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Review article

Early-stage research and new pharmacological targets in Alzheimer's dementia

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Abstract: Dementias are neurodegenerative conditions that affect millions of people worldwide. Among these, Alzheimer's disease is the most common form of dementia, characterized by extracellular amyloid plaques and neurofibrillary tangles of intraneuronal p-tau. This is currently an extremely important issue due to the global lack of disease-modifying treatments. For this reason, in recent years, the international medical community has been making substantial efforts to discover therapies that modify the disease, improve symp-toms, and treat the decompensations that occur in dementia. Innovative therapies, mono-clonal antibodies, vaccines targeting amyloid plaques, and even existing therapies that have been repurposed are currently being tested to see their effects in treating dementia. A diverse treatment profile, highlighted by a significant divergence between biological effi-cacy and clinical tolerability, is shown by analysis of data gathered in stages I and II. The findings demonstrate the intricacy of the therapeutic window in the treatment of Alzhei-mer's disease and the necessity of striking a careful balance between patient safety and pharmacological potency. The amyloid hypothesis is validated by the removal of patho-genic protein deposits, although titration techniques and patient selection criteria need to be improved due to the heterogeneity of adverse effects. The shift to crucial phase III re-search, which aims to determine the therapeutic significance of biomonitored plaque re-duction on functional cognitive decline, is supported by these data.

Keywords: Dementia, Alzheimer's disease, Mild Cognitive Impairment, new therapies, disease-modifying treatments, clinical trials, cognitive disorders

1. Introduction

Alzheimer's disease, the most common form of dementia, is a neurodegenerative disease that affects millions of people worldwide, causing a progressive cognitive decline, a progressive memory loss, and increasingly frequent behavioral fluctuations as the disease progresses [1, 2].

From a physiopathological perspective, this illness is characterized by the combination of tau-mediated neurofibrillary tangles, amyloid-beta plaque formation, and neuroinflammation. New ideas on the development of Alzheimer's disease include dysregulation of the gut-brain axis, which is linked to the intestinal microbiota, mitochondrial dysfunction, and genetic variables (APOE4, TREM2) [3–8].

It has been demonstrated that insulin can control brain activities in Alzheimer's disease, and there are theories concerning cerebral insulin resistance in neurodegenerative Alzheimer's disease [9].

New studies have shown that modifiable risk factors are particularly important in the onset of dementia. Twelve risk factors that can be prevented or modified were highlighted by the Lancet Commission in 2020. These consist of poor patient education, pharmaceutically uncontrolled high blood pressure, hearing impairment, chronic smoking, obesity developed in middle age or in the first life decade, depression, lack of physical activity, therapeutically uncontrolled diabetes, social isolation, alcoholism, repeated or high-impact head trauma and brain damage, and air pollution, especially in industrial areas [10].

The role of these studies is vital for the international medical community, as neurodegenerative diseases are increasingly common, as a conclusive example we have Alzheimer's disease which in 2022 reached seventh place in the ranking of all causes of death in the USA [11]. In the last 20 years, 1681 therapies have been analyzed, of which only 362 were against amyloid plaques, but unfortunately many of these therapies have not had proven effectiveness [12, 13]. Physical therapy, through sports, specific diet and cognitive training have proven to be extremely important in the treatment of these diseases [12, 14].

A major problem globally is that, although medicine has evolved enormously, there are only two disease-modifying therapies on some markets, aducanumab and lecanemab and a rather revolutionary therapy, Transcranial Magnetic Stimulation, which has shown beneficial effects [15, 16]. However, these therapies are not widely available and the price of these therapies is high for many patients with these conditions. For this reason, there is a great need for new disease-modifying therapies that can be introduced to all international markets and are also affordable for the patients.

A meta-analysis, conducted by Olubunmi Kusoro and published in 2025, comprising 13 independent studies, merging 30,257 participants between 54 and 93 years old, showed that the dementia diagnosis was made approximately 3.5 years since the onset of symptoms. Factors taken into account for patients with early onset were younger age at onset and diagnosis of frontotemporal dementia, both of which were predominantly associated with taking longer to be diagnosed [17]

The main biochemical methods for detecting Alzheimer's dementia are amyloid-β 42, amyloid-β 40, tau phosphorylated at T217 (p-tau217), total tau, tau phosphorylated at T181 (p-tau181), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) [18-20].

Currently, the medical and the pharmaceutical community are seeking solutions by developing new therapies and disease-modifying treatments, rather than merely symptomatic ones. In recent years, following the Covid pandemic, anti-amyloid monoclonal antibodies that have successfully passed clinical trials, such as Lecanemab and Donanemab, have begun to be marketed. These have shown an improvement in the cognitive capacity of patients with early-stage AD and MCI, thus marking a new beginning for the therapy and management of these patients [1].

1. Objectives of the article

The primary goal of this review is to carefully analyze the new generation of disease-modifying medicines for Alzheimer's disease that are now in the early stages of clinical research, including phase I and II trials. Given that the global research portfolio has grown significantly beyond the classical amyloid cascade hypothesis, now incorporating novel approaches to combat tauopathies, chronic neuroinflammation, metabolic dysfunctions, and oxidative stress, a stage analysis of emerging molecules is required to predict the therapeutic future. In this regard, we discuss the compounds' membership in certain pharmacological classes, the methodological design of the investigations, and the accompanying preclinical background.

The biological safety profile and clinical tolerability are examined in detail, as these are critical factors in the early assessment of risks and the avoidance of serious adverse events such as amyloid-related imaging abnormalities, ARIA. Furthermore, the study critically examines the structural heterogeneity of the recruited cohorts, which range from healthy volunteers (essential for initial pharmacokinetic and pharmacodynamic determinations) to patients with rigorously clinically staged and biomarker-defined cognitive deficits, using advanced PET techniques or cutting-edge plasma and fluid biomarkers like p-tau217. Finally, this approach is supported by a series of critical contextual observations aimed at identifying translational barriers, validating present approaches, and predicting future strategic orientations in the management of this neurodegenerative illness.

2. Materials and Methods

A multitude of articles were analyzed, describing a total of 54 drugs in various phases of clinical trials.

Recent articles from the last 5 years were selected, as well as some articles that, although slightly older than 5 years, are redundant with current studies. The keywords we used in the search were "disease-modifying treatment in AD", "disease-modifying treatment in MCI", "Effective disease-modifying therapies/treatments in dementia", "Phase I clinical trials of disease-modifying therapies in dementia", "Phase II clinical trials of disease-modifying therapies in dementia". The following factors were considered in this synthesis of early-stage therapies: safety profile, pharmaceutical class, selected patient groups, type of study, whether or not guinea pigs were used, adverse effects of these drugs, patients chosen for the study (ranging from healthy to patients with varying degrees of cognitive impairment), and preliminary efficacy of these therapies.

