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Alzheimer's Disease: A Systematic Review of Novel Therapies and Vaccines

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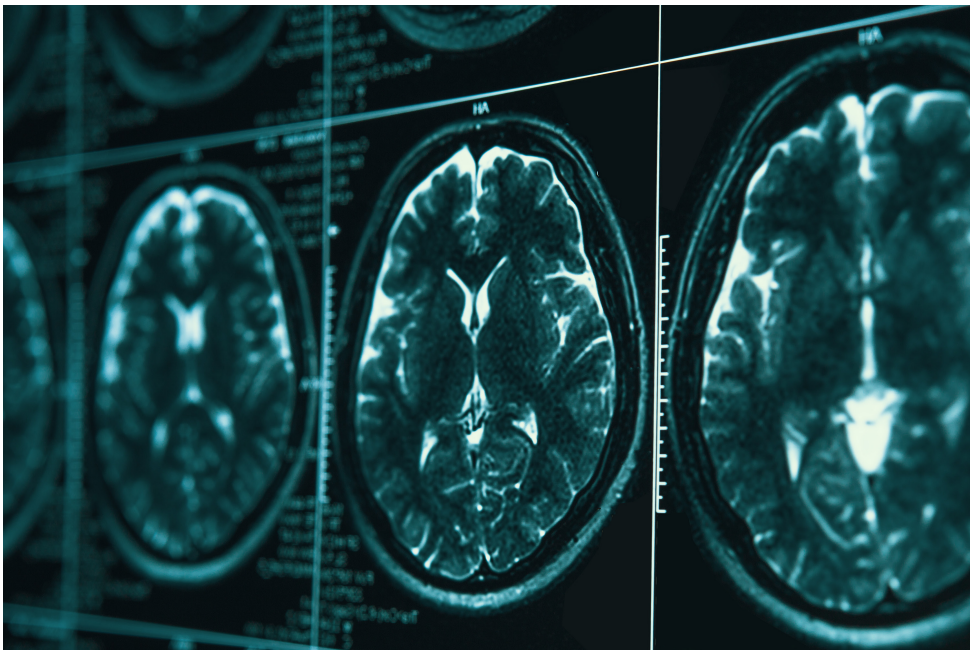

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Abstract

Alzheimer's disease (AD) is a neurodegenerative disorder and the fifth leading cause of death in the United States as of 2021. Current FDA-approved therapies, including cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and memantine, provide symptomatic relief but do not modify disease progression. The anti-amyloid monoclonal antibodies, lecanemab and donanemab, modestly slow cognitive and functional decline in early-stage AD. This review provides a comprehensive overview of the mechanisms underlying AD and research efforts aimed at understanding and treating the disease. Additionally, this paper explores ongoing clinical trials investigating novel treatments such as immunotherapies and small-molecular inhibitors targeting AD biomarkers. Regenerative medicine approaches, including gene and stem cell therapies, show promise in these trials. By understanding current research and future potential for these trials, this review aims to explore strategies for managing and potentially curing AD.

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1. Introduction

Alzheimer's disease is very prevalent in the US, as 7 million Americans currently live with this neurodegenerative disease. By 2050, this number is projected to rise to nearly 13 million.[1] As of 2021, Alzheimer's is the 5th leading cause of death among people aged 65 and older.[1] Furthermore, the likelihood of developing AD after the age of 45 is one out of every ten men and one out of every five women.[2] There is a substantial need for improved treatment and medication because, following the initial diagnosis, Alzheimer's patients live between 3–11 years, and 42% of long-term AD patients go into hospice.[2]

1.1 Alzheimer's Stages

Alzheimer's disease has three general stages depending on symptom progression.[3] The earliest quantifiable stage presents mild symptoms, including difficulty remembering the names of new people, short-term reading memory loss, misplacing items, difficulty planning, and difficulty organizing objects.[3] As AD progresses to the middle stage, the patient begins to present many of the disease's moderate symptoms. This stage lasts the longest and includes indications such as forgetting personal history, mood swings, spatial/temporal disorientation, trouble controlling bladder/bowels, changes in sleep patterns, and getting lost.[3] This stage typically necessitates greater assistance from caregivers. Finally, late-stage AD is the most severe and requires continuous assistance.[3] Patients experience loose awareness of recent experiences, difficulty communicating, and are vulnerable to infections like pneumonia.[3] Due to the severity of this stage, families will typically hire at-home caretakers or send their loved ones to a memory care facility for professional assistance.[3]

