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Review Article

Novel interventions for Alzheimer's disease

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Abstract

Alzheimer's disease (AD) presents a complex clinical landscape, notable for progressive mental deterioration and restricted treatment choices. AD exhibits a multifaceted pathology, limiting treatment possibilities, highlighting recent advancements in pharmacological, non-pharmacological, and technological approach. This review discussed the emerging therapies targeting amyloid-β, tau, and neuroinflammation, as well as innovative techniques, such as gene therapy, nanotechnology, and stem cell therapy. This review shows how these novel approaches have the potential to change the treatment of AD and give patients and caregivers new hope. It's a time while AD is better managed and the lives of those impacted are enhanced through the integration of conventional and innovative strategies. This review further discusses the hurdles and potential strategies for transitioning this intervention from research to clinical application.

Keywords: Alzheimer's disease, Novel interventions, Amyloid-β, tau, Neuroinflammation, Gene therapy, Nanotechnology, Stems cell therapy.

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1. Introduction

AD is a chronic devastating neurodegenerative disorder in which increasing age is the strongest non-modifiable disease risk factor. This is a condition that develops, initially characterized by mild cognitive decline and perhaps ended with losing the capacity to react to environment and continue the discussion.[1] The parts of the brain responsible for memory, cognitive decline from AD compromises language skills and daily functioning,[2] this leads to neurodegenerative brain diseases.[3] Care for people who have dementia come at an enormous cost to households as well as society as a whole. Therefore, it poses an important issue for global economics and public health.[4] The Worldwide Cost of Disease Study (GBDS) 2019 projects that between 2019 and 2050, that will be a remarkable 166% increase in dementia evaluates, impacting the lives of within 152.8 million individuals worldwide.[5] The predictions are in accordance with those WHO data estimates. Additionally, it will be predicted that the greatest number of these observed rises in dementia cases up to 33% may occur in countries with low sociodemographic index ratings, such as India (SDI).[6] The overall measure for the SDI is the typical number of years education for people over the age of 15, the overall fertility rate, and the lag-distributed per capita income. India ranked in fourth place worldwide in 2019 for dementia burden, and by 2050, it will have surpassed the US and Japan for the leading position .[7] Below **Table 1** represent the current therapy use in the treatment of AD.

2. Detection Technique of AD

Early detection and evaluation of AD are evident for several strong reasons. Early detection helps patients plan for their future care by allowing them to develop their objectives. It allows one to make thoughtful choices regarding matters of well-being, money, and laws whilst ensuring that the necessary assistance systems are accessible.[19] In addition, early identification allows access to several treatments and interventions that could stop the illness's progress or minimize symptoms. While there presently exists no known cure for multiple medications and therapeutic approaches can help manage symptoms and improve general wellness.[20]

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Table 1: Current therapy and uses of AD

Medication	Mechanism	Uses	Reference
Memantine	Memantine mediated by blocking the action of glutamate, a harmful neurotransmitter to brain cells in high amounts. It also inhibits ion channels regulated by NMDA receptors, reducing the calcium enter into the cell. This reduces excitotoxicity, a process that can damage brain cells. Ultimately, memantine modulates neuronal activity, cognitive restoration and symptoms relief of AD.	AD	8
		Post stroke dementia	
		Parkinson's dementia	
		Huntington's disease	9
		Neurodegenerative diseases (neuroprotection).	
Donepezil	Donepezil works by inhibiting enzyme acetyl cholinesterase (AChE), preventing the breakdown of acetylcholine (ACh). This increases ACh levels in the brain, enhancing cholinergic transmission and improving cognitive function and memory.	Hyperkinetic disorder	10
		Autism	
		Down syndrome	
		Neurotrauma	11
		Stroke	
		Mixed dementia	12
Galantamine	Galantamine works by inhibiting enzyme acetyl cholinesterase (AChE), increasing acetylcholine (ACh) levels in the brain. It also stimulates nicotinic receptors, enhancing cholinergic transmission and improving cognitive function and memory.	Inhibiting Acetyl cholinesterase (AChE) Increasing Acetylcholine (ACh) levels	13
			14
		Stimulating Nicotinic Receptors	15
		Enhancing Cholinergic Transmission	16
Rivastigmine	Rivastigmine works by inhibiting AChE and BuChE, increasing acetylcholine levels, and enhancing cholinergic transmission. This improves cognitive function, memory.	Down syndrome	17
		Attention Deficit Hyperactivity Disorder (ADHD)	18
		Autism spectrum disorder	

