mild to moderate AD , 5 and 10 mg/day of donepezil improve cognition
- A study of hippocampal volume in 67 mild-to-moderate AD patients indicated that 5 and 10 mg/day of donepezil slowed the reduction of the hippocampal volume
- donepezil increases blood flow in the frontal lobe, and reduces hippocampal atrophy

- Most recently, several studies have reported improved cognitive function in AD patients with high doses of donepezil (23mg/day) versus the more commonly used dose (10mg/day), although the most recent report showed no difference
- Although donepezil has not been approved for the treatment of mild cognitive impairment (MCI), which is considered to be a common

precursor to AD, it has been reported that donepezil delays the progression to AD by about one year

Galantamine (Razadyne, Reminyl)

- It influences the cholinergic system in two ways: it is both:
- 1- a potent activator of the muscarinic and nicotinic receptors
- 2- a weak inhibitor of acetylcholinesterase
- galantamine improves cognitive functions and reduces amyloid plaque levels in the brain

- major side effects: are gastrointestinal, and include nausea, diarrhoea, vomiting, along with dizziness and agitation; however, these side effects tend to disappear with time.
- doses ranging from 16 to 32mg/day, showed improved cognition and attention in mild AD
- In patients with severe AD, the treatment has been found to have

beneficial effects

- treatment stabilised cognition and improved regional cerebral blood flow
- the treatment failed to display positive effects in MCI patients

Rivastigmine (Exelon)

- it is used for the treatment of mild to severe AD. While it was first developed in capsules, it is also currently available in transdermal patches which provide additional benefits and release the medicament over a 24-hour period.
- side effects: mostly affect the gastrointestinal system and include nausea, vomiting, diarrhoea, agitation, depression, and fatigue.
- these side effects are more prominent at the beginning of the treatment and tend to disappear over time

- It has recently been found that
- co-treatment of rivastigmine with citicoline improves cognitive functions,
- but co-treatment with memantine does not show any additional benefits over rivastigmine treatment alone
- In addition, rivastigmine nasal spray (which results in higher bioavailability) and rivastigmine-hybrid drugs are also being investigated

- In addition, rivastigmine also inhibits butyrylcholinesterase, another enzyme which can break down acetylcholine.
- For a subgroup of patients who have the specific butyrylcholinesterase K-genotype, who show a slower rate of cognitive decline compared to patients without the K-genotype, it has been found that the genotype influences the efficiency of the treatment.
- several studies show the dual inhibition of both cholinesterases maximises benefits,

- Ladostigil:
- is a compound that combines the cholinesterase inhibitory activity (from rivastigmine) and monoamine oxidase inhibitory activity
- modulating the processing of amyloid precursor protein
- is currently being tested in a Phase II clinical trial

- **Memogain:**
- is the inactive form of galantamine.
- is produced as a nasal spray
- more efficiently than equivalent doses of galantamine, with fewer side effects

Tacrine (Cognex)

- due to liver toxicity this treatment was discontinued
- non-toxic form of tacrine, named hupertacrine
- affects the cholinergic system, specifically it is an agonist of the α-7-nicotinic acetylcholine receptor (α7-nAChR).
- Phase I/II clinical trials have indicated that doses of up to 2 mg, in conjunction with either rivastigmine or donepezil, improve verbal and language fluency and attention without evident side effects
- the development of the drug was halted during Phase III clinical trials, due to severe gastrointestinal side effects

Memantine (Ebixa)

- is the only approved drug for AD that does not affect the cholinergic system, and instead is an antagonist of the NMDA glutamate receptors in the brain
- Its main action is to block the Ca2+ influx by binding to the NMDA receptors
- This reduces the release of glutamate in the synaptic regions, thus lowering the toxicity associated with high glutamate levels.
- memantine is able to improve cognition, and reduce amyloid plaque numbers and AD-like pathology, either alone or in combination with acetylcholinesterase inhibitors

- Side effects : headache, confusion, sleepiness, dizziness, and high blood pressure.
- memantine treatment improves cognitive behaviour, and reduces some other neurological symptoms associated with the disease, such as delusion, aggression, hallucinations, and irritability
- some studies have found that memantine increases the improvement in cognitive behaviour when compared to acetylcholinesterase inhibitor treatments on their own

Treatments in Advanced Clinical Trials

- Prazosin: is currently used for the treatment of hypertension, post-traumatic stress disorder, and panic disorder
- prazosin may be of value in the treatment of aggressive behaviour in AD patients
- prazosin at 6 mg/day for eight weeks improved the behavioural symptoms of AD patients who displayed agitation/aggression