Other researched stages include preclinical AD, but this stage has only been recognized in research settings.[4] Since it is identified by core biomarkers, preclinical AD can last for years or decades, as identified by new imaging technologies.[4]

2. Physiological Markers and Background of Alzheimer's Disease

2.1 Physiological Overview

Alzheimer's disease is a systemic disease that dysregulates the peripheral and central immune parts of the brain.[5] Four major neurophysiological changes include amyloid plaques, neurofibrillary tangles, inflammation, and brain atrophy.[6]

Amyloid plaques disrupt cell-to-cell communication, leading to inflammation and neuron damage.[7] Neurofibrillary tangles are formed due to the abnormal aggregation of tau proteins, which disrupts neuron function and can lead to cell death.[8] In Alzheimer's disease, the brain overworks its immune response in an attempt to counteract the amyloid plaque and abnormal tau proteins.[9] This leads to chronic inflammation, which accelerates the progression/symptoms of AD.[9] Subsequent or simultaneous cell death and damage result in overall brain atrophy.[9]

2.2 B-amyloid Plaques

B-amyloid-42 is a 42-amino-acid peptide suspected of causing dementia and related symptoms in Alzheimer's patients.[10] This protein is formed by the breakdown of the amyloid precursor protein (APP) when an enzyme B-secretase is acted upon.[10] Secretase enzymes are a type of protease (enzymes that break down proteins) that are targeted to cleave transmembrane proteins and secrete them off of the cell membrane.[10]

B-Amyloid-42 is most often broken down by the neprilysin enzyme.[10] In wild-type patients, B-Amyloid-42 exists in its monomeric form and can be broken down easily.[10] In Alzheimer's patients, these monomers aggregate into dimers and eventually large, clustered plaques which are unable to be effectively broken down by such enzymes.[10] Notably, neprilysin activity is reduced in Alzheimer's which indicates less breakdown of B-Amyloid-42, resulting in the formation of such plaques.[10]

One specific study that emphasizes the importance of this protein was conducted by Amouri et al. in which human neprilysin (hNEP) was transferred to mouse models to evaluate its therapeutic potential in Alzheimer's disease.[10] Transgenic mice with overexpressed hNEP protein levels led to a reduced presence of amyloid plaques and inflammation.[10] Perhaps most notably, such an overexpression resulted in a reduction of memory impairment by approximately 50%.[10]

The downregulation of neprilysin is due to a multitude of factors, but one specific study conducted by Chen Liu et al. found that apolipoprotein E alleles, which assist with lipid transport in the brain, are the "main genetic determinants of Alzheimer disease risk." [11] The most common allele type is ε3 but individuals carrying ε4 are at an increased risk for Alzheimer's whereas individuals with ε2 are at a lower risk for Alzheimer's. The ε2 protective allele has a frequency of 8.4%, the common ε3 allele is at a frequency of 77.9% and the ε4 risk allele is at a 13.7% global frequency.[12] Notably, ε4 is increased to 40% frequency in patients with AD.[12]

This implies a genetic link to the apolipoprotein E allele function, thereby leading to a decrease of neprilysin, resulting in an increase of beta-amyloid-42 and a greater likelihood and physiology of plaques.[12]

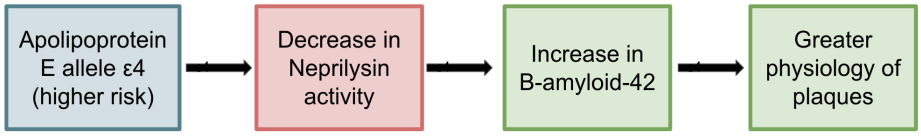

Figure 1: APOE ε4-Mediated Pathway to β-Amyloid Plaque Formation

Flowchart depicting the downstream effects of the APOE ε4 risk allele on neprilysin activity, β-amyloid-42 accumulation, and plaque formation.

