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RECENT ADVANCES IN ALZHEIMER'S DISEASE MANAGEMENT

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ABSTRACT: Alzheimer's disease is very common type of dementia in old age which is slowly progressive neurodegenerative disease associated with loss of cognitive functions. It is caused by several pathological pathways like amyloid-β (Aβ) deposition, hyperphosphorylated tau protein, excessive glutamatergic stimulation, cholinergic disorder, and neuroinflammation and oxidative stress. Currently, most of the drugs available for the management of Alzheimer disease, like cholinesterase enzyme inhibitors (*donepezil, rivastigmine, galantamine*) and N-methyl d-aspartate (NMDA) antagonist, *memantine*, are effective in treating the symptoms but do not cure the disease. Various research projects on Alzheimer's disease have failed or have been abandoned in the past decade due to adverse effects or lack of the efficacy. This can be due to starting of therapy in the late stages of disease, inappropriate drug doses or an inadequate understanding of the pathophysiology of AD. Recently there have been success in disease management with the approval of adacanumab and donanemab-azbt, which have been recently approved by FDA. Furthermore, there are many ongoing trials which are currently in various phases of development which, if successful, would provide multiple options to choose from, for better management of AD. This review highlights such recent advances as well as future targets in the disease treatment, which would aid physicians in optimizing patient care.

INTRODUCTION

Alzheimer's disease, named after the German psychiatrist, Alois Alzheimer is the most common type of dementia in the old age.[1] It is a slowly progressive neurodegenerative disease which leads to impairment of cognitive functions due to various pathological pathways like amyloid-β deposition, hyperphosphorylated tau protein, cholinergic disorder, neuroinflammation, excessive glutamatergic stimulation and oxidative stress[2].

Alois Alzheimer, in 1906, noticed the presence of amyloid plaques and a massive loss of neurons while examining the brain of his patient that suffered from memory loss and change of personality before dying and described this condition as a serious disease of the cerebral cortex.[3] Emil Kraepelin named this medical condition as Alzheimer's disease for the first time in the 8th edition of his psychiatry handbook.[4]

About 55 million people have dementia worldwide and it is estimated that this number may increase to 139 million by 2050 due to population aging. Also, among these patients, 44% are 75 to 84 years old patients and 38% are 85 years or older in age.[2]

Amyloid β is produced by the cleavage of its precursor, amyloid precursor protein (APP), by α-secretase and γ-secretase. Dysregulated accumulation of Aβ leads to the formation of senile plaques, subsequent phosphorylation, and aggregation of tau protein, resulting in the generation of neurofibrillary tangles (NFTs), neuronal loss, and synaptic dysfunction. Also, deposition of Aβ triggers mitochondrial dysfunction, initiating endo-plasmic reticulum (ER) stress and ultimately causing neuronal cell death.[5] (Figure 1)

Besides, other factors can cause neurodegeneration such as neuroinflammation, oxidative stress, and injury of cholinergic neurons.[6] In the last decade, several