AVP-923 (Nuedexta, Zenvia chemical name: ***dextromethorphan***

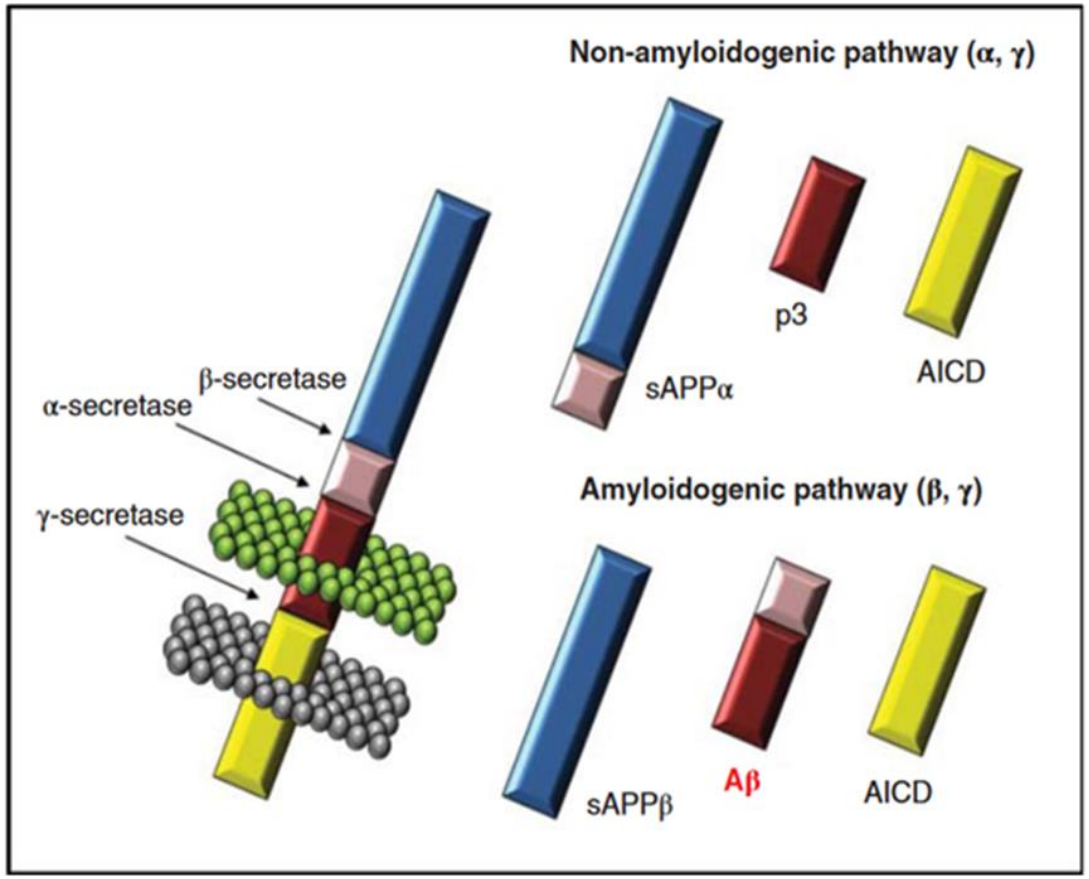
- weak antagonist of NMDA receptors and agonist of sigma-1 receptors
- The main effect of these treatments is to reduce glutamate excitotoxicity, though studies have reported that the combination also reduces agitation in AD patients
- AVP-923 is contraindicated in several groups of patients. Include: people with heart problems, thrombocytopenia, lupus-like syndrome, and hepatitis

Treatments in Research Phases

Targeting the Aβ-Producing Pathway

- APP cleavage pathways. In the non-amyloidogenic pathway (top), APP is cleaved by α-secretase then γ-secretase

- In the amyloidogenic pathway, APP is cleaved by β-secretase then γ-secretase,



Targeting Aβ

- Three proteases (α, β, and γ-secretase) are responsible for the processing of APP and alteration of Aβ formation. Therefore, a better therapeutic strategy could result in a reduction of Aβ production.
- New anti-amyloid drugs are now being researched for their ability to block or stimulate the secretase involved in the metabolism of APP.
- Several medicines that target Aβ are listed below.

γ-secretase inhibitors and modulators

- γ-secretase inhibitors (GSIs) have been tested in various transgenic mouse models. According to recent studies, GSIs decrease the production of Aβ peptides.
- nevertheless, throughout clinical development, γ-secretase inhibitors (GSIs) exhibited target-based toxicity.

- Currently, new Notch-sparing γ-secretase inhibitors with more brain penetrant action are being developed .
- the γ-secretase modulator NGP-555 [NCT02537938], launched in 2016, completed the Phase I clinical trial and was still not yet recruited in the Phase II trial.
- Other drugs such as avagacestat [NCT00890890], Semagacestat (major side effects such as skin cancer and infections), and tarenflurbil were also discontinued from clinical trials

List of γ-secretase inhibitors/modulators in clinical trials (clinicaltrials.gov).