2.3 Neurofibrillary Tangles

Current research has observed fundamental malfunctions in neural synapses due to AD, and this interferes with the dynamic nature of the neuronal network.[13] Neurofibrillary tangles (NFTs) are abnormal intracellular aggregates of unusually phosphorylated tau proteins.[13] Tau is a protein

associated with microtubules, and neurons with NFTs exhibit fewer cytoskeletal microtubules and tubulin-associated proteins.[13] This extreme phosphorylation results in an abnormal tau localization from an axonal to a somatodendritic location, which often results in the aforementioned microtubule deregulation and tau aggregation.[13]

NFTs are microscopic lesions, and pathologists cannot use morphological stains to visualize them, so silver impregnation staining techniques or thioflavin S are typically employed.[14] Furthermore, there are immunohistochemical approaches that target abnormally phosphorylated tau that can be performed in specialized neuropathological laboratories.[14] As a matter of fact, Alois Alzheimer, who later became the namesake for this disease, described the prevalence of fibrous inclusions that represented neurofibrillary tangles and represented a hallmark neuropathological feature of this disease.[14]

Recent studies claim that the extent and distribution of NFTs correlate with the degree of dementia and the extent of the illness experienced by the patient.[14] Due to this correlation, it can be reasonably assumed that NFTs have some sort of physiological effect on the brain's ability to function.

2.4 Chronic Inflammation

As the presence of B-amyloid plaques and neurofibrillary tangles increases, chronic inflammation can also be seen due to the overworking of the immune system.[15]

Chronic inflammation seen in neurodegenerative diseases such as Alzheimer's may be due to glial cell malfunction.[15] Microglia play a role in the brain's immune system by removing toxic pathogens or debris.[15] In Alzheimer's disease, however, there is evidence that such immune cells can become overactivated and their downstream chemical processes can result in neuroinflammation.[15] Microglia also play a crucial role in synaptic pruning by degrading unnecessary synapses, and hyperactivity of these cells can also play a role in the brain atrophy mentioned previously.[15]

Triggering receptor expressed on myeloid cells 2 (TREM2) is expressed on microglia and is a risk factor for Alzheimer's.[16] TREM2 mutations have been

found to increase susceptibility to the disease.[16] One specific mutation is the R47H variant where an arginine residue is replaced by a histidine amino acid instead, resulting in an inability to clear tau and B-amyloid in early-stage Alzheimer's disease.[16]

2.5 Brain Atrophy

The loss of connections between neuronal networks and a high volume of cell death results in overall brain atrophy.[17] Greater brain atrophy is correlated with higher levels of cognitive impairment.[17] Brain atrophy is not reversible.[17] However, researchers are analyzing potential treatments to slow the progression of this prognostic factor.

Smith et al. examined the link between vitamin B intake and brain atrophy. Vitamin B supplements have been found to lower homocysteine levels.[17]

For context, high homocysteine levels are hypothesized to cause brain atrophy due to increased oxidative stress and DNA damage.[18] Through a randomized controlled trial, the researchers treated an experimental group with vitamin B tablets and a control group with a placebo.[17] The vitamin B supplement group had a 22.5% decrease in homocysteine levels and, over 24 months, the rate of neural shrinkage in the patient population who received the supplements was 30% less than the placebo group.[17] More specifically, vitamins B6, B9 and B12 have been shown to reduce cognitive decline and atrophy rates.[17]

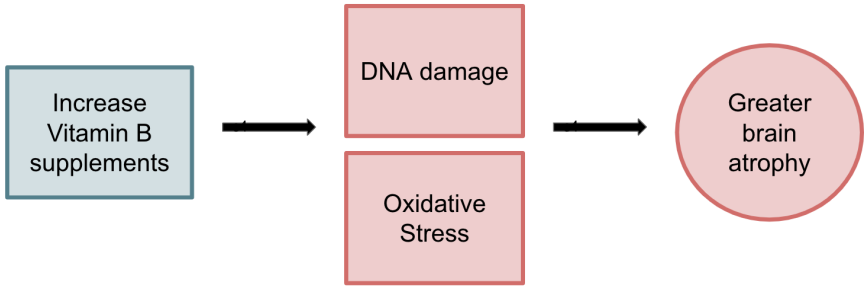

Figure 2: Homocysteine-Induced Brain Atrophy Mechanism

Flowchart illustrating the connection between homocysteine levels and brain atrophy as context for the Smith et al. paper

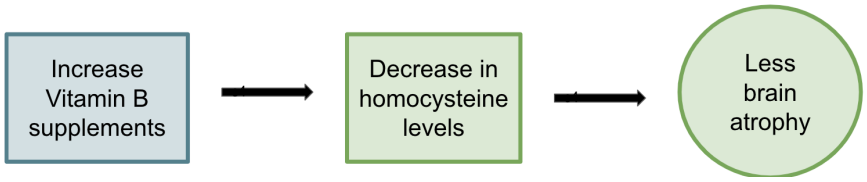

Figure 3: Vitamin B Supplementation and Reduced Brain Atrophy

Flowchart summarizing the findings of Smith et al. on the beneficial effects of vitamin B supplementation.