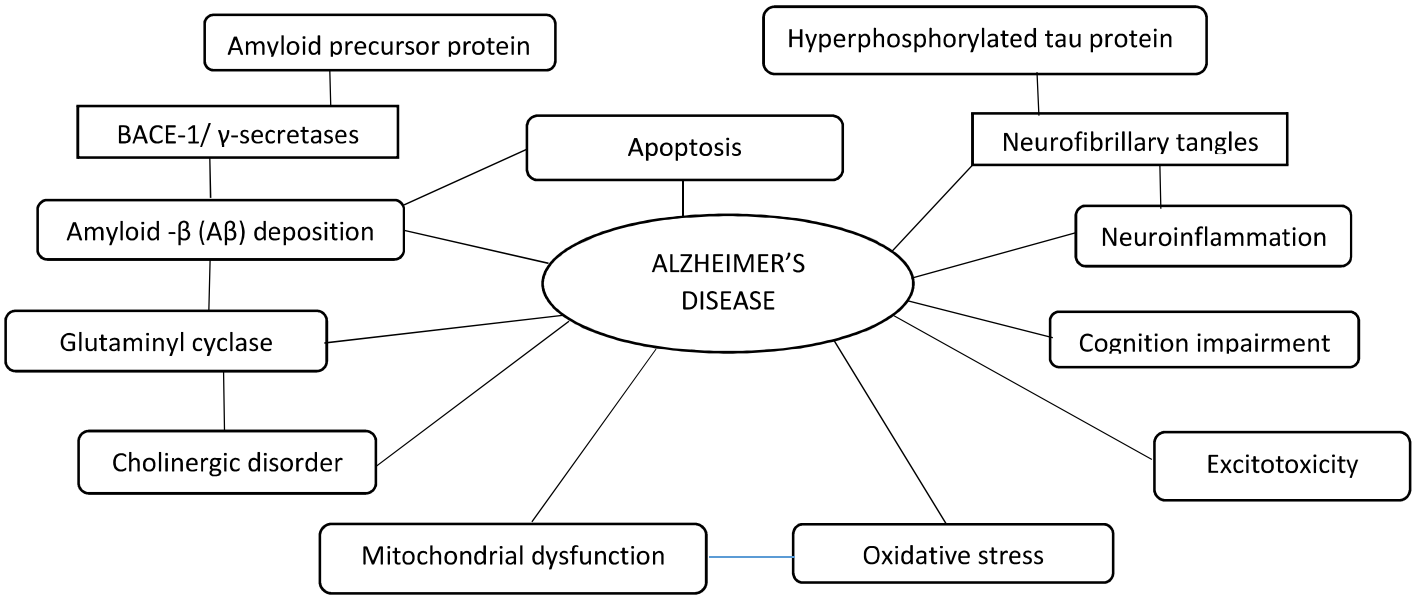


Figure 1: ***Mechanisms related to pathogenesis and progression of Alzheimer's disease***

research projects on Alzheimer's have been failed or have been abandoned due to lack of efficacy or adverse effects.[7] This can be due to starting of therapies in late stages of disease, inappropriate drug dosage, wrong main target of the treatment, or incomplete understanding of the pathophysiology of AD.

Only two classes of drugs, including inhibitors to cholinesterase enzyme (donepezil, galantamine, rivastigmine) and antagonists to N-methyl d-aspartate (NMDA) - memantine, were approved for treatment of Alzheimer's disease by FDA till 2021, which are effective only in treating the symptoms of AD, but do not cure or prevent the disease.[8] In 2021, **monoclonal antibody (Anti Aβ),** Adacanumab was approved, and on July 6, 2023 Lecanemab and recently, on July 2, 2024, Donanemab-azbt was approved by US FDA.

Therefore, this review, mainly focuses on future theories for the development of new therapies for AD.

Current Landscape in Treatment Research for AD

Potential targets:

1. **Amyloid Beta and Tau protein:** Cleavage of amyloid precursor protein (APP) by β-secretases (BACE-1) or γ-secretases produces insoluble Aβ protein. So, the therapeutic approach is to disassemble and degrade amyloid plaques chemically or by recruiting microglia and activating phagocytosis to stop the neuronal damage elicited by the protein accumulation. Active or passive immunotherapies are the most widely studied strategies due to their precise response, although some adverse effects like autoantibodies induction, edema or hemorrhage have been reported. [9]

a) **Reduction of Aβ42 production** (γ-secretase inhibitors, β-secretase inhibitors, α-secretase potentiation)

- ***γ-secretase inhibitors:*** These drugs inhibit γ-secretase, which processes APP as well as the Notch receptor—an essential regulator of cell differentiation and signaling. Interference with the Notch pathway has led to adverse effects and failures in clinical trials. For instance, **Semagacestat** was associated with cognitive decline, increase in infection rate, and increased skin cancer incidence; Avagacestat caused dose-dependent toxicity; and **Tarenflurbil** exhibited poor brain penetration and clinical inefficacy.[5]
- ***β-secretase inhibitors:*** The β and ɣ-secretase leads to the generation of shorter insoluble peptide fragments (~39-43 amino acids) known as Aβ-fragments by cleaving APP in neuronal cells which possess a distinct neurotoxic effect leading to neurodegeneration, amyloid angiopathy, mitochondrial dysfunction and inflammation. Drugs in pipeline are: Verubecestat: oral BACE-1 inhibitor, Lanabecestat: decreased plasma and CSF Aβ, Elenbecestat , and Umibecestat.[10]

- ***α-secretase potentiation:*** Agents that activate the PI3K/Akt pathway or act as selective GABA receptor modulators are assumed to activate α-secretase also, so suggested as potential therapeutic drugs for AD

b) Reduction of Aβ-plaque burden: aggregation inhibitors, drugs interfering with metals

Aggregation inhibitors (anti-amyloid aggregation agents): directly interact with the Aβ peptide to inhibit Aβ42 fiber formation. Drugs include scyllo-inositol (ELND005) and Peptidomimetics (KLVFF, γ-AA)

Drugs interfering with metals: Abnormal accumulation of metal ions such as iron, copper, and zinc has been associated with the pathophysiology of AD. In a phase 2 study of 3 months, PBT2 succeeded in13% reduction of CSF Amyloid β and an cognition function improvement in patients with early AD. Drugs in pipeline include Deferiprona and PBT2.[10]

c) Promotion of Aβ clearance (active or passive immunotherapy):

