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Novel Therapeutic for Alzheimer's Disease and **Dementia**

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Abstract : Currently untreatable, Alzheimer's disease (AD) is a neurological illness that progresses over time. This article examines the difficulties and developments in creating potent AD therapies. Targeting the fundamental causes of the disease is challenging due to its complicated pathology and blood-brain barrier obstruction. Notwithstanding these obstacles, scientists are looking for promising treatment options. These include utilizing neuroprotective drugs, lowering neuroinflammation, focusing on tau and amyloid beta protein, and utilizing regenerative medicine techniques like gene therapy. For the purpose of identifying the best therapeutic targets and assessing their efficacy, trustworthy biomarkers and sound clinical trial design are essential. Additional difficulties are brought on by the intrinsic variability of AD and the difficulties involved in patient selection. There is potential for resolving these problems with precision medicine and enhanced diagnostics. sustained funding and cooperation among academic institutions, Government and business play a crucial role in advancing development. Through putting research first, encouraging collaboration, and making sure there is enough money, we can create efficient therapies and eventually find a solution for AD.

***IndexTerms* - Alzheimer disease, dementia, Therapeutic target, therapeutic approach, clinical trials , safety and efficacy**

I. INTRODUCTION

Alzheimer's disease : The progressive neurodegenerative disease known as Alzheimer's disease targets the nerve cells in the brain. This type of dementia is the most prevalent. a generic word for cognitive decline that is severe enough to affect day-to-day functioning, including memory, language, problem-solving, and other cognitive functions.

Symptoms of Alzheimer's disease include:

Symptoms	Description
1.Difficulty with Planning and problem solving:	People with Alzheimer's may find it difficult to plan and follow through with task.
2. confusion with familiar task:	Like driving, managing medication paying bills become difficult.
3.new problem with speaking or writing :	May have difficulty finding the right words.
4.decreased or poor judgement :	Can lead to risky decision.
5. withdrawal from social activities :	Person may withdraw from social activities and hobbies that they once enjoyed .

Table 1 Symptoms of Alzheimer Disease (AD)

Dementia: (smrutibhransh) A condition when a person's memory, cognition, or decision-making abilities are compromised to the point where it becomes difficult to carry out daily tasks. Prevalence: Alzheimer's disease being the most prevalent form. The no. is An estimated 24 million people world wide have dementia with projected to double every 20 years until at least 2040, primarily due to an aging population.

Countries	Age	Gender		Percentage%
		Male	Female	
India	>55years >65 years	Less suceptible	More suceptible	7.4%(8.8 million people live with dementia
America	>65 years :representing 1 in 9 people in this age group (10.7%)	Less suceptible (2 million)	More suceptible (4 Million)	1.79%
China	>65 years old	Less susceptible	More susceptible	30%
Japan	>60 years old	Less susceptible(2.0	More susceptible(3.8%)	3.68%

		%)		
Africa	>60 years old	Slightly less often than women	Slightly more often than men	1.60%
Brazil	>65 years old	Less susceptible(33/ 1000,000)	More susceptible(47/1000,000)	1.45%s

Table 2 Worldwide epidemiology & Age group prevalence under AD & Dementia

Impact : Alzheimer's disease causes the loss of brain cells and the shrinking of the brain. Alzheimer's disease is the most common cause of dementia, characterized by a progressive loss of memory, thinking, behavior, and social skills. These alterations have an impact on how people function.

Unmet medical needs Cognitive performance declines as a result of degenerative illnesses like dementia and Alzheimer's disease. Both conditions currently have no known cure, and many unmet medical requirements exist. The need for efficient therapies that can halt or delay the disease's course is one of the most pressing unmet needs. The majority of available treatments are only able to temporarily relieve symptoms. Additional needs include improved diagnostic instruments. Alzheimer's and dementia diagnoses can be challenging and time-consuming at the moment. Obtaining the necessary care and making future plans for oneself depend on timely and correct diagnosis. Improved support for caregivers is another unmet need. Giving Alzheimer's or dementia patients' care can be extrem . Access to resources such as support groups and respite care is crucial for caregivers. Here are a few particular unmet medical needs related to dementia and Alzheimer's disease:

1.Treatment that slow or stop the progression of the disease.
2.Better diagnostic tools.
3.Better support for caregivers.
4.Treatments for behavioral and psychological symptoms of dementia (BPSD)
5.Treatments for co-occurring medical conditions
6.More effective ways to manage pain
7.Improved communication strategies
8.End-of-life care.