3. Diagnosing Alzheimer's

3.1 Overview

The modern diagnosis of AD is primarily based on a biological evaluation of the patient's status rather than an evaluation of presenting clinical symptoms due to its unique neuropathologic markers.[19] Because of this, core biomarkers have been identified to serve as diagnostic and staging criteria, and abnormalities indicate the presence of Alzheimer's disease. [20] AD is a progressive disease, and abnormalities in brain imaging and biomarkers can be identified before the onset of symptoms. Typically, these abnormalities result in increasing levels of disease-related changes in brain structure, eventually leading to the progression of symptoms.

3.2 Categorization of Biomarkers

According to current research, there are three broad categories that summarize the biomarkers associated with AD: core biomarkers of AD neuropathologic change, non-specific biomarkers also involved in other diseases and biomarkers of common pathologies.[19] These are then further categorized by the pathogenic process measured by the biomarker.[19]

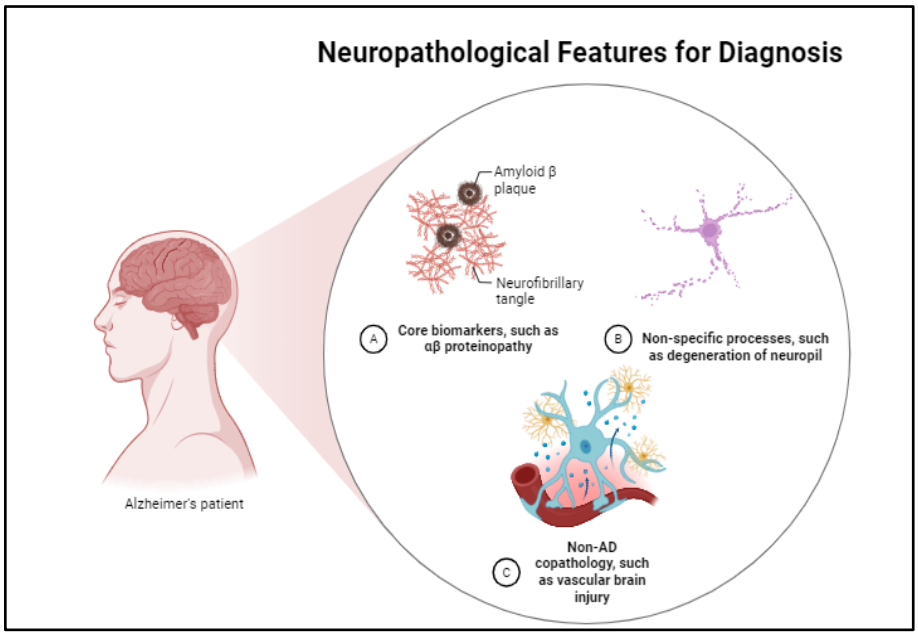

Figure 4: Biomarker Categories for AD Diagnosis

Overview of the major categories of neuropathological features that are used as diagnostic criteria for AD and examples of specific biomarkers in each category.

3.3 Diagnosis

The core biomarkers AB proteinopathy and phosphorylated and secreted AD tau are the primary biomarkers used to diagnose AD.[21] The presence of phosphorylated and secreted AD tau can be identified using a plasma biomarker assay, and AB proteinopathy can be determined using an Amyloid PET scan.[21]

3.4 Staging

Both AB proteinopathy and phosphorylated and secreted AD tau can be used to stage AD, but AD tau proteinopathy, as identified by CSF testing, plasma biomarker assays, or a Tau PET, can also be used to stage AD and provide a prognosis.[22] Dysfunction of the neuropil and Astrocytic activation, both biomarkers of non-specific processes, can be used to stage AD disease, and CSF testing, plasma assays, and, in some cases, anatomic MRI, FDG, and PET scans identify the presence of these biomarkers.[22]

However, in practice, physicians typically stage AD based on the progression of symptoms and relative impairment of their ability to complete daily tasks.[22] This results in the commonly used early, middle, and late-stage designations, but these stages are often correlated with the progression of the aforementioned biomarkers.[22] Because of current research involving biomarkers, a preclinical stage is also possible, which identifies Alzheimer's markers before symptoms occur.[22]