2.1. Conventional approaches for the diagnosis of AD

2.1.1. Health evaluation and profile

Primary assessment tool for AD involves looking at the patient's medical profile and their clinical condition. Healthcare professionals undertake extensive interviews with patients and caregivers to find out health concerns, medical profile, and intellectual impairment. They evaluate a variety of things, such as functional and behavioural limitations and alterations to thinking, memory, language, and ability to solve problems.[21] Standardized tools, such as the cognitive assessment tool or the Montreal Cognitive Assessment (MoCA), may applied by physicians during the clinical evaluation to assess cognitive function and test for dementia. These tests evaluate a patient's language, attention, memory, and spatial awareness to figure out how mentally able they are. Medical record documentation, prescribed drug use, and past illness and surgery of dementia are all collected during the medical background exam.[22]

2.1.2 Brain imaging tequnique

Advanced neuroimaging techniques, including fMRI, facilitate the Clinical management and treatment of AD by visualizing brain changes, detecting amyloid plaques, and monitoring treatment efficacy. FMRI measures neural activity indirectly, assessing changes in blood flow and oxygenation.[23] It helps study brain function during tasks or rest, revealing large-scale brain networks. Techniques like fluoro-deoxy-d-glucose (FDG)-PET complement fMRI, providing insights into synaptic activity and potential AD markers.[24]

2.1.3Cognitive Assessments

Cognitive Assessment are crucial for diagnosing AD and measuring cognitive dysfunction, helping identify specific impairments and track progress over time.[25] Subscale on thinking skills of the AD evaluation Scale (ADAS-Cog) is a comprehensive neuropsychological instrument specifically designed AD clinical trials evaluate interventions across broad cognitive impairment that include cognitive control , decision making abilities.[26] Through patient interviews, the CDR scale evaluates cognitive and functional status, providing a standardized rating system across several key categories across multiple categories, utilizing interviews with patients and informants to assign a score of 0-5 indicative of cognitive impairment severity. These

instruments facilitate the quantification of cognitive decline and dementia severity.[27]

2.1.4 Physical exam and diagnosis test

1. Enquire about drinking alcohol, nutrition, and diet.
2. Check every single drug.
3. Examine blood pressure, temp and pulse.
4. Give attention to the lungs and heart.
5. Implement additional measures to prevent general health decline and mitigate potential risks associated with cognitive impairment.[28]

A health evaluation and diagnostic test help identify health issues that may cause dementia-like sings. These issues, such as depression, sleep, and vitamin deficiencies, can often be treated and reversed. If the diagnosis is Alzheimer's or another dementia, join our online community ALZ Connected for support and connection with others who understand what you're going through.[29]

2.1.5 Neurological examination

The medical professional will attentively monitor the individual throughout the neurological examination to look for problems that might suggest neurological conditions other than Alzheimer's.[30]The doctor will investigate for evidence of brain tumors, dementia, brain stroke, accumulation of serum in the cerebral cortex, and Parkinson's diseases cause difficulties brain function.

The doctor will conduct a neurological exam to assess:

1. Reflexes
2. Coordination and balance
3. Muscle tone and strength
4. Eye movement
5. Speech and language.[31]

2.1.6 Sensation and feeling

Additionally, brain imaging studies like CT or MRI scans may be ordered. If the initial evaluation rules out Alzheimer's or other dementias, but symptoms persist or worsen, further testing or a second medical opinion may be necessary to determine the underlying cause.[32]

2.1.7 Simple urine test for AD

Researchers discovered a link between AD and elevated urinary acetic acid levels, a by-product of formaldehyde. This study revealed that Alzheimer's patient show elevated level of formic acid individual in early stages exhibit distinct differences compare to healthy individuals.[33]The findings suggest that formic acid has been identified as the potential biomarker for early detection of AD , potentially enabling timely interventions and improved disease management.