In this paper we reviewed novel therapeutic approaches in 5 categories –

- ✓ Anti amyloid therapy
- ✓ anti-tau therapy
- ✓ anti neuroinflammatory therapy
- ✓ neuro protective agent including N methyl D aspartate (NMDA) receptor modulator,
- ✓ brain stimulation

II. PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE AND DEMENTIA

Alzheimer's disease is the most common form of dementia, affecting millions of people worldwide. Dementia is a term used to describe a decline in cognitive function that results in difficulties with daily life. Even though the exact cause of dementia and Alzheimer's disease is unknown, a number of factors are believed to be linked, including:

Protein misfolding: The buildup of abnormal proteins in the brain is one of the primary characteristics of Alzheimer's disease. The two main proteins under consideration are amyloid-beta and tau. Amyloid-beta forms sticky plaques between nerve cells, while tau forms tangles inside brain cells. These proteins eventually lead to death by obstructing the communication channels of nerve cells. An example of the amyloid beta plaques associated with Alzheimer's illness Turns on Alzheimer's disease is believed to be brought on by the buildup of two abnormal proteins in the brain, tau and amyloid beta, even if the precise etiology of the illness is unknown.

Amyloid beta : Amyloid beta is a sticky protein fragment that aggregates to form plaques between brain cells. By interfering with neural processes, these plaques impair neuronal

Tau: Tau is a protein that frequently helps to preserve the structure of neurons. Alzheimer's disease causes the tau protein to tangle and become abnormal inside neurons. These tangles impair the flow of nutrients and other necessary substances across neurons, ultimately leading to cell death.

Other dementia

Amyloid plaque: Misfolded protein clumps called amyloid plaques develop in the voids left by nerve cells. It is believed that a major contributing factor to Alzheimer's disease is these proteins' aberrant configurations. The brain regions responsible for memory and other cognitive processes are where amyloid plaques initially appear..

Tau angles : The tau angle is located between the two lines that join the points M and G and T and G. Determining the mean and standard deviation of the Tau angle for three skeletal malocclusions was the aim of the current investigation.

Neuroinflammation: Neuroinflammation is characterized by a variety of cellular and molecular alterations in the brain and is defined as the activation of the brain's innate immune system in response to an inflammatory assault. From: Developmental and Reproductive.