3.5 Identifying Co-Pathology

Dysfunction of neuropil can be used to identify pathology, and this is accomplished by CSF testing, plasma biomarker assays, or anatomic MRI, FDG, and PET scans.[23] Vascular brain injury and a-synuclein, both biomarkers of non-AD copathology, can be used to determine pathology using MRI/CT and CSF testing respectively.[23]

3.6 Diagnosis in Practice

Abnormality on certain group A biomarkers is sufficient for an AD diagnosis.[24] Studies show that group A biomarkers appear abnormal well before symptoms arise, and that the biomarkers coincide with the beginnings of abnormal amyloid PET scans that define the initial state of AD.[24] Although some individuals may present with group A biomarkers but never experience symptoms of AD, it is not safe to assume that these individuals do not have AD.[24] The disease still exists in its initially detectable stage, and clinical judgment must always be used when administering diagnostic tests to these individuals.[24] Furthermore, due to the issue of co-pathology, physicians must take into account the notion that other diseases, such as Parkinson's, present similarly to AD.[24] Additional testing, such as group B testing, would suggest that AD is a dominant contributor to symptoms.[24]

The most common psychiatric evaluation to determine which stage the patient is in is through the Mini-Mental State Examination (MMSE).[25] As research developed, the MMSE has been surpassed by the Montreal Cognitive Assessment (MOCA) and is deemed the most suitable.[26] MOCA is a ten-minute assessment that utilizes 30 items to assess visuospatial reasoning and executive function along with other cognitive domains relevant to AD.[26] The MMSE did not test for frontal lobe executive function,

making MOCA a more precise patient diagnosis tool to distinguish between mild cognitive impairment and early AD.[26]

4. Past Research and Therapies

4.1 Drug Treatments

The U.S. Food and Drug Administration (FDA) has approved seven drugs for the treatment of Alzheimer's disease.[27] Five of these drugs, donepezil, rivastigmine, galantamine, memantine, and memantine combined with donepezil work to improve symptoms.[27] Memantine protects the brain from glutamate, which is a neurotransmitter that, in excess, can overstimulate neurons, causing them damage.[27] The other drugs do not cause any brain changes.[27]

The other two drugs, aducanumab and lecanemab, work to alter the biology of Alzheimer's disease.[41] These drugs slow the cognitive and functional decline of people in the early stages of Alzheimer's by removing beta-amyloid from the brain.[41] Aducanumab, however, has since been discontinued as the drug has been found to be ineffective in late-stage clinical trials even though the company repeatedly pushed for FDA approval.[41]

Drugs that are currently available for the treatment of Alzheimer's disease include cholinesterase inhibitors and an antagonist of the N-methyl-D-aspartate receptor.[28] These current drugs cannot reverse the progression of the disease and can only improve symptoms for a limited amount of time.[28] Many drug companies have experimented with anti-amyloid trials but have not had any success.[28] Currently, companies are focusing on interventions such as anti-tau interventions, neurotransmitter modification, anti-neuroinflammation, and neuroprotection interventions, as well as cognitive enhancement.[28]