Test -Measured urinary formic acid in Alzheimer's patients and healthy individuals

1. High urinary formic acid levels in Alzheimer's patients.
2. Significant correlation between cognitive deterioration and urine formic acid.
3. Better disease staging accuracy when combined with blood tests. Urinary acetic acid may be a useful biomarker for immediately Alzheimer's detection.[34]

2.1.8 Biomarkers in CSF: A Promising tool for Alzheimer's early detection

Recent advancements in AD biomarker studies have transformed diagnosis. Neuroimaging and biochemical analysis of cerebrospinal fluid (CSF), plasma, and urine have identified potential markers. CSF, being in directly interfacing with the brain, offers the most insight.[35] Three CSF biomarkers - Aβ42, total-tau, and phosphorylated-tau - show high prospective for identification. Additional biomarkers, including inflammation and reactive oxygen species indicators and urine-based markers, provide valuable information on disease progression.[36] However, no single biomarker can definitively diagnose AD; monitoring multiple markers simultaneously is recommended.[37]

Cerebrospinal Fluid (CSF) covering the brain, providing protection and cushioning. Despite the invasive and potentially painful process of obtaining CSF through lumbar puncture, it remains the most informative fluid for detecting neurodegenerative disease biomarkers.[38] CSF's direct interaction with the brain makes it an ideal source for tracking brain-specific activities and disease progression. Proteins and metabolites in CSF can serve as diagnostic marker for AD and neurological disorder.[39]

In the earlier stages of AD, including condition like mild cognitive impairment (MCI), CSF biomarkers are particularly valuable for diagnosis. Two key biomarkers, tau and amyloid beta (Aβ), are closely linked to AD's hallmark lesions: amyloid plaques and neurofibrillary tangles. These biomarkers will be discussed in detail in the next section.[40]

2.1.9 Generative model teqnique for detection for AD

Convolutional Neural Networks (CNN) and Generative Adversarial Networks (GAN) to optimize the classification of MRI data for early (AD) detection. The novel method involves data annotation, GAN-based data enhancement techniques, and CNN-based feature extraction and classification. The approach aims to enhance image quality, detect artifacts, and improve diagnostic accuracy, ultimately contributing to the medical field and enabling early detection of AD.[41] **Figure 1** represents the AD detection pipeline using GAN and CNN.

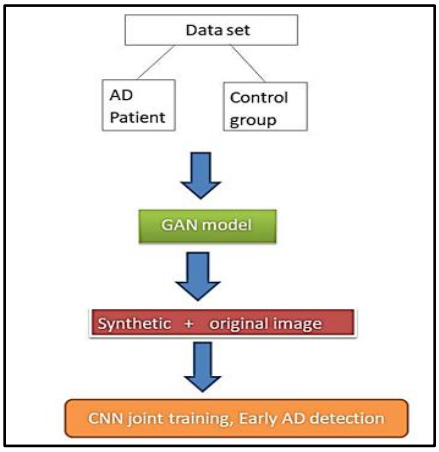

Figure 1: AD detection pipeline using GAN and CNN

3. Novel interventions in Alzheimer's

There is a pressing need for novel interventions in AD due to limited treatment options, increasing prevalence, and lack of disease-modifying therapies. The complexity of the disease, involving multiple pathological mechanisms, requires a comprehensive treatment strategy. Patients and caregivers face significant unmet medical needs, including managing symptoms and slowing disease progression.

3.1 Steam cell therapy

Animal models of AD are being utilize to evaluate the effectiveness of the cells and compounds. These include microRNAs, cytokines, chemical inhibitors, and exosomes. Stem cell transplantation has shown promise, improving synaptic connections and cognitive function. These stem cells can transform into brain cells, potentially repairing damaged neural circuits and promoting new brain cell growth Stem cells can be categorized into three types based on their tissue source.[42]

1. Autologous (self-derived)
2. Allogenic (donor-derived)
3. Induced Pluripotent Stem Cells (iPSCs)

Stem cell originated from various tissue including embryonic, bone marrow, placental amniotic fluid, menstrual blood and dental plug.[43]Below table describe the type of stem cell which can use in treatment of AD.