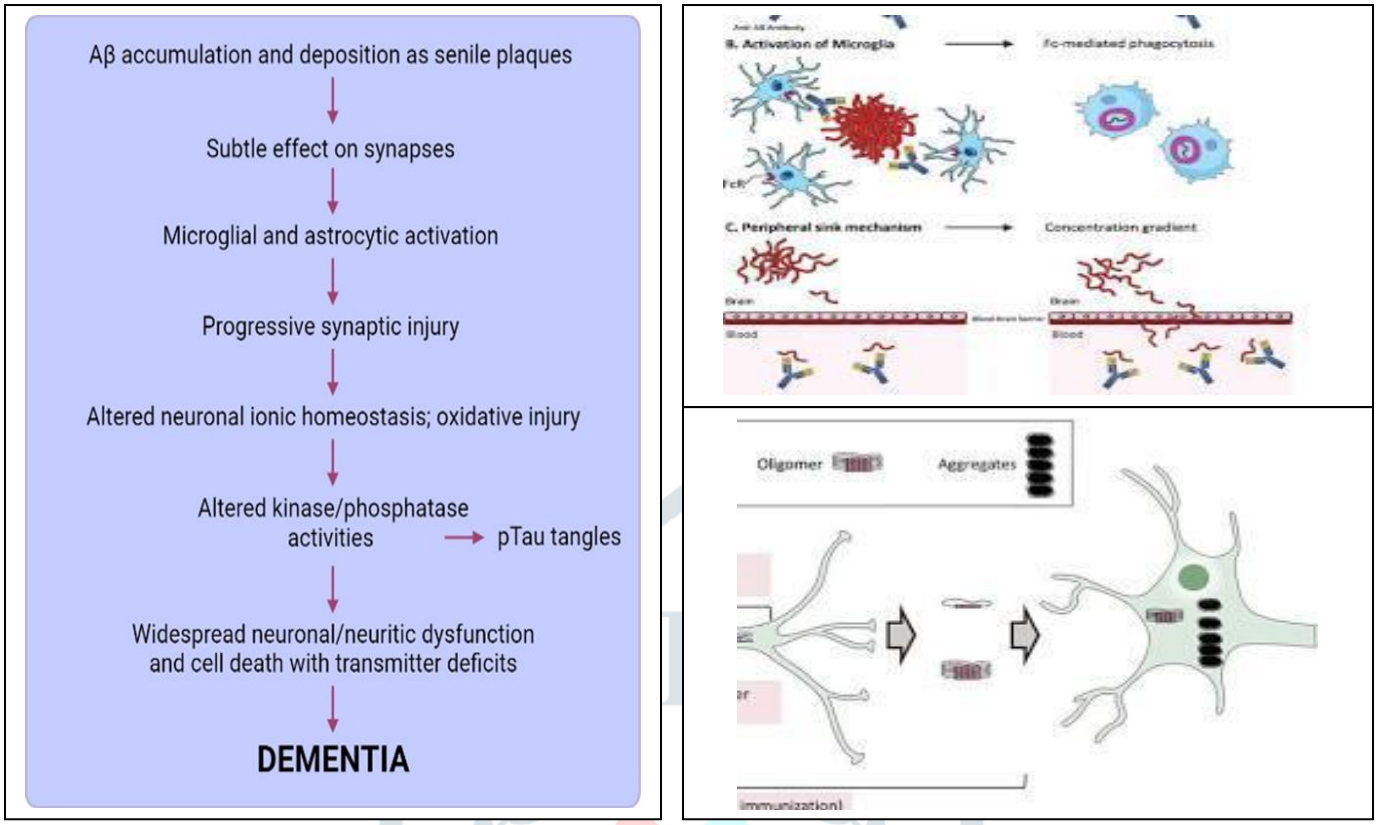

Fig 1 a) Pathogenesis of Dementia b) β- Amyloid Proteins & inactivating antibodies c) Oligomers & forms aggregates of Tau proteins

Toxicologyicine- Although there has been substantial progress in our understanding of Alzheimer's disease (AD), there is still a barrier in turning this knowledge into practical treatments. The following are some major obstacles:

Complexity of the disease: A complicated interaction between protein accumulation, inflammation, and other biological processes causes AD rather than a single cause. It might not be sufficient to focus on just one element.

Blood-brain barrier: The blood-brain barrier, a barrier that protects the brain, is difficult for many prospective medications to get through. Treating the brain directly presents a unique set of difficulties.

Limited understanding of disease progression.: We are not entirely sure of the precise order in which things happened in AD. This makes determining the best time for intervention and assessing the efficacy of treatment challenging.

Modeling the disease: It can be challenging to accurately replicate AD in animal models or cell cultures. This may result in treatments that show promise in the lab but are unsuccessful when tested on humans.

Long development timeline and high costs: Investment in possible treatments, particularly those with a greater failure rate, may be discouraged by the protracted and costly process of developing and testing new medications.

Individual variability: AD can manifest differently in each person. Developing one-size-fits-all treatments might not be effective, requiring personalized approaches.

III. Therapeutic Targets and Strategies:

Alzheimer's disease (AD) is a neurological condition that affects memory, thought, and behavior and results in a progressive loss of cognitive function. Although there isn't a cure for AD at the moment, researchers are looking at a number of novel therapeutic targets and approaches that could be used in the future.

1. Targeting Amyloid Beta (Aβ): Aβ plaques are a characteristic feature of AD. One of the main therapeutic approaches has been to either clean the existing plaques or reduce the formation of Aβ.

2. Anti-amyloid antibodies: One of the hallmarks of AD is the presence of Aβ plaques. Reducing the production of Aβ or cleaning the existing plaques has been one of the key treatment options improvement so far.

3. BACE inhibitors: An important characteristic of AD is the existence of Aβ plaques. One important therapeutic option has been to lower Aβ generation or clear the existing plaques.

4. Targeting Tau Protein: Tangles of tau are another indicator of AD. Inside neurons, these tangles develop and impair neuronal function.

5. Tau aggregation inhibitors: The purpose of these medications is to stop tau proteins from clumping together. Opens in a new window www.frontiersin.org

6. Tau aggregation inhibitors for AD- Tau immunotherapy: Similar to anti-amyloid antibodies, this approach uses antibodies to target and clear tau tangles.

- Neuroinflammation: Chronic inflammation in the brain is increasingly recognized as a key player in AD.

Anti-inflammatory drugs: These drugs aim to reduce inflammation in the brain, potentially slowing disease progression.

Opens in a new window arthritisaustralia.. Antiinflammatory drugs for AD

- **Other Therapeutic Targets:**

1. **Synaptic dysfunction:** Some treatments target neurotransmitters or their receptors in an effort to enhance neuronal transmission.
2. **Neuroprotective agents:** The goal of these medications is to shield neurons against AD-related harm.
3. **Lifestyle and diet interventions:** Dietary and activity changes may assist in reducing risk factors and delaying the onset of disease.
4. **Challenges in Developing Effective Treatments:** The complexity of AD makes it difficult to translate scientific knowledge into practical therapy. Here are a few major obstacles
5. **Blood-brain barrier:** The blood-brain barrier makes it harder to deliver medications to the brain.
6. Limited understanding of disease progression: It's challenging to choose the best time for intervention because we don't fully understand the precise sequence of events in AD.
7. **Accurately modeling the disease:** It's difficult to build trustworthy models of AD in laboratories to evaluate treatments.
8. **Long development timeline and high costs:** The process of creating and evaluating new medications is time-consuming and costly.