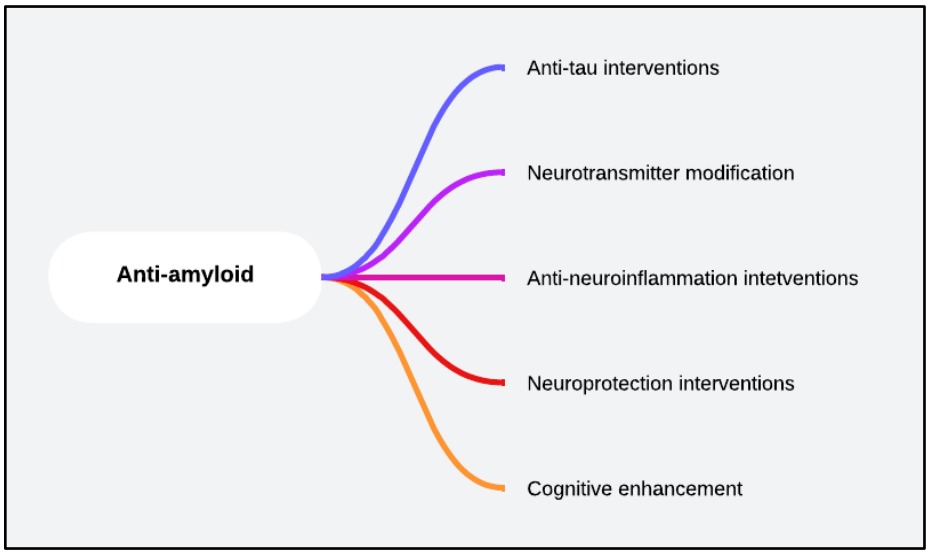

Figure 5: Evolution of Therapeutic Targets in AD

Schematic illustrating the shifting of companies' focus on anti-amyloid immunotherapies to alternative intervention strategies.

4.2 Vaccines

Research has been done on vaccinations as a treatment for Alzheimer's disease, but there have been challenges in developing a vaccine that balances inducing enough of an immune response but not too much that it causes excess immune activation.[29]

One type of vaccination that has been researched is UB-311, an anti-amyloid-B active immunotherapeutic vaccine developed by Vaxxinity.[30] Anti-amyloid vaccines are convenient, affordable, and accessible means of treating and preventing Alzheimer's disease.[30] Studies have shown that UB-311 was safe, well-tolerated, and generated a robust immune response.[30] Additionally, there are immunotherapies targeting tau, microglia, and gut-brain axis still under development.[31]

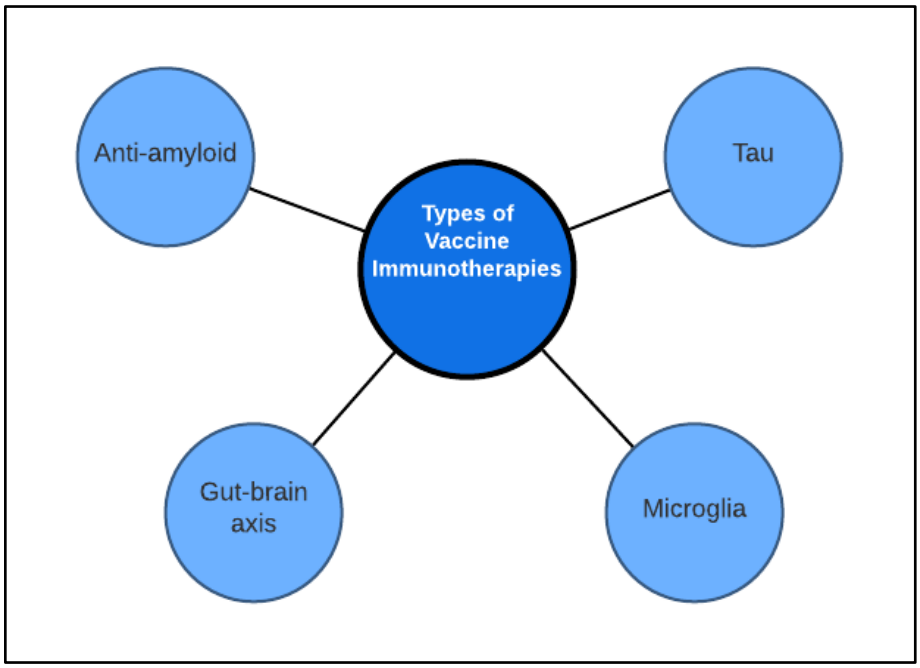

Figure 6: Vaccine Immunotherapy Targets in AD

Classification of vaccine immunotherapies under investigation for Alzheimer's disease.

4.3 Recent Treatment Strategies

Recently, the development of drugs that aim to alter the progression of Alzheimer's disease has been a priority.[33] This is due to current treatments, such as donepezil and galantamine, primarily targeting symptoms versus the progression of the disease.[33]

For the past thirty years, AD pharmaceuticals have focused on therapies that target amyloid B, however, the treatments have failed to show any significant benefit in phase III trials.[33] Due to this, researchers began shifting their focus toward tau-targeting therapies, as tau protein seems to appear more closely correlated with cognitive decline than amyloid B.[33] There are currently several anti-tau immunotherapies in the early stages of clinical research.[33] One anti-tau vaccine and four monoclonal anti-tau antibodies have reached phase II clinical trials.[33]

4.4 Current Treatments

4.4.1 Mild to Moderate

In order to treat mild to moderate-stage Alzheimer's, there are two types of treatments: cholinesterase inhibitors and immunotherapy drugs.[34]