The search also included articles that analyzed phase I or II clinical trials, but from there only therapies that had sufficient data and had real potential to become a disease-modifying treatment were selected. After choosing an appropriate treatment to be studied in this article, all relevant articles were searched for it.

Therapies that did not specify their affiliation with one of the phases of clinical trials were excluded, as were those that, although in a clinical trial phase, refer to neurological diseases and not to a form of dementia. This article did not cover several therapies whose manufacturers or research centers abandoned studies before they were completed, such as natural medicines or those used in other diseases but found to have no good effect on individuals with severe neurodegenerative disorders.

Sources represented another criterion for selecting research studies, being chosen only articles from international journals and reliable sources, the selected journals and articles are indexed in Web of Science, Google Scholar, Scopus.

3. Results

3.1. Phase I of the analysis of new therapies

Phase I represents the first exposure of animals with cognitive disorders that are subjected to experiments, volunteers, usually people suffering from this disease or healthy people, to the drug being studied, in order to analyze the absorption of the drug, its distribution, possible toxicity during therapy, metabolism, excretion, and, from an administration perspective, the time interval between doses and the maximum tolerated dose [21].

The ALN-APP is a novel, experimental RNAi drug, administered intrathecally using an innovative mechanism that targets the amyloid precursor protein, researched for the treatment of Alzheimer's disease and for curing patients with cerebral amyloid angiopathy. A randomized, double-blind study was conducted on 20 patients with AD, divided into three cohorts, who received a single dose of 75 mg ALN-APP. The patients tolerated the doses administered quite well, the side effects

were mild and tolerable by the patients, and two months after administration of this therapy, a reduction in Aβ 42 and Aβ 40 in CSF was observed by 49% and 71%, respectively. [22].

The ALZ-101 is a vaccine that contains oligomerically stabilized Aβ42, which stimulates the body to produce a humoral immune response that targets a toxic oligomeric structure with low Aβ levels. In a double-blind study, 26 eligible participants were vaccinated with this drug, while others received a placebo. The vaccine was well tolerated, which means that it has achieved its immediate goal, generating a physiological humoral response by the body targeting Aβ oligomers, with an impact on associated biomarkers [23].

The APNmAb005 is an antibody that has the unique property of binding to tau neurofilaments and immunizing them. This drug is currently being tested in a double-blind study on guinea pigs (mice) and 40 healthy subjects [24].

The AV-1959D is a vaccine that acts on the N-terminal epitope of the Aβ peptide, which is immunogenic in mice, rabbits, and primates. The current randomized, multicentric, double-blind study aims to demonstrate the safety and tolerability of the vaccine, with its efficacy to be analyzed in subsequent stages [25].

The Centella asiatica is a well-known medicine in the East for its ability to improve cognitive function. That is why it is undergoing more extensive testing in a randomized, double-blind clinical trial involving 48 patients, in order to analyze its effects, which are quantified through laboratory tests and imaging investigation methods [26].

The Choline alfoscerate belongs to the class of phospholipids containing choline, used in patients with cognitive disorders, but a randomized, double-blind, placebo study was conducted on a group of 100 subjects with MCI, which showed safety in administration[27].

The NIO752, a new drug by Novartis that is undergoing testing, is currently in phase I clinical trials to evaluate its safety, pharmacokinetics, and pharmacodynamics. This drug is designed to serve a dual purpose for patients with progressive supranuclear palsy and patients with Alzheimer's disease. This randomized study is being conducted on 24 patients with early-stage Alzheimer's disease, divided into two groups [28].

The OLX-07010 is a new oral drug that has small molecules of tau self-association in its structure, which has the ability to aggregate tau, as tau neurofilaments are involved in the onset of Alzheimer's disease. In phase I, which is still ongoing, it was initially tested on mice, then on a group of healthy adults. It has shown favorable results, indicating that the therapy did not cause any observable adverse effects, it prevented the continued accumulation of insoluble tau in the brain, decreased insoluble tau phosphorylation, and increased insoluble tau proteolysis [29-32].

The Psilocybin, a psychedelic ingredient derived from hallucinogenic mushrooms, is currently being studied to demonstrate its effects in treating MCI. By monitoring neurogenesis markers such as SOX2, DCX, CC3, and others, correlated with MMSE scores, increased neurogenesis was observed in individuals with MCI [33, 34]. Other studies have been conducted in the past, including one involving 33 patients, but the results varied [35].

The SHR-1707 is a humanized anti-Aβ IgG1 monoclonal antibody that binds to Aβ monomers to block the formation of β-amyloid plaques and trigger the microglial phagocytosis of Aβ. This new therapy is still in phase 1 of clinical trials, a double-blind randomized study conducted on 92 healthy young adults. Studies conducted in this phase have demonstrated the safety and tolerability of the doses, with extremely limited adverse effects, the most common being dysgeusia and fatigue [36].

The Senolytic drugs, such as the combination of Dasatinib and Quercetin, target the cellular senescence process. These therapies are capable of eliminating senescent cells and also removing their toxic components. Common factors for aging and for predicting the progression to Alzheimer's disease are usually cognitive abnormalities

and mobility issues. There is currently a theory that suggests that the accumulation of senescent cells can lead to the release of pro-inflammatory, apoptotic, and toxic byproducts, known as the senescence-associated secretory phenotype (SASP), which may exacerbate cognitive decline. Currently, the research into the use of these therapies in treating dementia is in phase I clinical trials. The patient group selected was small, consisting of only five patients with some form of early-stage dementia. The tolerability of this therapy was very good, but no visible improvement in cognitive capacity or neuroimaging was observed [37, 38].

The MSCs from cord blood are mesenchymal stem cells derived from human umbilical cord blood (hUCB-MSCs). Following animal studies with positive amyloid biomarkers, a decrease in amyloid was observed. In the phase I study, nine patients with mild to moderate dementia were selected and given three repeated intracerebroventricular injections of MSCs. No dose-limiting toxicities were observed, but no visible improvement in cognitive ability was observed either, which is why a phase II clinical trial will be initiated [39].

The PR006 is currently, a structurally experimental gene therapy that releases the granulin gene GRN. It uses an adeno-associated virus vector of serotype 9 called AAV9. Tests on mice emphasized an improvement in lysosomal lipofuscin pathologies and a significant reduction in neuroinflammation after administering the therapy. A phase 1/2 study is currently underway on a small group of patients. Within just two months, three cases of deep vein thrombosis and pulmonary embolism have been reported. There was also one death caused by respiratory acidosis, but this was not attributed to the therapy [40].