Drug/clinical trial identifier	Clinical trial phase	Mechanism of action	Dates	Sponsor	Status	Reason
Semagacestat [NCT01035138]	Phase III	γ-secretase inhibitor	Study started in March 2008; Ended in May 2011	Eli Lilly & company	Terminated	No clinical efficacy and Skin cancer and some adverse effects detected.
Tarenflurbil [NCT00380276]	Phase III	γ-secretase modulator	Study started in Sep 2006; Ended in Dec 2008	Myrexis Inc.	Terminated	Low γ-secretase modulator potency, poor CNS penetration
Avagacestat [NCT00890890]	Phase II	γ-secretase inhibitor	Study started in May 2009; Ended in July 2013	Bristol-Myers Squibb	Terminated	Adverse effects: cerebral microbleeds, Glycosuria and skin cancer
NGP 555 [NCT02537938]	Phase I	γ-secretase modulator	Study started in Jan 2016; Ended in Dec 2016	Neuro Genetic Pharmaceuticals inc.	Phase I Completed	Not yet recruited in phase II study

β-secretase inhibitors

- In the amyloidogenic pathway, APP is cleaved by β-secretase and generates Aβ peptides leading to neurodegeneration.
- In the last few years, several β-site amyloid precursor protein cleaving enzyme or BACE inhibitors launched in clinical trials.
- Still, many of them have failed in double-blind, placebo-controlled clinical trials in patients with mild-to-moderate AD

- List of BACE1 inhibitors in clinical trials (clinicaltrials.gov).

Drug/clinical trial identifier	Clinical trial phase	Dates	Sponsor	Status	Reason
LY2886721 [NCT01561430]	Phase I	Study started in March 2012; Ended in August 2013	Eli Lilly and company	Terminated	The study was closed due to anomalous findings in the hepatic biochemical parameters of some participants.
Elenbecestat (E2609) [NCT02956486]	Phase III	Study started in October 2016; Ended in Jan 2020	Eisai co. Ltd. Biogen	Terminated	Unfavorable risk-benefit ratio including no evidence of potential efficacy, and the adverse event profile of being worse than placebo.
CNP520 [NCT02565511]	Phase II/III	Study started in August 2017; Ended in April 2020	Novartis Pharmaceuticals	Terminated	Worsening of cognitive function in participants.
Verubecestat [NCT01953601]	Phase III	Study started in November 2013; ended in May 2019	Merck Sharp and Dohme Corp.	Terminated	The decision to stop the study taken by the external Data Monitoring Committee
Atabecestat [NCT02569398]	Phase II/III	Study started in October 2015, Ended on December 20, 2018	Janssen Research & Development, LLC	Terminated	Elevations in liver enzymes in subjects

α-secretase enhancers

- In the non-amyloidogenic pathway, APP is processed by the α-secretase enzyme . α-secretase cleaves the lysine 16 and leucine 17 peptide bond of APP, produces soluble amyloid precursor protein (sAPPα), and the membrane-tethered C83, which is further processed by γ-secretase to produce p3 and AICD

α-secretase decreases the formation of Aβ formation and also exhibited neuroprotective action

Hence, for the development of disease-modifying drugs, α-secretase enhancers provide an attractive strategy.

Different compounds have been investigated to stimulate the non-amyloidogenic pathway.

Fewer compounds are reached in the clinical trial stage owing to a lack of selectivity toward α-secretase and associated issues of toxicities.

- EGCg (epigallocatechin gallate, EGCG) [NCT03978052] is a promising α-secretase activator currently in the clinical trial recruiting phase.
- a retinoid, acitretin, a retinoic acid receptor agonist mainly used to treat severe psoriasis, has also been reported to enhance alpha-secretase expression and crossing the blood-brain barrier