- .Neuroprotective agents: One class of medications under investigation as a possible treatment for Alzheimer's disease (AD) is neuroprotective compounds. By a variety of methods, these medications seek to shield neurons from the harm that AD does. Here are a few instances of newly developed neuroprotective treatments for AD
- Acetylcholinesterase (ACHE): Acetylcholine inhibitors are a neurotransmitter crucial for memory and learning, and these medications function by raising their levels. As of right now, glutamine, rivastigmine, and donepezil are authorized AChE inhibitors for AD.

Acetylcholinesterase (AChE) inhibitors for AD

- NMDA receptor antagonists: While overactivation of N-Methyl-D-aspartate (NMDA) receptors can cause neuronal injury, they are important for memory and learning. The NMDA receptor antagonist memantine is licensed for the treatment of moderate-to-severe AD. Opens in a new window www.semanticscholar.org

NMDA receptor antagonists for AD

- Antioxidants: One main cause of AD is oxidative stress. Antioxidant substances may aid in shielding neurons from harm brought on by free radicals. Antioxidant supplementation has showed promise in certain studies; nevertheless, additional study is needed to validate the supplements' effectiveness in treating AD.

Antioxidants for AD

- **Lithium:** Lithium is used to treat bipolar disorder because it has the ability to stabilize mood. According to recent study, it might also have neuroprotective properties and slow the onset of AD. Opens in a new window www.amazon.in

Lithium for AD

- **Natural products:** Numerous natural compounds, including green tea extracts, resveratrol, and curcumin, have demonstrated neuroprotective qualities in pre-clinical research. To find out how well they work to treat AD, more research is necessary.

1. Anti-inflammatory therapies:

Being investigated as anti-inflammatory therapies for AD: An innovative new method of treating Alzheimer's disease (AD) is anti-inflammatory therapy. More and more research is pointing to the brain's chronic inflammation as a major contributor to AD. The goal of these treatments is to lessen brain inflammation, which may delay the course of the illness. Numerous mechanisms and targets exist.

2. Microglial modulation:

In the brain, immune cells called microglia are involved in the removal of waste and injured cells. Microglia in AD have the potential to become persistently active and to promote inflammation. Medication that can regulate microglial activation and encourage a more neuroprotective phenotype is being studied by researchers..

Microglial modulation for AD

3. Cytokine inhibition:

Signaling molecules that are part of the immune response are called cytokines. A few different cytokines contribute to neuroinflammation. For the treatment of AD, medications that specifically target pro-inflammatory cytokines are being investigated.

- **Cytokine inhibition for AD**

1. Infliximab and other TNF-alpha inhibitors:

One cytokine that encourages inflammation is TNF-alpha. TNF-alpha inhibitors are being studied for their potential to lessen neuroinflammation in AD. TNF-alpha inhibitors, including infliximab, are used to treat autoimmune illnesses.

2. Regenerative medicines: Although they are still in their infancy, regenerative medicine treatments for Alzheimer's disease (AD) show promise for the future. In contrast to conventional drugs that treat symptoms, regenerative medicine seeks to replace or repair damaged brain tissues or cells. The following are a few possible uses of regenerative medicine for AD.

3. Stem cell therapy: Stem cells can differentiate into a variety of cell types. In the brains of AD patients, researchers are investigating the use of stem cells to replace damaged neurons or to encourage the creation of new ones.

4. Biomarkers and Clinical Trial Design: Accurate biomarkers are essential for identifying the appropriate targets and tracking the effectiveness of treatment. A strong clinical trial design guarantees that treatments are evaluated in the right populations using the right outcome metrics.

5. Overcoming Patient Selection and Heterogeneity: Multimodal medicines and precision medicine offer potential solutions to the heterogeneity of the disease. • More advanced patient selection techniques and better diagnostics are essential to the success of clinical trials. Continued Investment and Collaboration: It will take consistent funding from the government, business, and academic sectors to defeat AD. Promoting international cooperation makes progress faster and makes use of the brightest minds

on the planet. Research on AD has a promising future. It is possible to create efficient therapies and eventually discover a cure for these terrible illnesses if we have an unshakeable dedication, keep making investments, and collaborate with one another.

IV. CONCLUSION:

In conclusion, the development of novel therapeutics for Alzheimer's disease and dementia offers a glimmer of hope for millions struggling with this debilitating condition. While the path forward necessitates further research to refine promising avenues and navigate potential challenges, the multifaceted approach targeting amyloid plaques, tau tangles, neuroinflammation, and neuroprotection holds immense promise for not only managing symptoms but potentially modifying disease progression. This exploration of novel therapies paves the way for a future where Alzheimer's and dementia are no longer inevitable consequences of aging.

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