The Laromestrocel, Lomecel-B, is an allogeneic medicinal signaling cell (MSC) that is believed to be able to modify the Alzheimer's disease course through its pleiotropic actions. In a randomized, double-blind phase I/II study conducted at 10 centers on 120 participants with early-stage Alzheimer's disease from the US, safety and efficacy were tested. One case of grade 3 anemia, three cases of grade 4 acute respiratory failure, and two cases of lumbar radiculopathy were reported. In terms of cognitive capacity improvement, the results were favorable, as quantified by MoCA and MMSE scores [41, 42].

The The ACI-35.030 and JACI-35.054 are anti-phosphorylated tau vaccines and have been declared safe after the first stage of clinical trial testing. In this stage of a double-blind, randomized study, eight patients with MCI or early-stage AD were selected. The vaccines have successfully demonstrated safety and administering tolerability as well as the potential to prevent AD and other tauopathies [43].

3.2. Phase II analysis of new therapies

Phase II is usually conducted on relatively small groups of patients with MCI, early-stage Alzheimer's disease, or even more advanced stages of neurocognitive decline. At this stage, the drug must provide clear benefits in terms of a certain proportion of cognitive improvement, pharmacological evidence, and increased confidence in this therapy in order to create research hypotheses for Phase III [21].

The ABBV-552 modulates synaptic vesicle glycoprotein, which increases synaptic plasticity and creates neuroprotection. Structurally, it is a small molecule. It is currently being tested in phase 2 clinical trials, but unfortunately, not much specialized data have been presented [44, 45]

The ABBV-916 is a human IgG1 monoclonal antibody that has the ability to attach to β-amyloid to modify the third position of the amino acid. This therapy has been shown to significantly reduce dense β-amyloid plaques in the brain. The dose was a single, weekly intravenous injection, and benefits were observed after only three months of administration [46]

The ACI-24.060 is a liposomal anti-amyloid vaccine currently in phase II trials. In phase I of the study, patients with prodromal Alzheimer's disease, with amyloid plaques present and without any anti-dementia treatment, demonstrated safety and

an adequate pharmacodynamic response. The innovation of this study comes from the fact that in the second phase, out of 21 selected patients, a large proportion of them suffer from Down syndrome. What makes this study unique is the fact that these patients had β-amyloid plaques. The data collected so far show safety and effective pharmacodynamic response, and a new, much-optimized variant of the basic ACI-24.060 has been created [47-49].

The AL002 is a human anti-TREM2 agonist monoclonal antibody. TREM2 is a receptor to which microglia attach themselves so due to TREM2 level problems, microglia will determine β-amyloid accumulation. In phase 1, randomized, double-blind clinical trials, 64 healthy volunteers who were administered a single dose were analyzed. The study showed that a single dose demonstrated the safety, tolerability, pharmacokinetics, and pharmacodynamics of AL002 and no serious adverse events that could have been caused by the therapy. Currently, AL002 is being evaluated in Phase II randomized, double-blind clinical trials to investigate its effects on cognitive decline and neurodegeneration in patients with early-stage Alzheimer's disease [50-52].

The Alopregnanolone is an endogenous neurosteroid, for which a phase 1b/2a cohort study has been initiated to demonstrate its capacity for neurogenesis and oligogenesis and, in particular, to restore cognitive function in patients suffering from Alzheimer's disease. The current phase 1b/2a study on 24 patients has so far shown a positive influence on the hippocampus, white matter integrity improvement and, in the case of neurons, functional connectivity improvement. It is currently in phase two clinical trials [53, 54].

The ALZN002 is an immunotherapy vaccine designed to treat mild to moderate forms of Alzheimer's disease type dementia. A group of 20 to 30 patients with mild to moderate Alzheimer's disease type dementia were analyzed. To date, no unacceptable adverse reactions have been reported, with the vaccine currently in phase two of clinical trials [55].

The UB-311 is an active immunotherapeutic vaccine targeting β-amyloid plaques, which in phase I trials has been shown to be well tolerated and to generate a durable antibody response. In phase II clinical trials, in a randomized, double-blind study of 43 participants, patients were observed to have a slower decline. No significant differences were observed between the treated groups [56].

The APH-1105 and ID1201 are both β-secretase modulators that stimulate the PI3K/Akt pathway to treat mild to moderate forms of Alzheimer's disease. The novelty is that APH-1105 is administered intranasally. Currently, safety, tolerability, and efficacy are being analyzed in phase II clinical trials [57-59].

The Baricitinib is a Janus kinase (JAK) inhibitor. This drug binds to cytokine, interleukin, interferon, and colony-stimulating factors. This drug is currently in phase II trials, but results show that the likelihood of it being used in dementia therapy is low [60, 61].

The Bepranemab is structurally an IgG4 antibody that has the ability to bind to 235-250 amino acids in the tau gene near the microtubule binding site. For this therapy, three phase I studies were conducted to demonstrate the safety, tolerability, and pharmacokinetics of the drug. A randomized, double-blind, phase II clinical trial involving 466 patients is currently underway. The patients selected for this study suffer from MCI or early-stage Alzheimer's disease. This study aims to reveal the impact on patients' cognitive abilities [62, 63].

The BCG is a routine vaccine used to prevent Mycobacterium tuberculosis, but it is also used as a treatment for bladder cancer. It is currently being studied in phase II trials because, due to peripheral inflammatory changes, there is a hypothesis that BCG could be used as a form of protection for AD [64- 65].

The Tianmabianchunzhigan is an active substance extracted from Gastrodia, a dried tuber of the species Gastrodiae elata, Orchidaceae, which has been shown over

time to have the potential to improve cognitive capacity [66]. One extremely important thing about this drug is that it is designed to treat vascular dementia. In the second phase of the randomized, double-blind clinical trial, after being tested on laboratory rats to demonstrate safety and show that it can improve learning capacity and memory, 160 patients with mild to moderate vascular dementia were selected. Studies to date have shown substantial benefits in terms of safety and efficacy in the treatment of vascular dementia, especially in cases caused by bilateral occlusion of the common carotid artery [67].

The CT1812 is a Sigma-2 receptor antagonist currently in phase II clinical trials for the treatment of Alzheimer's disease. The study conducted for this therapy, entitled SHINE, is a phase II, randomized, double-blind, ongoing trial involving 16 patients with mild to moderate Alzheimer's disease. The results obtained so far show the potential efficacy of this drug [68, 69].

The Palmitoylethanolamide is a cannabinoid-based agent currently undergoing clinical trials to analyze its effect on agitated patients and those with Alzheimer's disease or frontotemporal dementia. To date, this therapy has achieved its safety and tolerability goals. Over time, this molecule has been shown to have neuroprotective and anti-inflammatory properties. An interesting feature of this drug is that it is being studied for patients with frontotemporal dementia. In the phase II monocentric, randomized, double-blind study, 48 patients with frontotemporal dementia were selected to see the impact of this therapy. This study is based on the fact that co-ultramicronized palmitoylethanolamide combined with luteolin has increased efficacy in slowing the progression of cognitive and functional symptoms. The therapy was well tolerated, with almost imperceptible adverse effects, and in patients with frontotemporal dementia, an amelioration in disease progression was observed, with a smaller decrease in the ADCS-ADL score. However, no significant effect on frontal executive functions and behavioral symptoms was observed [70-72].