Prevention of amyloid aggregation

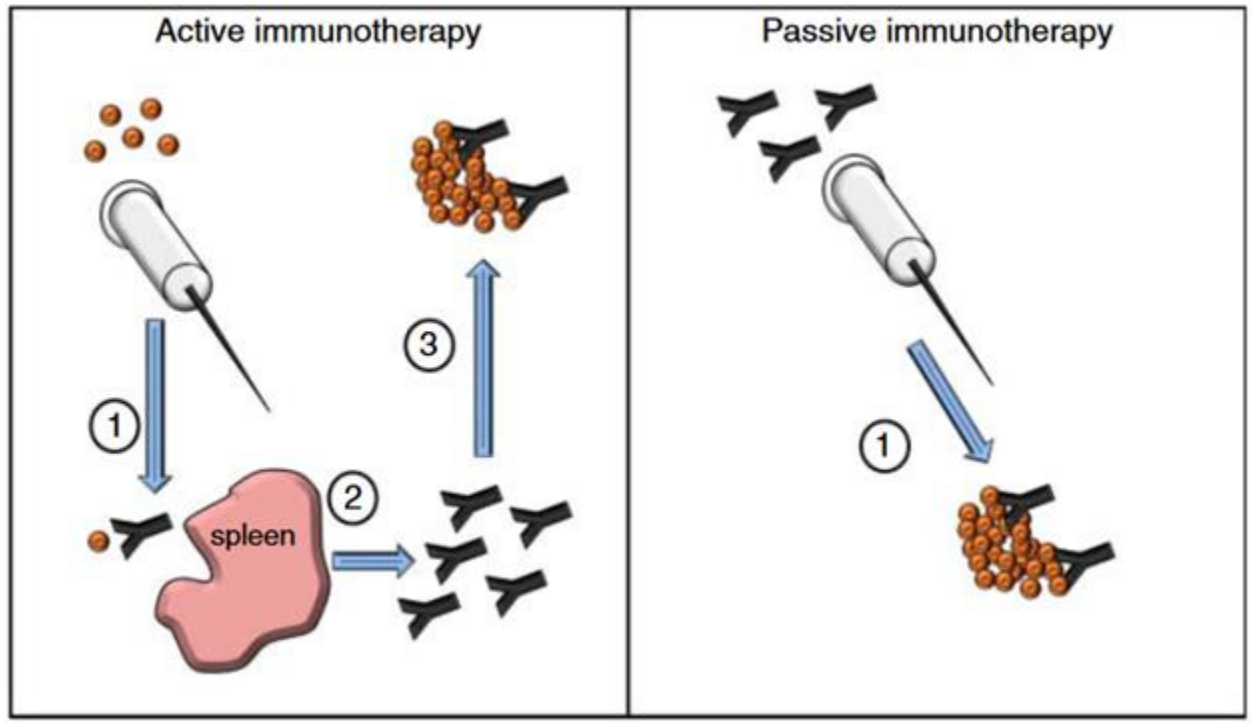
- Aβ42 has been identified as a key component of amyloid plaques in Alzheimer's disease brains .
- In preclinical and clinical studies, tramiprosate has been evaluated for the treatment of AD.

- Tramiprosate is an oral amyloid anti-aggregation agent evaluated in patients with mild to moderate AD. Unfortunately, tramiprosate failed in phase 3 clinical trial phase due to its side effects associated with gastrointestinal (nausea, vomiting)

- a prodrug (ALZ-801) of tramiprosate has novel anti-amyloid oligomer action and is recommended as a fast-track designation from the U.S. Food and Drug Administration for AD treatment.
- colostrinin, a polypeptide derived from ovine colostrum, has been shown to fully inhibit Aβ42 aggregation in individuals with mild and moderate AD. However, the current status of colostrinin in the clinical trial is unknown.

- **Immunotherapy**

- Immunotherapy for AD is currently being tested with the aim of removing Aβ plaques from the brain.
- Immunotherapy can be divided into two types: active immunotherapy and passive immunotherapy.
- Active immunotherapy involves the stimulation of the immune system by injecting substances (such as antigens) which can trigger phagocytic capacity of microglia.
- Passive immunotherapy involves the injection of agents such as monoclonal or polyclonal antibodies , directly attack their targets (i.e. senile plaques for Aβ immunotherapy)


Active immunotherapy
Passive immunotherapy
1
2
3
spleen
1

Active Immunotherapy (Aβ)

- AN-1792 was the first immunotherapy compound tested and in a Phase II clinical trial, four patients developed meningoencephalitis and in 2002 the development of this vaccine was terminated.
- Other immunotherapy are currently in the research phase:
- CAD106
- ABvac40
- UB-311
- AF20513
- ACC-001
- AD02, …

Active Immunotherapy (tau)

- **AADvac1** is an active immunotherapy peptide consisting of amino acids 294–305 of the tau sequence.

An initial Phase I clinical trial also reported that the vaccine was generally safe, and that the vaccine provoked a strong immune response A Phase II clinical trial is currently ongoing (NCT02579252).

- **ACI-35** is a liposomal vaccine which consists of 16 copies of tau fragments including phosphorylation at positions S396 and S404

Passive Immunotherapy (Aβ)

- In contrast to active immunotherapy, passive immunotherapy has more ongoing clinical trials, and more compounds have been tested.

- **Aducanumab** (BIIB037) is a human IgG1 monoclonal antibody against a conformational epitope of Aβ. Recent results have highlighted that in human and mouse models of AD, aducanumab reduces amyloid plaque load and restores calcium homeostasis
- . However, in one study, some adverse effects were reported in more than one-half of patients given a higher dose. Aducanumab is currently recruiting patients in two Phase III clinical trials

- **Solanezumab** is a monoclonal IgG1 antibody raised against the central sequence of Aβ. A clinical trial of solanezumab (LY2062430) terminated in Phase III in October 2019 [NCT02760602] due to the failure of the EXPEDITION 3 study. still being established in people with a genetic mutation that might put them at risk for developing Alzheimer's disease in a Phase 2/3 clinical trial [NCT01760005]

- In two Phase III clinical trials in mild to moderate AD, solanezumab at first failed to produce significant improvements, although the assessment of secondary outcome measures indicated that it can be beneficial in mild AD.
- of these latest results, a Phase II/III clinical trial is enrolling patients (NCT01760005) while a Phase III clinical trial is currently ongoing

- **Other products:**
- Gantenerumab:IgG1 antibody
- Crenezumab is an IgG4 immunoglobulin
- BAN2401 : a human IgG1
- LY3002813: an IgG2 antibody
- AAB-003
- Bapineuzumab : an IgG1 antibody

- **Gamunex**, is an Intra Venous Immunoglobulin (IVIg) mix purified from human plasma.
- It has been tested in AD as the immunoglobulins include natural antibodies against Aβ, as well as anti-inflammatory antibodies.