Table 2: Types of stem cell

S. No	Commonly used stem cell
1	Human Umbilical Cord Blood-derived Mesenchymal Stem Cells (hUCB-MSCs)
2	Bone Marrow-derived Mesenchymal Stem Cells (BM-MSCs)
3	Brain-derived Neural Stem Cells (NSCs)
4	Induced pluripotent stem cell
5	Embryonic Stem Cells (ESCs)[44]

3.1.1 Neural stem cells (NSCs)

Transplantation helps replace lost neurons and promote neurogenesis in AD. Transplanted NSCs directly compensate for damaged tissue and indirectly release beneficial cytokines. Preconditioning NSCs to express growth factors or enzymes enhances their effectiveness, improving cognitive function and reducing protein build-up. However, a potential limitation is the risk of NSCs transforming into non-neuronal glial cells.[45]

3.1.2 Embryonic stem cells (ESCs)

Have shown promise in treating AD. Transplanted ESC-derived neural progenitor cells can:

1. Transform into cholinergic cells, enhancing AD like spatial memory impairment observed in rat model Generate cholinergic neurons, promoting synapse formation in mouse hippocampal slices
2. Differentiate into GABAergic and cholinergic neurons, enhancing spatial memory and learning in mice Healing cognitive impairment in rat affected by radiations.[46]

However, ESC transplantation faces challenges:

1. Uncontrolled cell growth and tumorigenesis
2. Ethical concerns
3. Immunogenic limitations.[47]

3.1.3 Bone marrow-derived mesenchyme stem cells (BM-MSCs)

Are exuberantly researched for Alzheimer's management because of their accessibility and versatility. The mechanism of BM –MSC_s in AD is describe below in **Figure 2**

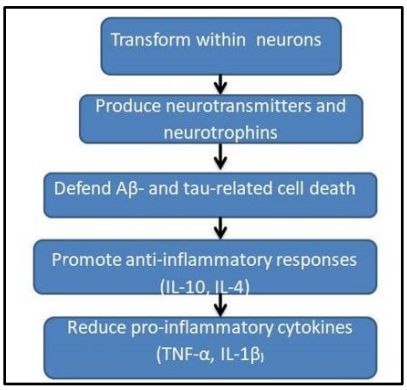

Figure 2: Mechanism of BM- MSC_S in AD

Intravenous BM-MSC administration improves cognitive function, spatial learning, and memory. This approach is less invasive and intracranial injection has advantage. However, potential issues include: Infiltration into multiple organs, Risk of thrombosis during therapy.[48]

3.1.4 Human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSCs)

Show promise in Alzheimer's treatment. They offer non-permanent collection, minimal immunogenicity, and high differentiation potential. Studies with in animal models and phase I/IIa clinical trials demonstrate safety and efficacy. HUCB-MSCs secrete beneficial molecules, inhibiting tau phosphorylation, removing amyloid-β plaques, promoting neurogenesis, and rescuing synaptic density. These effects reduce Aβ-dependent pathology and improve cognitive function in Alzheimer's models.[49]

3.1.5 Induced pluripotent stem cells (iPSCs)

It offers a promising Alzheimer's treatment. Generated from patients' cells, iPSCs provide personalized therapy. They reduce disease pathologies, improve neurological function, and ameliorate memory impairment. Preclinical models demonstrate long-term survival. Clinical trial NCT00874783 evaluates iPSC-derived cells in familial Alzheimer's patients. However, neurons from Alzheimer's patients show abnormal protein levels and increased inflammation susceptibility, limiting iPSC benefits.[50]

3.1.6 MOA of stem cell therapy

Cell replacement therapy using stem cell for AD replaces damaged brain cells, protects existing ones, reduces inflammation, and promotes repair. Key pathways involve cell growth, inflammation regulation, and neuroprotection. Benefits include improved cognitive function, enhanced brain repair, and reduced inflammation. However, challenges remain, including cell survival, tumor risk, and immune rejection. Neural Stem Cells (NSCs), Mesenchymal Stem Cells (MSCs), and Induced Pluripotent Stem Cells (iPSCs) are being researched for therapeutic potential.[51]

3.1.7 Example

Researchers have been exploring the investigational stem cell treatments for AD. One of the research is highlight adult neurogenesis, which is the process by which new neurons are formed in the adult brain. This process has been shown to decline with age, but researchers believe that stimulating neurogenesis could help to improve symptoms of AD.[52] Several investigation have examined the therapeutic effect of stem cell on neurogenesis and cognitive improvement in AD. For example, one study used mesenchyme stem cells while stem cell therphy show promices to enhances neurogenesis in cognitive function of mouse model of Alzheimer. While these findings are promising, more research is needed to fully understand the potential of stem cell therapy for AD.[53]