The TW001 is orally administered and contains edaravone as its active ingredient, which is an antibody that neutralizes radicals, thus targeting oxidative stress. It is currently undergoing a phase II randomized, double-blind clinical trial on a group of 150 patients with early-stage Alzheimer's disease. To measure the benefits of this new therapy, a new score was used. The Cognitive-Functional Composite score was used to analyze cognitive ability, and the biomarkers Aβ42, Aβ40, pTau, and total Tau (tTau) were also measured. To date, it has been demonstrated that edaravone has the ability to penetrate the blood-brain barrier in order to reduce oxidative stress, which is why it is currently being tested to see if it has a beneficial effect on Alzheimer's patients [73].

The EX039 is a drug that increases the activity of the N-methyl-D-aspartate (NMDA) receptor. It is currently in phase II clinical trials, in a randomized, double-blind study on a group of 120 patients with MCI and mild Alzheimer's disease type dementia. At present, there is not much data on the effectiveness of this therapy [45].

The ExPlas is blood plasma collected from healthy individuals who currently engage in intense physical exercise. This new idea for Alzheimer's disease therapy may have rejuvenating properties. It is in phase II of a randomized, controlled, double-blind study on 60 patients with MCI or early-stage AD. The usefulness of this new therapy is still uncertain [45].

The Interleukin-2, which acts on regulatory T cells, is compromised in Alzheimer's disease. The impairment of the immunomodulatory mechanisms of regulatory T cells causes a proinflammatory response by the immune system. In this randomized, double-blind, phase II study, 38 patients were analyzed for 4 weeks. It was observed that this drug was safe and well tolerated, and it led to changes in inflammatory mediators, making it a promising therapy for treating the Alzheimer's disease [74, 75].

The Posdinemab, is a monoclonal antibody in phase II clinical trials that acts against phosphorylated tau, which is responsible for the development of Alzheimer's

disease. This study is extremely important because it included 2,563 patients with symptomatic Alzheimer's disease in its early stages. This therapy has been declared a failure because plasma increases in phosphorylated tau were observed in all analyzed groups and clinical criteria were not met in patients with early-stage Alzheimer's disease [76].

The Sabernetug is a monoclonal antibody currently in a phase II, randomized, double-blind study in a group of patients with Alzheimer's disease, amyloid-positive and with PET scans [77, 78]. This treatment has proven safe in the first phase of clinical trials and is currently in phase II of clinical trials [79]. A decrease in AD-related proteins was observed in the CSF analysis, but more concrete results are expected after testing this drug on a large group of patients suffering from AD. This positive response was given by increasing the dose and increasing the duration of exposure to the drug [78, 80].

The Levetiracetam is a drug commonly used to treat epilepsy, and due to its use in patients with cognitive disorders, it has been observed to have a certain effect in improving cognitive function. This therapy is in phase II of a randomized, double-blind study conducted on 34 adults with MCI and Alzheimer's disease in the US. It has been observed that high doses of this drug do not diminish hippocampal hyperactivity, have fairly good brain penetration, and improve specific aspects of cognitive decline such as episodic memory function [81-85].

The L-serine is a non-essential amino acid that plays a vital role in protein synthesis, sphingolipid formation in the brain, and cell proliferation. Its mechanism of action is notable for activating glycine receptors and upregulating PPAR-γ, which determines neurotransmitter synthesis, neuroprotection, and also has anti-inflammatory effects. For this reason, a randomized, double-blind phase II clinical trial was initiated to examine its effects on patients with Alzheimer's disease. A marked decrease in ADAS-Cog score and improved cognitive function were observed in the vast majority of patients with Alzheimer's disease, with favorable changes in hippocampal volume and cortical thickness. The results show that it could improve cognitive function and, of course, the associated clinical parameters [86, 87].

The Ceperognastat, is a central nervous system OGA inhibitor. It had a visible safety profile in phase 1 clinical trials and is now in a randomized, single-center, double-blind phase II trial. In phase I, it was observed in mouse subjects that it reduced tau proteins, but in phase II, it did not show significant evidence of clinical benefit in early-stage Alzheimer's disease [88].

The Montelukast is biochemically and pharmacologically, a leukotriene receptor antagonist used in the treatment of asthma and allergic symptoms. Studies in mice have shown reductions in neuronal injury and memory deficits, decreased neuroinflammation, improved learning and memory in these animals, and hippocampal neurogenesis was encouraged. Two different phase II studies were conducted, one randomized study on 70 patients with mild to moderate Alzheimer's disease and another double-blind study on 32 patients with MCI and Alzheimer's disease, also in the early stages. The results obtained from the studies showed that statistically it would have some impact on improving cognitive function [89, 90].

The Nanolitium is a new lithium-based therapy. Lithium has been used for a long time in the treatment and management of psychiatric disorders and for this reason it is believed to have a potential effect on neurodegenerative diseases. For this reason, this new therapy was included in studies to test its effectiveness and is already in phase II testing. It is a randomized, double-blind study currently underway that will show the exact benefit it could have in treating neurodegenerative disorders. [91].

The XPro1595, also known as pegipanermin or simply XPro, is structurally a protein designed to bind to and inhibit TNF, which is found at high levels in Alzheimer's patients. The goal of this treatment is to prevent the progression of the disease, and this new therapy, which has already passed phase II and is moving on to phase

III, has been shown to cross the blood-brain barrier. This double-blind, randomized study analyzed patients with early-stage Alzheimer's disease and positive inflammation biomarkers. This therapy has been shown to reduce TNF, thereby reducing inflammation and eliminating side effects [92, 93].

The Pepinemab, or VX15/2503, is a monoclonal antibody that works by blocking the activity of semaphorin 4D, SEMA4D. SEMA4D is a protein involved in neuroinflammation and neurodegeneration. What makes this study innovative is that this therapy targets Huntington's disease as well as other neurodegenerative diseases. It has currently passed phase II, a randomized, double-blind clinical trial involving 301 participants, 179 of whom had early-stage disease. This study showed that this therapy brought about significantly greater cognitive improvements, and it was also found to reduce caudate tissue in the region affected by Huntington's disease by approximately 26% [94-96].

The Rapamycin is an antibiotic widely used in medical practice against infections, but it has recently gained increased attention in anti-aging therapy and is currently in phase II clinical trials to see if it could also have an effect on Alzheimer's disease. This study is being conducted on 15 patients with Alzheimer's disease, and biomarkers will be analyzed to track the impact of the therapy in treating Alzheimer's disease [97, 98].