4.4.1.1 Cholinesterase Inhibitors

Understanding cholinesterase inhibitors stems from understanding acetylcholine. Acetylcholine is a neurotransmitter that is crucial to memory, learning, attention, and involuntary muscle movement.[34] Alzheimer's disease, however, correlates with too little of the neurotransmitter, inducing symptoms of memory loss.[35] Because of this, one treatment approach focuses on increasing the levels of this neurotransmitter in patients.[35] Cholinesterase is the enzyme that naturally breaks down acetylcholine in the human body.[35] Knowing this, cholinesterase inhibitors reduce the breakdown of acetylcholine and increase its physiological level. As a result, cholinesterase inhibitors serve as a promising treatment pathway for AD.[35]

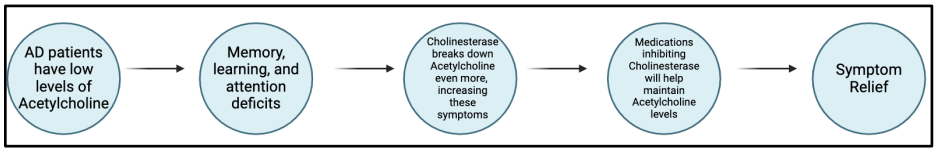

Figure 7: Cholinesterase Inhibitor Justification.

Figure illustrating the role of acetylcholine in the human brain and the symptoms that arise when its levels are reduced. Cholinesterase, a naturally occurring enzyme, further depletes acetylcholine, so medications that inhibit cholinesterase can help elevate acetylcholine levels and alleviate certain symptoms of Alzheimer's disease.

The three main cholinesterase inhibitors on the market are galantamine, rivastigmine, and donepezil.[35]

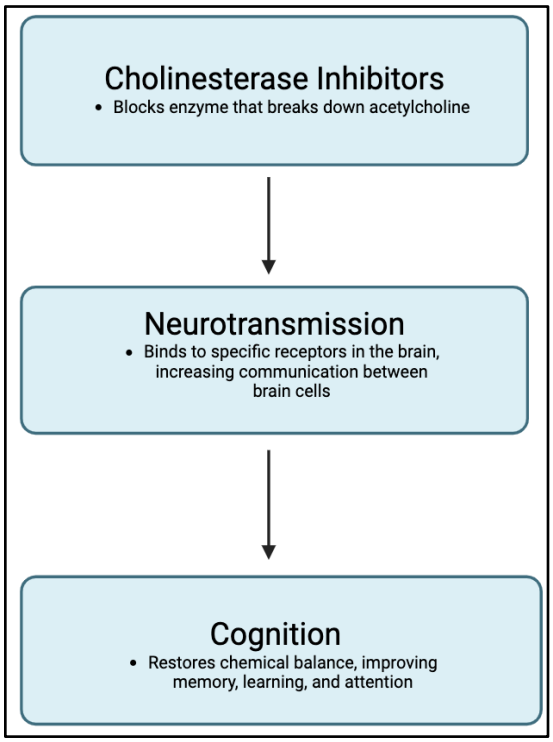

Figure 8: Cholinesterase Inhibitors Mechanism.

Figure illustrating how cholinesterase inhibitors (galantamine, rivastigmine, donepezil) elevate acetylcholine levels to alleviate symptoms of Alzheimer's disease.

All three medications follow the same mechanism of action that is displayed in the figure above.[37] For galantamine, the most common side effects are decreased appetite and weight loss.[38] This medication is known to have the least amount of side effects when compared to rivastigmine and donepezil.[39] However, doctors are most likely to prescribe donepezil first as it is the most cost-friendly and has better tolerability in patients.[40]

4.4.1.2 Immunotherapy Drugs

Immunotherapy drugs such as lecanemab and donanemab are FDA-approved treatments for Alzheimer's disease as well.[36]

To provide a physiological background, amyloid precursors are broken down into the beta-amyloid protein.[41] For patients with Alzheimer's, the beta-amyloid protein is abnormally high, and this leads to the formation of clumps or plaques.[41] Such plaques physically disrupt neural communication and can

block synaptic signaling, thereby reducing the ability of patients to store memories.[41] Immunotherapy drugs are anti-amyloid drugs that physiologically reduce the presence of amyloid plaques.[41]