3.2 Immunotherapy

A particular strategy that shows promise for halting or postponing the development of AD is immunology Work is being conducted on several forms of A peptide therapy for AD using strategies like tau pathology and mAbs which target Aβ peptide.[54]

3.2.1 Antibody therapies for AD

The process by which of Aβ plaque reduction for all mAbs is believed to involve microglia activation through fibrillar Aβ phagocytosis and subsequently endosomal/lysosomal system harm. Each authorized monoclonal antibodies (mAb) concentrates on one particular category of Aβ species. Aducanumab targets a wide variety of Aβ species, showing a stronger preference for species with a increases molecular weight.[55] The extent to which microglia eliminate only the species identified by the mAb is unknown, as is the possibility that active microglia can phagocytize both labelled and unlabelled protein clumps, such as tau and Aβ. Research indicates that monoclonal antibodies (mAbs) that target oligomeric Aβ, like aducanumab, may have a therapeutic effect by preventing Aβ aggregation.[56] Mechanism of Antibody in AD is in **Figure 3**fig. no. 3

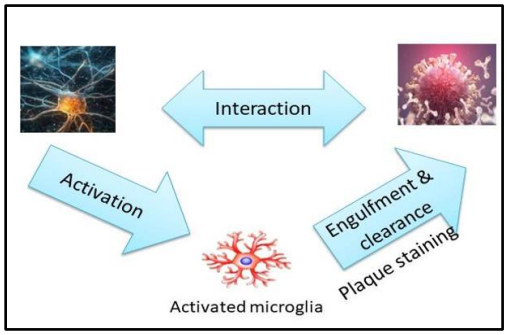

Figure 3: Mechanism of action of antibody therapy in AD

3.2.2 Active vaccinations against AD

Currently under consideration for possible active vaccine therapy for AD are several targets There have been reports of about 140 (85%) immunization treatments versus Aβ deposition and 25 (15%) against tau, but no AD vaccine has received FDA approval.[57] The creation of an Aβ42 trimmer DNA vaccine could offer a way of avoiding AD or slow down the disease's progression. Targeting the amino acid N-terminal epitope of the Aβ peptide, the DNA vaccine AV-1959D is effective in AD mouse models and immunogenic in rabbits, non-human primates, and mice The vaccination in mice did not have any negative short- or long-term effects, as determined by repeated dose safety studies. Over time, mice given the vaccination showed increased levels of anti-Aβ antibodies Tau phosphorylation can be significantly decreased by early immunization with a recombinant Aβ3–10-keyhole limpet hemocyanin vaccine; however, such antibodies are not clinically effective when given to let.[58]

3.2.3.Example

One example of immunotherapy to treat AD is Bapineuzumab, aims to eliminate excess beta amyloid protein in Alzheimer affected brain. In clinical trials,

Bapineuzumab has shown promise in exhibits potential in lowering beta amyloid level with mild to moderate AD.[59]

3.3 Gene therapy

Gene therapy facilitates the intracellular delivery of genetic material, thereby mitigating mutated gene expression and eliciting therapeutic effects.[60] Vectors, including viral (adenoviral, retroviral, lentiviral) and non-viral (cationic lipid, polymeric, ceramic-based nanomaterial) systems, enable targeted gene expression.[61] Vector-Mediated Gene Transfer .Viral vectors, modified to preclude replication, facilitate efficient gene transfer. However, immunogenicity and toxicity concerns necessitate the development of non-viral alternatives.[62]

3.3.1. AAV2-BDNF treatment

The nervous system of the body includes a protein termed BDNF, or abrineurin, which is generated by the BDNF gene. This protein that belongs to the growth factor family performs an essential part in the growth, differentiation, and maintenance of new cells and synapses, ultimately ensuring the survival of neurons.[63] The entorhinal the cortex, a crucial memory-related part of the brain that is generally damaged by Alzheimer's early in the disease progression, is where BDNF is generated. Patients who have AD have lower levels of BDN.[64]

3.3.2 Example

One example of gene therapy for the treatment of AD utilizes an adenosine virus vector to introduce gene encoding neurotropic factor and beta amyloid degradation enzymes. This approach, known as CERE-110, has shown promise in reducing beta-amyloid levels and improving cognitive function.[65]

3.4. Nanotechnology

Nanotechnology offers promising solutions for neurological diseases like Alzheimer's and Parkinson's, through innovative peptide nanofibers, drug delivery systems, and neuron communication bridges, despite challenges in toxicity, visualization, and lifespan.[66]
Theranostics, a multifunctional Nano medicine platform, synergistically integrates diagnostic and therapeutic modalities to address neurodegenerative disorders.[67]
Nano medicine Advancements.