Active immunotherapy: This approach involves immunization with Aβ or phosphorylated tau peptides, or synthetic peptides such as polymerized ABri-related peptide (pBri). These antigens elicit a B-cell–mediated antibody response against pathogenic epitopes. Vaccines under investigation include UB-311 (targets Aβ1–14 and demonstrated strong immunogenicity in phase II trials), CAD106, CNP520, ABvac40, GV1001, ACC-001, and AF20513.[5]

Passive immunotherapy: Passive immunotherapy involves the passive inoculation of monoclonal antibodies (mAbs) or polyclonal antibodies that act against Aβ peptides, making the inflammatory process developed by T cells unnecessary. Drugs in pipeline includes Crenezumab, Gantenerumab, LY3002813.[5]

2. **5-HT receptors:** 5-HT6R and 5-HT7R are the most extensively studied serotonin receptors due to their brain distribution and cognitive properties reported in vivo. 5-HT6R induces signaling that changes cholinergic, glutamatergic and monoaminergic brain signaling with least peripheral adverse effects.[11]
3. **Glutaminyl cyclase:** Glutaminyl cyclase plays a vital role in synaptotoxic Amyloid β oligomer formation with pro-inflammatory potential. It converts glutamate residue to AβpE3 peptide at position 3 of the N-terminal of truncated Aβ that may contribute to tau hyperphosphorylation. Drugs in pipeline includes Belinostat, Amlexanox and Acipimox.[12]
4. **Neuroinflammation:** TNF-α (Tumor necrosis factor-α) plays a significant role in neuronal excitotoxicity, synaptic loss and inflammation. Drugs in pipeline are NE3107, AL002: Monoclonal antibody targeting TREM2 receptors to promote microglial clearance of Aβ, TB006: Monoclonal antibody targeting Galactin 3, Edicotinib (JNJ-40346527): Colony-stimulating factor-1 receptor (CSF-1R) inhibitor and Pepinemab: Monoclonal antibody directed at semaphorin 4D to reduce inflammation. [13]
5. **Growth factor promotion:** growth factors have the role to regenerate neurons. Drug in pipeline is ATH 1017 (fosgonimeton)
6. **Stem cell therapy:** Stem cells have capacity to differentiate and proliferate throughout the lifetime of the organism. So, these cells can serve as the most appropriate choice for cell replacement therapies. These includes hNSCs (human Neural Stem Cells), hUC-MSCs (human Umbilical Cord Mesenchymal Stem Cells) and Autologous ADSCs (AstroStem).[14]
7. **Natural compounds:** In recent years, bioactive compounds derived from plants, animals, and fungi have shown therapeutic potential due to their anti-inflammatory, antioxidant, and neuroprotective properties. These natural agents may modulate key molecular pathways implicated in AD pathology. [15]
8. **Nanoparticle based delivery systems:** NPs enter the brain by crossing or disrupting the BBB. Diverse systems, including liposomes, polymeric NPs, solid-lipid NPs, and inorganic NPs, micelles, and NP based immunotherapy have been investigated to relieve AD symptoms, target AD hallmarks, and target moieties to diagnose AD.[16]

   Liposome : Osthole, Galantamine HBr,
   Micelles: Resveratrol, curcumin,
   Solid Lipid NPs: Rivastigmine, Donepezil
   Polymeric-NPs: Quercetin, Memantine
   Nanoemulsions: Huperazine A
   Magnetic NPs: Quercetin, SiRNA

Table-1: Trials in their various phases of development for the treatment of Alzheimer's disease