- while the first studies in humans also reported beneficial effects of IVIg , subsequent Phase II and Phase III clinical trials have failed to confirm early results.

Passive Immunotherapy (tau)

- RO7105705
- ABBV-8E12
- BIIB076 is a human anti-tau monoclonal antibody

Aducanumab

- Aducanumab is an investigational human monoclonal antibody that revealed significant benefits on measures of cognition and function such as memory, orientation, and language.
- Aducanumab (BIIB037) reduced the level of amyloid plaques in the brain.
- FDA grants accelerated approval for Aduhelm (aducanumab-avwa) to treat Alzheimer's Disease in June 2021 and declared as new medicine has been approved for Alzheimer's patients. After approval, drug companies must do Phase IV confirmatory trials to evaluate their products' benefit; if the drug does not work as anticipated, the FDA can remove it from the market.

- donanemab is an investigational antibody that targets a modified form of beta-amyloid called N3PG, completed phase 2 clinical trial.

Anti-Tau strategies

- Tau proteins, or axonal microtubule-associated protein (MAP), are important for:
- regulators of microtubule assembly
- spatial organization
- axonal organelle transport.
- However, excessive tau phosphorylation has been suggested as a potential contributor to the formation of neurofibrillary tangles in AD
- hyperphosphorylation of tau proteins exhibit tau protein dissociation from the microtubules, disturbance of axonal transport structure, starvation of neurons, and ultimately neuronal death

Tau phosphorylation and aggregation inhibition

- Tau phosphorylation and aggregation inhibitors are used to alleviate tauopathy as well as tau aggregation.
- TRx0237 is a second-generation tau protein aggregation inhibitor that has reached in Phase III clinical trial to determine the safety and efficacy of TRx0237 16 mg/day and 8 mg/day in treating subjects with Alzheimer's disease.
- This study is estimated to complete by June 2023 [NCT03446001]. Another compound, LY3303560, acts as a tau phosphorylation inhibitor, currently in Phase II clinical trial

- Glycogen synthase kinase-3 (GSK3) inhibitors are another approach for reducing tau hyperphosphorylation, the enzyme mainly responsible for converting tau to hyperphosphorylated tau protein
- Tideglusib [NCT00948259] is a GSK3 inhibitor, an orally available, Tideglusib entered in Phase II clinical trial and tested in mild to moderate AD participants in December 2008. However, tideglusib ascertained safer in the trial but missed its primary endpoint, and some of the secondary endpoints thus showed no significant clinical benefits

- Cyclin-dependent kinase 5 (CDK5)

CDK5 regulates various functions such as maintaining synaptic plasticity, neurotransmitter release, neuron migration, and neurite outgrowth.

Targeting CDK5/p25 may be a beneficial alternative for the treatment of Alzheimer's disease.

Butyrolactone-I is a CDK5 inhibitor that blocks the activation of CDK5 kinase and prevents neuronal death

Tau aggregation inhibitors

- **Tau-tau interactions** are responsible for the formation of NFTs. Hence, for slowing Alzheimer's disease progression, various compounds which inhibit tau-tau interaction have been tested in studies .
- Methylene blue (MB) is a member of the phenothiazine family. Methylene blue showed promising results in preliminary and in vivo studies in animal models. However, in May 2020 trial of Methylene blue was suspended in Phase II [NCT02380573] (Pending enrollment of new subjects if new funding was obtained) in Phase II and the estimated study completion is July 2023.
- cohort analysis as the modified primary outcome in a Phase III clinical trial of low dose, 4mg twice a day, Leuco-Methylthioninium Bis (Hydromethanesulphonate) monotherapy showed promising results for the treatment of mild AD patients