1. Targeted pharmacodelivery via ligand-conjugated nanoparticles.
2. Magnetic nanoparticle-mediated tumour volumetric reduction.
3. Antiretroviral therapy enhancement via nanoparticles.[68]

Emerging Nano therapeutics

1. Liposome-encapsulated haemoglobin: Enhanced permeability in ischemic territories for stroke monitoring.[69-70]
2. Cerium oxide nanoparticles (CeO2 NPs): ROS scavenging and neuroprotection against neuropathic injury.

Mechanistic Insights
Theranostics enables

1. Personalized medicine through precision diagnostics.[71-72]
2. Optimized pharmacokinetics and pharmacodynamics.
3. Enhanced therapeutic efficacy and reduced toxicity.[73]

3.4.1 Peptide Nanofiber in neurology

Self-assembling peptides and amphiphilic molecules enable neural regeneration and repair through dynamic nanofiber meshes. These biocompatible matrices, responsive to physiological ionic environments, promote axonal growth and restore functional vision in optic tract injury models.[74] Incorporating RGD and IKVAV sequences, peptide frameworks enhance cell attachment, differentiation, and synapse formation.[75] Carbon-based Nano material's further facilitate neuronal growth, reduce astrocyte adhesion, and offer potential as implantable neuroelectrical bridges. These advances hold promise for translational applications in regenerative medicine, targeted drug delivery, tissue engineering, and neuroprosthetic interfaces.[76]

3.4.2. Example

One example of nanotechnology to treat AD is the use of nanoparticles to deliver a drug called rivastigmine, which is used to treat cognitive symptoms of Alzheimer's. Researchers have developed nanoparticles made of poly (lactic-co-glycolic acid) (PLGA) that can cross the blood-brain barrier and deliver rivastigmine directly to the brain, improving its efficacy and reducing side effects.[76]

3.5. Therapeutic compound under investigation

3.5.1. MitoQ

A compound that may reduce Aβ peptide levels, oxidative stress, and synaptic loss. It may also improve cognition in transgenic mice.

3.5.2 TPI 287

It was initially identified that a microtubule-stabilizing material reduced the quantity of hyper phosphorylated tau in the cerebral cortex. However, severe hypersensitivity reactions AD patients throughout clinical trials.

3.5.3. Davenutide

An 8-amino acid peptide that may maintain microtubulesstability and reject hyper phosphorylated tau levels. In a phase I trial, it was well tolerated, but it didn't show a statistically significant difference in cognitive memory scores.

3.5.4. Safflower yellow

A compound that may improve scopolamine-induced memory impairment and attenuate Aβ1–42 induced memory impairment in rats.

3.5.6. Oxaloacetate

An intermediate of the Krebs cycle and gluconeogenesis that may inhibit Aβ-mediated synaptic activity in the hippocampus

Other therapeutic approaches under investigation include: Nerve growth factor (NGF) stimulation, Gamma amino butyric acid (GABA) receptor modulators, and Serotonin reuptake and somatisation secretion stimulants.

4. Discussion

Recent advances in AD research have led to the emergence of novel interventions, including immunotherapies targeting beta-amyloid and tau proteins, gene therapies aimed at modifying disease-causing genes, and lifestyle interventions focusing on diet, exercise, and cognitive training. Additionally, emerging technologies such as stem cell therapy, nanotechnology, and ontogenetic are being explored for their potential in treating Alzheimer's. These innovative approaches offer new hope for improving symptoms, slowing disease progression, and potentially preventing Alzheimer's, and ongoing research aims to translate these findings into effective treatments for this devastating disease**.**

5. Conclusion

AD remains a terrible neurodegenerative condition with notable unmet medical needs. Fortunately, recent advances in nanotechnology, peptide engineering, and neurodegenerative therapies offer promising novel interventions. Self-assembling peptide nanofibers, targeted drug delivery systems, and neuron-communication bridges demonstrate potential in preclinical models. Furthermore, emerging strategies such as immunotherapy, gene editing, and stem cell therapy show encouraging results.

6. Source of Funding

None.

7. Conflict of Interest

None.

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