The Sargramostim, a recombinant human granulocyte-macrophage colony-stimulating factor, is currently in a phase II, randomized, double-blind study. This study involved a group of 20 participants with mild to moderate Alzheimer's disease. Treatment with this drug altered immune markers without adverse effects, and MMSE scores improved significantly [99-101].

The orexinergic system modulates a multitude of bodily processes, including aggressive behavior, stress, anxiety, and others. It is being studied in phase II trials for patients suffering from Alzheimer's disease who also exhibit clinically significant agitation and aggression [102].

The TB006 is a new treatment that has passed phase II of the study to determine its effectiveness in treating Alzheimer's disease. TB006 is an antibody designed to block Gal-3. Gal-3, or galectin-3, is a protein found in excessive amounts in the brains of these patients. In addition to patients with mild to moderate Alzheimer's disease, patients with severe forms of the disease were also selected for this study. A total of 157 patients were selected, but only 79 patients completed the study. The results showed cognitive improvement, and there were even signs of disease reversal [103].

The Trontinemab is a monoclonal antibody that works by eliminating amyloid plaques. This new therapy has been shown to eliminate these amyloid plaques and improve biomarkers. It recently completed phase II trials on a group of patients with Alzheimer's disease and is set to move on to phase III [104, 105].

The Valaciclovir is an antiviral drug that is widely used for treating of the herpes virus. The herpes virus becomes latent in the trigeminal ganglion and is believed to have a neurodegenerative effect in Alzheimer's disease. It was analyzed in a randomized, double-blind phase II study on a group of 36 participants, where improvements in MMSE scores, anti-HSV IgG titers, and even a decrease in beta-amyloid and p-tau levels were observed [106, 107].

The Varoglutamstat is a small molecule that works by inhibiting glutaminyl cyclase activity and is believed to have a significant impact on the development of Alzheimer's disease. t is currently being studied in phase IIa in a randomized, double-blind clinical trial on a group of patients with Alzheimer's disease. This new therapy has shown safety, tolerability, and some efficacy in early-stage Alzheimer's disease [108, 109].

The Xanamem is a selective inhibitor of type 1 11beta-hydroxysteroid dehydrogenase and is in phase II of double-blind clinical trials on a group of 72 participants with Alzheimer's disease. Therapy with Xanamem has shown evidence of clinical benefits [110-112].

The YangXue QingNao Wan (YXQNW) is a traditional Chinese medicine currently in phase II trials to assess its impact on Alzheimer's disease. This new therapy has been shown to inhibit Aβ deposition and have other beneficial effects, demonstrating potential in the treating this disease [113].

4. Discussion

4.1. Analysis of Phase I Therapies in Clinical Trials

Sixteen therapies currently in Phase I and Phase I/II have been analyzed in clinical trials. Almost one-third of the studies that published data on their results showed that the therapies had a benefit by improving cognitive ability and reducing amyloid or tau structures as early as Phase I, leading to higher expectations for the discovery of a disease-modifying therapy, Figure 2.

In phase I, the expectations do not necessarily refer to optimal results for cognitive healing, but rather to the study of absorption, distribution and metabolism, toxicity and maximum tolerated doses. Due to the possible undesirable adverse effects of these therapies, the studies were mostly done on animals. Some pharmaceutical companies allowed patients with cognitive disorders to participate in these studies, in order to observe, in addition to safety, the possible positive effect that these therapies would have from the beginning.

A very interesting thing is the variety of types of therapies aimed at treating AD, Table 1. The presented phase I clinical trials demonstrate a great diversification of the therapeutic arsenal against Alzheimer's disease. The aim is no longer just to "clean" the brain of amyloid plaques, but also to stop their production at the RNA level, to train the immune system, to regenerate neurons, or to use stem cells.

Table 1. Therapeutic categories studied in Phase I

Therapeutic Category	Therapies	Proportion of therapeutic class out of total therapies
Vaccines	ALZ-101, AV-1959D, ACI-35.030 & JACI-35.054	20.0%
New molecules	ALN-APP , NIO752, OLX-07010,	20.0%
Cell and gene therapies	MSCs, PR006, Laromestrocel	20.0%
Natural Molecules / Traditional / Supplements	Centella asiatica, Choline alfoscerate, Psilocibina	20.0%
Antibodies	APNmAb005, SHR-1707	13.3%
Reusing old medicines	Senolytic drugs (Dasatinib + Quercetin)	6.6%

The vaccines aim to train the patient's immune system, in this case the humoral response, to attack either amyloid, ALZ-101 on oligomeric stabilized Aβ42, AV-1959D on the N-terminal epitope of Aβ, or phosphorylated tau protein, the therapies ACI-35,030 and JACI-35,054. All studies mentioned in this category report good tolerability and safety. Their goal in Phase 1 seems to be rather to demonstrate the generation of a physiological immune response, their efficacy to be tested later, in Phase II studies in patients with Alzheimer's dementia.

New drugs and molecules are very promising. ALN-APP, an intrathecally administered RNAi drug, achieved a massive reduction of Aβ 42 by 49% and Aβ 40 by 71% in CSF after just two months. OLX-07010 acts on another front, preventing the accumulation and phosphorylation of the insoluble tau protein. Compared to vaccines that rely on the immune system, these new molecules intervene directly in the

mechanisms of plaque or filament formation, either at the RNA level or through self-association molecules.

Cellular and gene or biosynthetic therapies are part of the category with the most severe adverse effects mentioned in the text, but also with the potential to radically modify the disease. PR006, gene therapy with AAV9 vector, has reported many side effects, some of them very serious.

In this article there are various approaches regarding therapies with natural molecules, supplements and psychedelics, from Eastern medicine, Centella asiatica, phospholipids, Choline alfoscerate, to Psilocybin. Psilocybin stands out here by its mechanism: stimulation of neurogenesis, observed by the increase of SOX2, DCX, CC3 markers. This is a completely different approach from the elimination of amyloid or tau plaques, focusing on neuronal regeneration.

The antibodies studied involve monoclonal antibodies, SHR-1707 that act directly against Aβ plaques and antibodies that immunize against tau neurofilaments, APNmAb005. They are well tolerated, with limited, generally mild, adverse effects, such as dysgeusia and fatigue in SHR-1707.

Repurposing Old Drugs, the combination of Dasatinib + Quercetin, senolytic therapies aim to eliminate senescent cells and the secretory phenotype associated with senescence, SASP, which exacerbates cognitive decline. Although logically the reduction of neuroinflammation/SASP is solid, in the small experimental group used it did not demonstrate clinical or neuroimaging efficacy.

Clinically proven cognitive improvement was observed for Laromestrocel, which proved to be the only therapeutic agent and had clearly favorable results from the first phase of clinical trials, quantified by MoCA and MMSE scores, despite the severe adverse effects reported in the group of 120 participants.