ANTI-AMYLOID THERAPY			
NAME	**COMPANY**	**THERAPY TYPE**	**STATUS**
Donanemab (LY3002813)	Eli Lilly & Co	Passive Immunotherapy	Approved on 3rd July 2024
Remternetug (LY3372993)	Eli Lilly & Co	Passive Immunotherapy	Phase 3
Valiltramiprosate (ALZ-801)	Alzheon	Small molecule	Phase 3
ABBV_916 (N3pG_Abeta mAb)	AbbVie	Passive Immunotherapy	Phase 2
CT1812 (SHINE (COG0201) Study)	Cognition Therapeutics	Small molecule	Phase 2
ANTI-TAU THERAPY			
Bepranemab (UCB0107)	Hoffmann-La Roche, UCB S.A	Passive immunotherapy	Phase 2
BIIB080 (ISIS 814907)	Biogen, IONIS Pharmaceuticals	Tau DNA/RNA-based	Phase 2
Posdinemab (JNJ-63733657)	Janssen	Passive immunotherapy	Phase 2
LY3372689	Eli Lilly & Co	Tau small molecule	Phase 2
NEUROPROTECTIVE AGENTS/ Synaptic plasticity			
Fosgonimeton	Augment the activity of hepatocyte growth factor and its receptor		Phase 2/3
Buntanetap	suppress the translation of the mRNAs of neurotoxic aggregating proteins		Phase 3 completed
Hydralazine hydrochloride	Activate the Nrf2 pathway, Restore mitochondria, Activate autophagy		Phase 3
COGNITIVE ENHANCERS			
AR1001	Inhibit phosphodiesterase 5 protein		Phase 3
KarXT(xanomeline_trospium)	Muscarinic receptor agonist		Phase 3
Metformin	Antidiabetic		Phase 3
Piromelatine	Melatonin MT1 and serotonin 5-HT-1A receptor agonist		Phase 3
Tricaprilin	Semisynthetic medium chain triglyceride		Phase 3
DRUGS TARGETTING NEUROINFLAMMATION			
Masitinib	Tyrosine kinase inhibitor		Phase 3
NE3107	Inhibits NFκB/ERK pathway		Phase 3
Canakinumab	Anti-IL-1β antibody		Phase 2
AL002 (Biological)	Monoclonal antibody targeting TREM2 receptors to promote microglial clearance of Aβ		Phase 2
Pepinemab (Biological)	Monoclonal antibody directed at semaphorin 4D to reduce inflammation		Phase 1/2
REPURPOSING TRIALS			
Escitalopram Oxalate	Selective serotonin reuptake inhibitor		Phase 4
Sodium Oligomannate Capsule	Neuro-inflammation inhibitor, Amyloid β formation inhibitor		Phase 4
Spironolactone	Mineralocorticoid receptor antagonist (Anti neuroinflammation)		Phase 4
leucine methylthioninium	Inhibition of tau-hyperphosphorylation		Phase 3
Thalidomide	Regulation of β-secretase enzyme, BACE-1 modulator		Phase 3
Etazolate	α-secretase stimulation, GABAA-receptor modulator		Phase 3
Rilapladib	cPLA2 inhibitor, Inhibits LOX and COX pathway		Phase 2
Bexarotene	Activates RXR receptors		Phase 2
Riluzole	Inhibition of glutamate release Inactivation of voltage dependent sodium channels		Phase 2
Saracatinib	Inhibition of Src/Abl family of kinases and Fyn kinase, Inhibition of Aβ formation.		Phase 1

DISCUSSION

A wide range of old and novel therapeutive targets are currently being explored in the drug development pipeline of Alzheimer's disease. Although there are various advancements in the knowledge of Alzheimer's pathogenesis, but still the most common outcome of new drug clinical trials is the lack of efficacy. This can be due to the late disease stage of patients under trial because earlier therapy yeilds better results in AD. Data from studies involving 5-HT6 antagonists, tau inhibitors, and nicotinic agonists have also been disappointing. On the other hand, agents such as anti-Amyloid β vaccine, BACE inhibitors, and drugs that targets neuroinflammation have shown better results in text of clinical improvement and minimal toxicity.

The effectiveness of anti-amyloid monoclonal antibodies reinforces amyloid plaques as a valid therapeutic target in AD therapeutics. Similarly, the success of tau antisense oligonucleotides indicates that therapies decreasing abnormal protein production may be effective. Growing insights into neuroinflammation have also found several promising molecular pathways which could serve as targets for both monotherapy as well as combinations therapy

Recent AD drug therapies have incorporated multiple innovative features such as novel biomarkers, refined neuropsychological assessment tools, early stage patient recruitment , and innovative trial designs. In the near future, treatment is likely to move toward a 'precision medicine' approach, where customized treatment regimens are tailored to individual patients based on aberrant biomarkers, accompanied with characteristic neuropsychological and neuroimaging findings.

Treatment of the diverse disease population of moderate to advanced stages of AD also remains a major concern. Even some of the existing therapies do not provide, even a symptomatic relief, in moderate to advanced stages of AD. The lack of an effective therapy for these populations underscores a critical opportunity of further drug discovery and development.

To identify, validate, and include rationalized efficient clinical biomarkers as end-points is the another key requirement for AD drug development. Such specific biomarkers would enable objective measurement of disease severity in order to set a clinical end-point and also help to predict the results of clinical trial more accurately.

At the same time, continuous effort is being made towards drug repurposing/repositioning to modify the disease's molecular pathophysiology. Due to high attrition rates and lack of funds, the pharmaceutical industries have diverted their focus from the new drug

discovery and development programs to drug repurposing approaches. This approach is more cost-effective, easier and faster as compared to the traditional drug discovery process particularly with the help of modern computational and screening technologies.

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