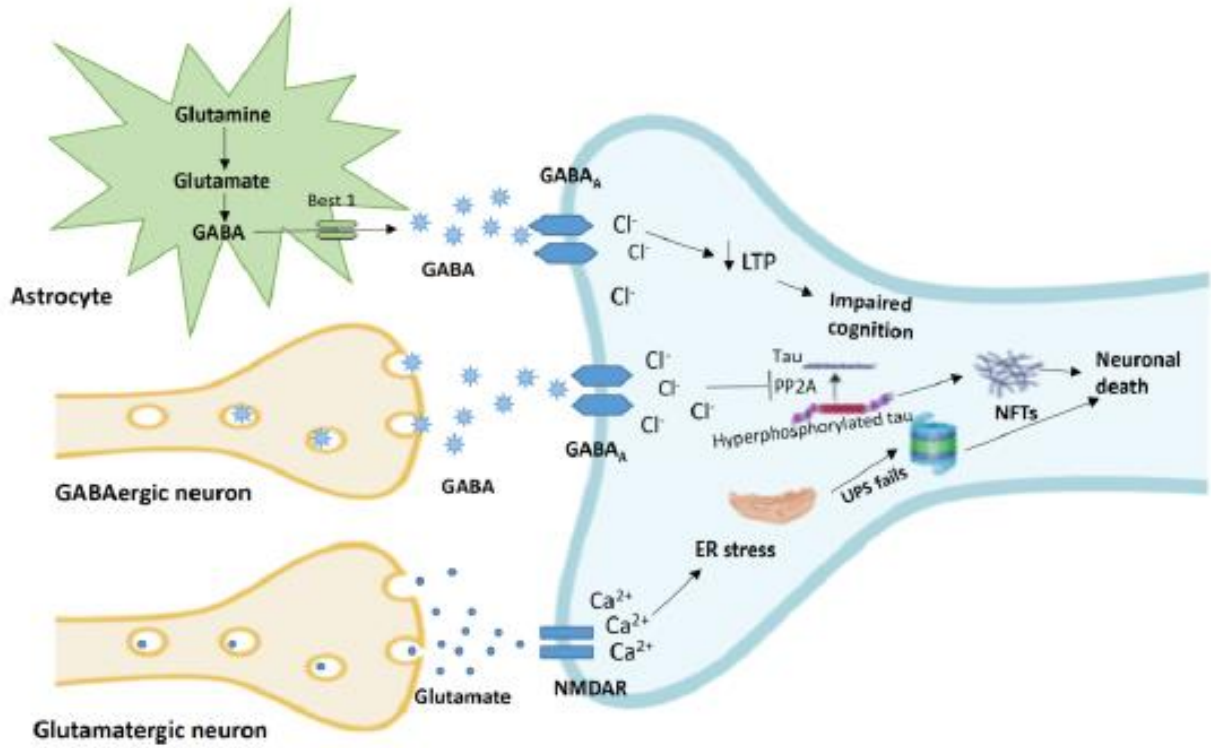
Microtubule stabilizers

- In AD, tau hyperphosphorylation is associated with microtubule disruption. In preclinical and clinical trials, several microtubule stabilizers have been tested to treat AD .
- **Paclitaxel** is an anti-mitotic agent terminated from the study due to its low penetration power through the blood-brain barrier .
- Recently, in April 2020, the recruitment of participants for safety, tolerability, pharmacokinetics, and pharmacodynamics study of a synthetic epothilone derivative, TPI- 287, for the Phase I trial has been completed . This trial is sponsored by the University of California, San Francisco [NCT01966666].

- IVIG (Intravenous immunoglobulin) is active immunotherapy and being developed by Shire/Alzheimer's Disease Cooperative Study (ADCS) for the treatment of mild-to-moderate Alzheimer's disease.
- Biweekly infusions of IV immunoglobulin at doses of 0.2 or 0.4 g/kg every 2 weeks for 18 months completed a Phase III study in December 2012, which evaluated the safety and effectiveness of (IVIG 10%) in mild to moderate AD patients [NCT00818662].
- IVIG revealed good tolerability for 18 months but did not show beneficial effects on cognition or function relative to participants who received a placebo

Neurotransmitter dysfunction

- The alteration of several neurotransmitters' transmission can trigger the progression of the disease.
- The role of cholinergic, glutamatergic, and serotonergic system alteration is reported in the early stages of AD.
- In the later stage of AD, GABAergic and dopaminergic systems appear to be affected


Glutamine
Glutamate
GABA
Best 1
Astrocyte
GABA
GABA$_A$
Cl$^-$
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Cl$^-$
LTP
Impaired cognition
GABAergic neuron
GABA
GABA$_A$
Cl$^-$
Cl$^-$
Cl$^-$
Tau
PP2A
Hyperphosphorylated tau
NFTs
Neuronal death
UPS fails
ER stress
Ca^{2+}
Ca^{2+}
Ca^{2+}
Glutamatergic neuron
Glutamate
NMDAR

Cholinesterase inhibitors (ChEIs)

- Presently, FDA-approved available treatment options in cholinesterase inhibitors **are:**
- donepezil, rivastigmine, and galantamine .
- The mechanism of acetylcholinesterase inhibitors (AChEIs) drugs is to inhibit acetylcholinesterase activity and blockade of hydrolysis of acetylcholine (Ach).
- Various classes of drugs increase the Ach level and reduce excitotoxicity via different mechanisms .

- Encenicline [NCT02246075] is an α7nAChR agonist and increases Ach response, but unfortunately, encenicline was withdrawn from the Phase II clinical trial in July 2015 due to gastrointestinal side effects.