Biomarker Improvement: ALN-APP therapy dramatically reduced CSF amyloid levels by 49% to 71%. OLX-07010 showed decreased tau phosphorylation and prevented insoluble tau accumulation. Psilocybin showed increases in neurogenesis markers, theoretically correlated with MMSE scores.

The senolytic drugs, Dasatinib + Quercetin, had no visible cognitive improvement. The use of MSCs from umbilical cord blood did not lead to visible improvements in cognitive ability, which is why it is moving to Phase II for further investigation.

Being Phase I studies, most are conducted on very small groups, 5 patients for senolytics, 8 for ACI/JACI vaccines, 9 for MSCs, 20 for ALN-APP, 24 for NIO752. However, exceptions are observed with unusually large groups for Phase 1: 120 participants for Laromestrocel, 100 for Choline alfoscerate, 92 for SHR-1707. This raises questions about adverse effects depending on race, comorbidities, age ranges, individual genetic makeup, environment of origin and other aspects.

The amyloid-β cascade remains a major target for ALN-APP, ALZ-101, AV-1959D, SHR-1707 therapies. There is an equally strong focus on tau protein like APNmAb005, OLX-07010 and ACI-35,030.

Traditional biological therapies, antibodies, vaccines, oral or intrathecal small molecules, report excellent tolerability, mild adverse effects, such as fatigue, dysgeusia. Complex gene and cell therapies, such as PR006, Laromestrocel, present extremely serious adverse events, their administration requires much stricter monitoring.

Regarding animal testing of therapies, changes in cognitive function in animals do not directly translate into cognitive function in humans. In animals, researchers cannot measure abstract reasoning or linguistic memory. Instead, it is based on physical and histological evidence that theoretically underlies the disease.

PR006, as a gene therapy, in mice demonstrated an improvement in lysosomal lipofuscin pathologies and a significant reduction in neuroinflammation.

MSCs, stem cell therapy, performed in animals showed a decrease in amyloid based on positive amyloid biomarkers. AV-1959D proved immunogenic in mice, rabbits and primates, it triggered an immune response, not necessarily better memory.

In animals, success means repairing the "mechanics" of the brain, by reducing inflammation, clearing amyloid plaques. It is assumed that if the "mechanics" are repaired in the animal, cognitive decline will be stopped in humans.

When making the leap to human patients, cognitive function is finally quantified by specific tools such as the MMSE or MoCA tests.

Although MSCs reduced amyloid in animals, no visible improvement in cognitive ability was observed in the 9 human patients. The same poor results are seen with the senolytic drugs, Dasatinib + Quercetin.

Phase I in animals confirms the biological mechanism and safety, but the real cognitive test comes in humans, through MMSE/MoCA scores, where, often, clearing biomarkers does not immediately translate into clearer minds.

4.2. Analysis of Phase II Therapies in Clinical Trials

Regarding Phase II, the results seem more encouraging. These therapies have demonstrated safety, tolerability, and efficacy in treating dementia, although many of them have been tested on small groups of patients.

Figure 2 shows that half of the drugs studied, for which data on benefits have been published, had statistically satisfactory results in Phase II, with great potential to help patients with Alzheimer's disease. Regarding Phase I therapies, their diversity is noteworthy Table 2.

Table 2. Therapeutic categories studied in Phase II

Therapy Category	Therapies	Proportion of therapeutic class out of total therapies
Monoclonal Antibodies or IgG	ABBV-916, AL002, Bepranemab, Posdinemab, Pepinemab, TB006, Trontinemab	20.5%
New Molecules and Small Molecules	ABBV-552, APH-1105 & ID1201, CT1812, TW001, EX039, Ceperognastat, Seltorexant, Varoglutamstat, Xanamem	26.5%
Reuse of Dementia Medications	BCG, Levetiracetam, Montelukast, Nanolitium, Rapamycin, Valaciclovir	17.6%
Natural molecules, supplements, plasma	Alopregnanolone, Palmitoylethanolamide, ExPlas, L-serina	11.8%
Anti-amyloid vaccines or immunotherapy	ACI-24.060, ALZN002, UB-311	8.8%
Proteins and Biosynthetic Molecules	Interleukin-2, XPro1595, Sargramostim, Sabernetug	11.8%
Traditional Chinese Medicine	Tianmabianchunzhigan, YangXue QingNao Wan	5.9%

Of all the drugs studied, 50% had a positive, but very small, effect on some therapies, and 29% did not have the desired effect.

Comparing the studies conducted in the two phases, it was observed that most of the studies were randomized, double-blind, Figure 1.

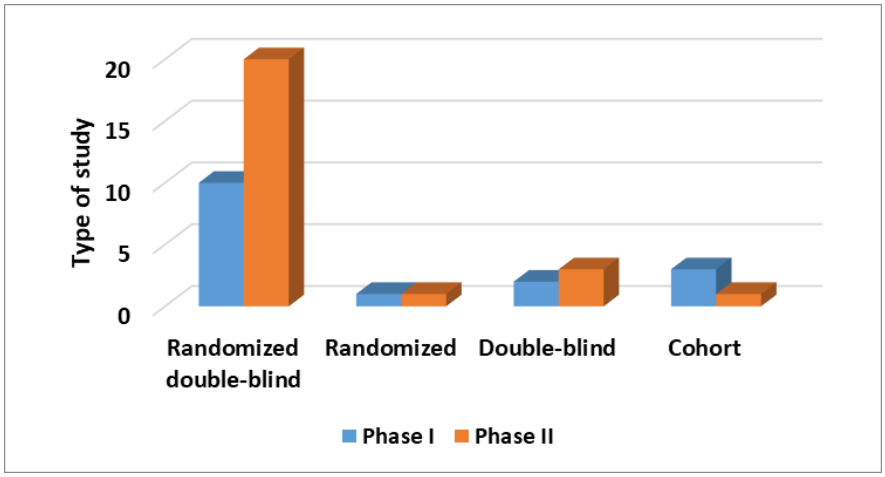

Figure 1. Conducted study types.

Most of the patients selected for this phase II study had Alzheimer's dementia, especially in its early stages or patients with MCI, but some therapies have also been studied for other forms of cognitive disorders such as vascular dementia, frontotemporal dementia and even Huntington's disease.