Lecanemab, brand name Lequembi, targets extremely neurotoxic Aβ aggregates, oligomers, and protofibrils.[41] Its goal is to remove plaques and prevent new ones from occurring.[41] This medicine has slowed decline by 27% and is delivered every two weeks.[42] Donanemab, brand name Kisunla, is given to AD patients every four weeks through IV infusion.[43] It has slowed decline by 22%.[44] Lecanemab targets the amyloid fibrils prior to plaque formation, while donanemab targets the clumped amyloid fibrils (plaques).[44]

4.4.2 Moderate to Severe

At this point in AD progression, the primary goal is to minimize symptoms to make the patient more comfortable. One treatment option is N-methyl-D-aspartate antagonist (NMDA), also known as memantine.[36] This drug is federally approved and has been helping patients with symptom relief for a few months longer than originally predicted.[45] Glutamate is regulated through this medication, which is hypothesized to decrease cell death.[36] On a molecular level, excessive glutamate causes nerve cells to become over-stimulated, leading to brain cell damage and death.[46] Essentially, unregulated amounts of glutamate may be causing the unwarranted cell death that is observed in AD patients.[36] Memantine regulates glutamate activity by blocking the NMDA glutamate receptors resulting in decreased glutamate neurotransmission, allowing for symptom relief in moderate to severe AD patients.[46]

Another FDA-approved medication is donepezil hydrochloride, often referred to as donepezil. Donepezil is a reversible acetylcholinesterase inhibitor that reversibly binds to acetylcholinesterase.[47] This binding causes it to inhibit acetylcholine hydrolysis, increasing its availability at synapses.[47] In other words, donepezil enhances cholinergic transmission which decreases AD symptoms. Donepezil has not shown any evidence of altering the progression of AD but has been proven to decrease cognitive symptoms.[47]

Both of these medications can be administered to patients simultaneously for optimal symptom relief.[36]

5. Discussion

Alzheimer's disease is an increasingly prevalent neurodegenerative disorder. As of 2024, 6.9 million Americans are living with Alzheimer's, and this number is projected to increase to up to 13.8 million by 2060, emphasizing the urgency for preventive or curative medical treatments.[48]

In contrast to general dementia, the progression of Alzheimer's disease is marked by specific pathological findings such as an increased prevalence of beta-amyloid plaques, neurofibrillary tangles, chronic inflammation, and brain atrophy.[48] These can be identified through imaging and laboratory testing such as CSF testing, plasma assays, MRI, FDG, and PET scans.[48] Pathology is both the effect of the disease and the cause of worsening health and dementia seen in patients.[48]

AD can be diagnosed using a combination of pathological findings and psychiatric evaluations. Because of this, precise staging can be conducted using the presence of biomarkers, and care teams can determine a prognosis as well as treatment plans based on the observed abnormalities and pathologies.

However, in practice, physicians can stage AD by analyzing symptom progression and impairment of the patient's ability to complete daily tasks.[48] The MOCA, or Montreal Cognitive Assessment, is the most suitable AD psychiatric assessment, which helps distinguish between cognitive impairment and early AD.[48]

In the future, researchers are gravitating towards further clinical trials for novel immunotherapy vaccines that target amyloid plaques. At the moment, researchers are aiming to develop a vaccine that balances immune response with excessive activation, and they aim to do so by using vaccines such as UB-311 as a model for other targeted therapies such as microglia, gut-brain axis, and tau-targeted immunotherapeutic vaccines.

Beyond the statistics, it is essential to remember and view each "number" as a person with their own unique stories, families, and lives. As the cognitive decline of patients increases, their quality of life declines. From difficulty remembering personal history to uncontrollable incontinence, patients' lives

and normalcies are stripped away and replaced with a lifestyle requiring continuous assistance.

This significant change takes a mental and emotional toll as well. One study found that 2 in 5 people with the disease suffer from significant depression.[49] Yet the burden of this disease takes a toll upon caregivers as well. Another study found that 3 in 5 caregivers for Alzheimer's patients had mild depressive symptoms at the start of the study, with 1 in 3 of their symptoms worsening in a longitudinal study over five years.[50] By helping "lower the statistic," researchers have the ability to truly change lives on an individual level as well.

This literature review presents an understanding of the statistics of Alzheimer's presence and the individual experience, zooming into the physiology and molecular basis of the disease to explore available medical treatments and potential breakthroughs.

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