- AD-35 is a cholinesterase inhibitor in Phase II clinical trial for multi-center, randomized, double-blind, parallel-group, placebo-controlled study for the treatment of subjects with mild to moderate AD [NCT03790982]

Ionotropic glutamate receptor antagonist

- An excessive amount of Aβ oligomers and plaques can activate NMDA receptors. The activation of NMDA receptors increases Ca2+ concentration in a postsynaptic neuron which further promotes excitotoxicity and neuronal .
- NMDA receptor antagonist memantine is prescribed to increase the symptomatic effect in mild to moderate patients of AD.
- Riluzole is a glutamate receptor antagonist. At present, riluzole is approved for Amyotrophic lateral sclerosis (ALS). The current status of riluzole [NCT03605667] for AD treatment is active, not recruiting in Phase II clinical trial

Muscarinic receptor 1 agonist

- In AD, cholinergic deficiency is a key factor responsible for cognition impairment. Agonists for muscarinic receptors may help to balance cholinergic neurotransmission in the brain by increasing acetylcholine release and binding to postsynaptic receptors.
- UV- 319 is a muscarinic receptor-1 agonist, currently in phase 1 clinical trial (clinicaltrials.gov) (clinicaltrials.gov)
- MK-7622 [NCT01852110]
- Tak-071 [NCT02769065].
- Furthermore, muscarinic acetylcholine-receptor agonists can induce cleavage of APP by non-amyloidogenic α-secretase, which has been demonstrated to limit Aβ production in cell culture

GABA antagonist

- γ-aminobutyric acid (GABA) acts as an inhibitory neurotransmitter in the CNS.
- GABAA, GABAB, and GABAC are three subfamilies of the GABA receptor

- GABAA receptor is further enhanced by activated NMDA receptors.
- In astrocytes, glutamate is responsible for the synthesis of GABA,
- In AD, long-term potentiation (LTP) is suppressed by the excessive release of GABA, resulting in impaired cognition.
- Activation of the GABAA finely resulting in hyperphosphorylation of tau and neuronal death
- Allopregnanolone injection acts as a GABA modulator and is in Phase I clinical trial study in Oct 2019 [NCT03748303]

Calcium channel blockers

- Epidemiological evidence shows that mild to severe hypertension enhances the chances of dementia.
- Nilvadipine [NCT02017340] is a calcium channel blocker used for the treatment of hypertension. But unfortunately, the study of nilvadipine at a dose of 8 mg found no overall effect on slowing the rate of cognitive decline in a population spanning mild to moderate Alzheimer's disease

Neuroinflammation

- In AD, microglial cells and astrocytes are mainly involved in the pro-inflammatory and inflammatory response in the CNS.
- Microglial cells are resident macrophages present in CNS. These cells have a crucial role in neurogenesis, neuronal plasticity, and immune defense mechanism against foreign stimuli.
- Microglial cells remain in resting state in the absence of foreign stimuli . Any insult to the brain results in morphological changes and activation of microglial cells.
- Activated microglial cells move toward the site of injury. These cells release pro-inflammatory mediators, cytokines, IL-6, IL-1β, TNF-α, and other neurotoxic agents that further exacerbate the inflammatory condition .

- **microglial inhibitors**

several drugs such as

- alzhemed,
- azeliragon,
- flurizan,
- CHF5074 [NCT01723670]

poor clinical efficacy, all of these are terminated from the clinical studies.

- **BPN14770**, an allosteric inhibitor of phosphodiesterase-4D, has reached in Phase II clinical trial

Oxidative stress

large-scale epidemiological studies showed promising results that eating food rich in antioxidant supplements, β carotene, and vitamin C and vitamin E is related to a lower risk of AD dementia

- Benfotiamine is a thiamine derivative and acts as a synthetic variant of vitamin B1. Various studies reported that increasing brain thiamine levels could show beneficial results in AD patients .
- Currently, benfotiamine [NCT02292238] is being developed by Burke Medical Research Institute and Columbia University and reached in Phase II clinical trial in June 2014 but not yet recruiting patients

Neurotrophic factors

Neurotrophins belong to a class of growth factors and play a pivotal role in neuronal survival and differentiation, modulation of the dendritic spine, synaptic plasticity, and apoptosis

Nerve growth factor (NGF)

- In the brain, nerve growth factors and mature NGF help in cholinergic neurotransmission.
- Various medicines and NGF brain delivery methods are being studied to increase NGF activity and enhance cholinergic transmission.

Brain-derived neurotrophic factor (BDNF)

- Brain-derived neurotrophic factor is a neurotrophin that is responsible for neurogenesis and is mainly found in various regions of the brain such as the cerebral cortex, entorhinal cortex, and hippocampus .
- reduced BDNF levels were observed in AD patients
- In animal models of AD, BDNF showed beneficial effects. For instance, to improve BDNF in the brain, sustained BDNF gene delivery using viral vectors resulted in elevated BDNF levels in the brain.