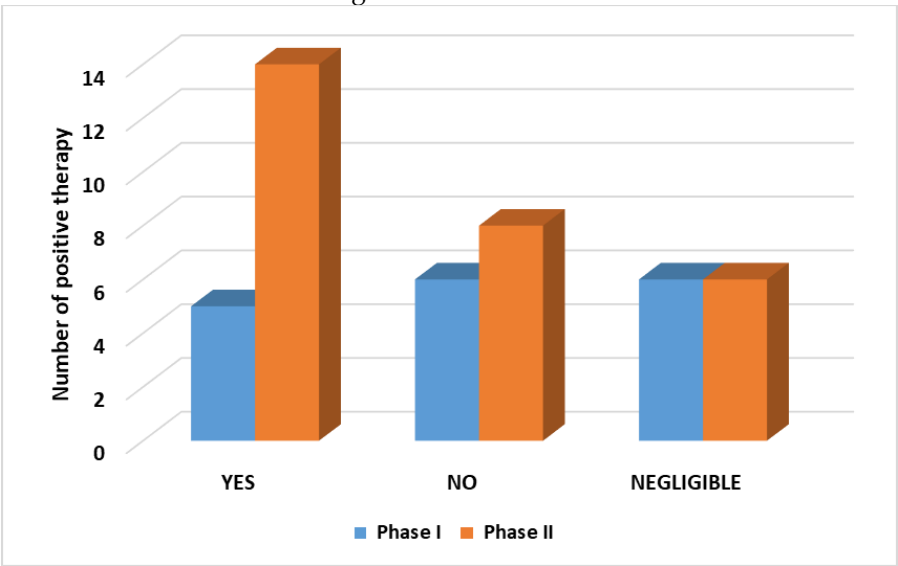

Figure 2. Benefits related to improved cognitive function in patients in the two stages of clinical trials.

The monoclonal antibody therapies studied in phase II ABBV-916, Trontinemab that target the elimination of β-amyloid plaques and the therapies AL002, Pepinemab, TB006 that reduce neuroinflammation or act at the microglial level have recorded amazing results, signs of disease reversal and cognitive improvement. The therapies Bepranemab, Posdinemab, which lead to the elimination of Tau proteins, were not effective, Posdinemab was declared a total failure, because it increased the level of phosphorylated tau in plasma.

Novel molecules and modulators that act on very specific pathways focus on neuroprotection and modification of fine brain chemistry. One innovative aspect is the mode of administration, such as APH-1105, which is administered intranasally.

The data are promising in terms of safety, but efficacy is still in the early stages of evaluation.

Exploiting the beneficial side effects of known drugs is an extremely smart and pragmatic approach, since the safety profile of these drugs is already known. Valaciclovir demonstrates the viral hypothesis of Alzheimer's, thereby decreasing amyloid and p-tau, while Levetiracetam improves episodic memory function, although it does not reduce hippocampal hyperactivity at high doses.

Natural supplements and traditional medicine surprise with their effectiveness. L-serine has a visible positive impact on hippocampal volume and cortical thickness. Tianmabianchunzhigan is distinguished by the fact that it is specifically dedicated to vascular dementia, not just Alzheimer's, having substantial benefits after carotid occlusions.

Vaccines aim to train the immune system to attack amyloid. A remarkable study is the one for ACI-24,060, which innovatively includes patients with Down Syndrome who present with amyloid plaques, demonstrating an innovative approach.

TB006 therapy not only improved cognition, but may even reverse the disease. Pepinemab produced significant cognitive improvements and reduced caudate atrophy by approximately 26%. As for L-serine, it caused a marked decrease in ADAS-Cog scores, including favorable physical changes in hippocampal volume and cortical thickness. Levetiracetam improved episodic memory function. Montelukast statistically has an impact on improving cognitive function, initially demonstrated by repairing memory deficits and neurogenesis in mice. Allopregnanolone positively influences the hippocampus, white matter integrity and functional connectivity of neurons. Palmitoylethanolamide slowed the progression of functional and cognitive symptoms, with a smaller decrease in ADCS-ADL scores, especially targeting patients with frontotemporal dementia. Valaciclovir improved MMSE scores. Sargramostim also significantly improved MMSE scores.

ABBV-916 therapy was noted to be remarkable in that the benefits, observed by reducing dense amyloid plaques, were observed after only three months of administration. TB006 therapy is the only therapy mentioned that included patients with severe forms of Alzheimer's and showed signs of reversing the disease. Most of the others focus only on the early stages of AD. There have also been notable failures such as Baricitinib, Posdinemab and Ceperognastat.

From the point of view of structural neuroprotection we have two therapies that would have a positive effect. Allopregnanolone which improved white matter integrity and L-serine which led to favorable changes in hippocampal volume and cortical thickness.

An extremely interesting thing is the variety of the number of patients selected for phase II therapies, from extremely small groups of <30 patients to inexplicably large groups that enrolled over 1000 patients, Figure 3.

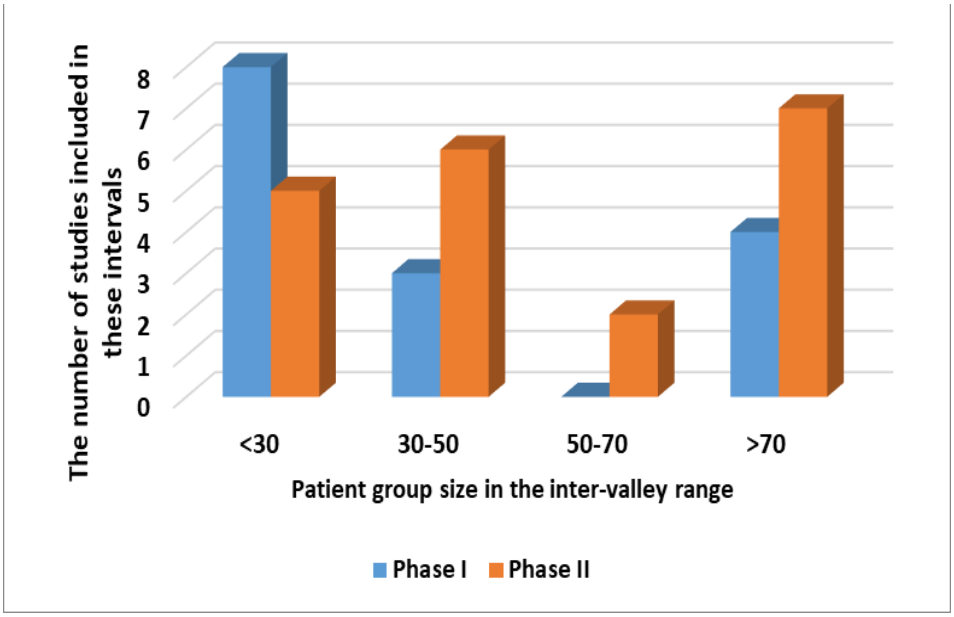

Figure 3. Number of patients on whom studies were conducted, included in ranges.

5. Limitations of the study

The main limitation of this review derives from the preliminary nature of the data analyzed, phase I and II studies are predominantly exploratory in nature, these phases focus on safety and on changes in surrogate biomarkers that do not always translate into a real or sustainable clinical benefit.

Although this research provides important insights into the topic, the results must be interpreted in the context of some inherent methodological constraints. First, the data selection procedure included a non-systematic literature search to detect trends and major directions. Although reference works were included, the research landscape still allows for the incorporation of fresh sources in future assessments. The results are also taken in light of the variety of the studies examined and the inherent reliance on early-stage research. This diversity reflects the current state of the literature, giving the findings a somewhat exploratory tone. The field under investigation is highly dynamic, with continually developing evidence. This emphasizes the reality that current ideas provide a vital foundation for discussion, but they will undoubtedly be revised and supplemented when new research directions become accessible.

Because the failure rate is high in the transition to phase III trials in the field of Alzheimer's disease, the current conclusions must be interpreted with caution, being influenced by the small size of some samples.

The biggest limitation is that success in Phase II does not guarantee success in Phase III. Phase I and II studies are done on small numbers of people, sometimes even under 50-100 people.

6. Novelty of the Study

The novelty of this review lies in the comprehensive and integrated approach of the therapeutic landscape in early stages of clinical development Phases I and II of clinical trials, an essential area for a better understanding of future treatments in Alzheimer's disease and beyond.

Compared to works that synthesize existing therapies, this work offers a fairly critical and objective analysis of therapies in phases I and II of clinical trials. It compares, analyzes and reviews monoclonal antibodies, vaccines and other disease-modifying therapies, to analyze how many of them have the potential to cure this disease.

The paper presents the main current research directions, with an emphasis on their benefits, the type of treatment, but also useful information about the study.

Early clinical trials that aim to evaluate the safety, tolerability and preliminary efficacy of these treatments are described and analyzed.

The paper also highlights how these therapies attempt to intervene on the pathological processes involved in disease progression, such as the accumulation of beta-amyloid or p-tau. In this context, the paper contributes to a better understanding of the current state of research and future perspectives in the development of disease-modifying treatments, especially for Alzheimer's disease.

7. Conclusions

A total of 54 drugs in phase I and II clinical trials were analyzed. 16 drugs in phase I, 38 drugs in phase II.

The results of the first phase of clinical trials were encouraging. The vast majority demonstrated safety and tolerability of doses, while only two therapies showed significant adverse effects.

Therapeutic strategies have evolved beyond the simple elimination of protein accumulations, migrating towards a systemic vision. The success of approaches aimed at cellular regeneration, regulation of inflammatory processes and even the hypothesis that viral infections would be linked to dementia, demonstrate that cognitive decline is increasingly recognized as a condition with a multifactorial etiology. The change in focus towards the genetic suppression of the production of toxic elements and the training of the physiological immune response indicates a transition from palliative or purely reactive treatment, to interventions with the potential to definitively alter the course of the disease.

Tolerability, safety, pharmacokinetics and pharmacodynamics have been successfully demonstrated in most therapies. At this point, almost all vaccines have demonstrated good tolerability and safety.

If we compare the batches, we see that the future is not necessarily of universal molecules. The batch of 21 patients with Down Syndrome or the one of 48 with frontotemporal dementia suggests that success could come from personalized therapies for specific patient niches, rather than a "magic bullet" for batches of thousands of people.

The superior results in Phase II, compared to Phase I, indicate that establishing an optimal dose and expanding the patient batches allow for the demonstration of clear statistical benefits. The successes reported in this stage, validate alternative hypotheses, such as viral, inflammatory or cellular senescence. Therapies targeting structural neuroprotection, hippocampal volume, and white matter integrity appear to offer more promising results in terms of long-term stability of executive functions compared to approaches focused strictly on the elimination of protein plaques.

There is a significant methodological barrier to translating results from animal models to human subjects. While in preclinical stages success is defined by correction of brain “mechanics” and histological parameters, testing in humans reveals that restoration of biomolecular balance does not guarantee restoration of higher cognitive functions. This discrepancy suggests that structural integrity and biomarker clearance are necessary but insufficient conditions for functional recovery, highlighting the complexity of the architecture of human memory and reasoning.

Due to an expanding therapeutic landscape, characterized by a multitude of selected patients, currently in various stages of clinical trials, the prospect of developing a curative treatment for this disease is extremely promising.

The advancement of medicines into advanced stages of testing reveals a significant shift in perspective: physical neuroprotection and disease progression reversal are no longer theoretical but rather attainable clinical aims. The data shows that interventions that can halt brain tissue atrophy, support neurogenesis, and maintain white matter integrity have the greatest impact on stabilizing functional decline. The

existence of diametrically opposed results within the same testing phase, ranging from remarkable reversal of severe symptoms to marked failures of exacerbation of pathological markers, suggests that success depends on identifying the optimal therapeutic window and on the biological heterogeneity of cohorts, which varies inexplicably by many dimensions.

Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, M.G., A.R., S.M., A.P., D.O., L.A., A.B. ; methodology, M.G., A.R.; software, M.G., S.M., L.B. ; validation, A.R., S.M., A.P., D.O., L.A., A.B. ; formal analysis, M.G.; investigation, D.O., L.A., A.B.; resources, A.R., S.M. ; data curation, A.P., D.O.; writing—original draft preparation, M.G., S.M.; writing—review and editing, A.R., S.M.; visualization, A.P., D.O.; supervision, M.G., S.M.; project administration, M.G., S.M; funding acquisition, M.G.All authors have read and agreed to the published version of the manuscript."

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Abbreviations

MCI	Mild Cognitive Impairment
AD	Alzheimer's Disease
PET	Positron Emission Tomography
MMSE	Mini-Mental State Examination
USA	United States of America
P-tau217	Phosphorylated tau at threonine 217
P-tau181	Phosphorylated tau at threonine 181
NfL	Neurofilament light chain
GFAP	Glial Fibrillary Acidic Protein
FDG-PET	Fluorode oxyglucose (FDG) positron emission tomography (PET)
Aβ	β-amyloid
SASP	Senescence-associated secretory phenotype
GRN	Gene Regulatory Networks
MSC	Mesenchymal Stem Cell
MoCA	Montreal Cognitive Assessment
I.v.	Intravenous
IgG1	Immunoglobulin G antibody subclass
JAK	Triggering receptor expressed on myeloid cells 2
ADCS-ADL	Comparative Study on Alzheimer's Disease – Daily Activities Scale
PPAR-γ	Peroxisome Proliferator-Activated Receptor gamma
ADAS-Cog	Alzheimer's Disease Assessment Scale–Cognitive Subscale
OGA	O-GlcNAcase
TNF	Tumor Necrosis Factor
SEMA4D	Semaphorin 4D
HSV	Herpes simplex virus
APOE4	Apolipoprotein E
TREM2	Triggering Receptor Expressed on Myeloid Cells 2

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