- PKC modulator bryostatin 1, also appears to exert immunomodulatory effect.
- Bryostatin 1 showed an increase in cognitive ability in preclinical studies. The neuroprotective effects of bryostatin 1 are reported due to its ability to induce synaptogenesis by elevating levels of synaptic growth factors in the brain, such as BDNF.
- completed the Phase II clinical trial study in August 2020

Molecular targets for the drugs

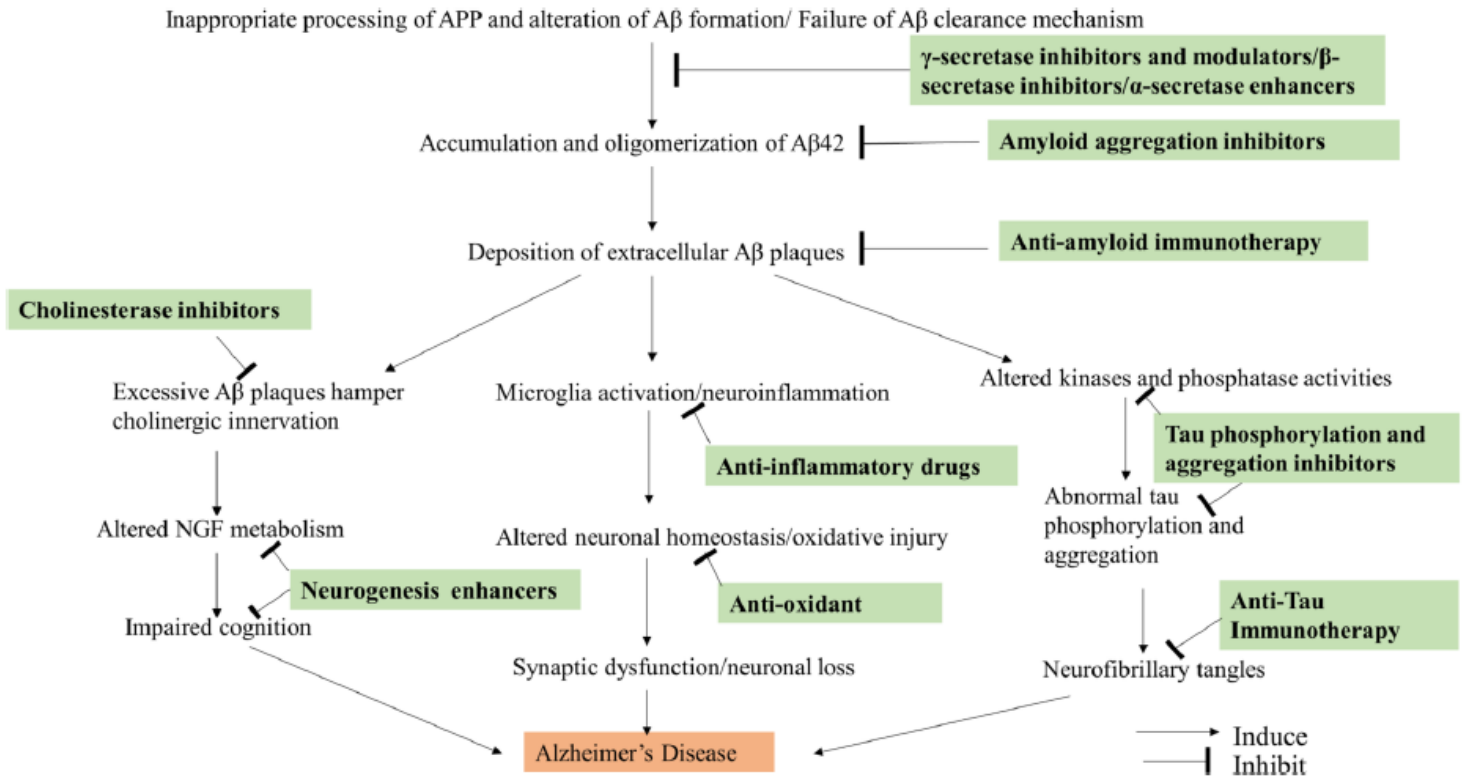

Fig. 3. Mechanisms involved in Alzheimer's Disease progression and molecular targets for the drugs.

Conclusion

- There is currently no cure or disease-modifying treatment for Alzheimer's disease
- NMDAR antagonist and cholinesterase inhibitors do not block the formation of Aβ plaques and NFTs, hence, they do not seize the progress of dementia.
- they lead to a temporary slowdown in the loss of cognitive function. Interestingly, many drug candidates reached various clinical trial phases, but due to adverse effects and lack of therapeutic efficacy, most of the compounds did not succeed in Phase II/III trials. Therefore, understanding the comprehensive pathogenesis of AD is required before focusing on novel drug development. Moreover, the attention in AD drug development is also shifting from treatment to prevention.

Thanks for your attention