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Alzheimer's Disease: Innovative Approaches and Emerging Strategies in Holistic Management

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Abstract

Background: Alzheimer's disease (AD) represents one of the most pressing healthcare challenges of our time, affecting millions globally and presenting complex pathophysiological mechanisms that extend beyond traditional amyloid-focused therapeutic approaches. As conventional pharmacological interventions demonstrate limited efficacy, the growing understanding of AD pathophysiology has spurred the exploration of alternative, non-pharmacological interventions targeting diverse biological pathways.

Objective: This narrative review examines emerging approaches, including novel cellular, mitochondrial, as well as, peptide-based and advanced non-pharmacological interventions such as cognitive training and neuromodulation techniques, and comprehensive lifestyle modifications. The integration of transcranial direct current stimulation (tDCS), virtual reality (VR) applications, dietary interventions, and lifestyle optimization represents a paradigm shift toward personalized, multi-modal strategies that target various aspects of cognitive decline and neurodegeneration.

Methods: The article integrates literature-based evidence, expert interpretation, and conceptual trends. Selected interventions include cellular, mitochondrial-targeted approaches, neuroprotective peptides, polyenylphosphatidylcholine, cognitive training, neuromodulation (tDCS, hyperbaric oxygenation, ozone therapy,

Results: These interventions address multiple mechanisms implicated in AD, such as synaptic dysfunction, mitochondrial impairment, neuroinflammation, and oxidative stress. Several modalities—particularly those involving neural regeneration, peptide delivery, and neuromodulation—demonstrate promising results in preclinical and early clinical studies according to the literature. Lifestyle modifications and cognitive training continue to show preventive and supportive value. A growing body of evidence supports integrative approaches tailored to individual needs and disease stages.

Conclusion: Innovative and non-pharmacological management of AD represent a paradigm shift toward more holistic, mechanism-driven, and potentially synergistic care models. Further research is needed to optimize these strategies and integrate them into clinical practice for improved patient outcomes.

Keywords

Alzheimer's disease; Neuronal death; Hippocampal-derived stem cell; Targeted Brain Specific Precursor Stem Cells; Hippocampal atrophy; Neuroimaging biomarker; Precursor Stem Cells.

Introduction

Alzheimer's disease, characterized by progressive cognitive decline and neurodegeneration, affects over 50 million people worldwide, with projections indicating a substantial increase as global populations age (Alzheimer's Disease International, 2022). Traditional therapeutic approaches, primarily focused on cholinesterase inhibitors and NMDA receptor antagonists, have shown modest benefits at best, prompting researchers to explore innovative alternatives that address the complex, multifactorial nature of AD pathogenesis.

The contemporary understanding of AD encompasses multiple interconnected pathways, including amyloid aggregation, tau protein dysfunction, neuroinflammation, oxidative stress, synaptic dysfunction, and metabolic dysregulation. This complexity necessitates a holistic approach that combines emerging pharmacological interventions with comprehensive non-pharmacological strategies designed to optimize cognitive function, enhance neuroplasticity, and improve overall quality of life for patients and their families [1].

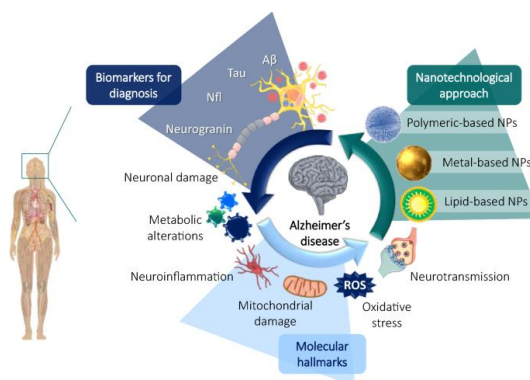


Figure 1: Graphic Abstract. Source: Cano A, Turowski P, Ettcheto M. (2021) Nanomedicine-based technologies and novel biomarkers for the diagnosis and treatment of Alzheimer's disease: from current to future challenges. J Nanobiotechnol. 19:122.

The repeated failures of A β -targeted clinical trials have cast considerable doubt on the amyloid cascade hypothesis, fundamentally reshaping the field's approach to AD management and highlighting the limitations of single-pathway interventions. Emerging evidence suggests that AD pathology begins decades before clinical symptoms manifest, creating a critical window for preventive interventions that could potentially delay or prevent disease onset [2]. The heterogeneity of AD presentations, with varying patterns of cognitive decline and neurodegeneration, underscores the need for personalized treatment approaches that consider individual genetic, lifestyle, and clinical factors. Recent advances in biomarker research have revealed that AD exists on a continuum, with preclinical stages offering opportunities for early intervention before irreversible neuronal damage occurs.

The concept of cognitive reserve has gained prominence as a protective factor against AD, suggesting that individuals with higher education, social engagement, and cognitive activity may maintain function despite underlying pathology [3]. This understanding has shifted focus toward interventions that can build and maintain cognitive reserve throughout the lifespan [4]. The recognition that vascular health, metabolic dysfunction, and systemic inflammation contribute to AD risk has expanded the therapeutic landscape to include interventions targeting these modifiable factors. Modern approaches increasingly emphasize the importance of addressing comorbid conditions such as diabetes, hypertension, and depression, which can accelerate cognitive decline and complicate AD management [1].

The development of digital therapeutics and technology-assisted interventions has opened new possibilities for scalable, accessible treatments that can be delivered remotely and adapted to individual needs. Artificial intelligence and machine learning applications are beginning to transform AD diagnosis, prognosis, and treatment selection through the analysis of complex datasets including neuroimaging, genetic information, and digital biomarkers [5]. The integration of patient-reported outcomes and caregiver perspectives has become essential for developing meaningful interventions that address real-world challenges faced by families affected by AD. Furthermore, the recognition of AD as a family disease has led to comprehensive approaches that support both patients and caregivers throughout the disease trajectory.

Emerging biomedical approaches include the use of neural stem cells, which offer the potential for neuroregeneration and synaptic repair in damaged brain regions [6]. Mitochondrial-targeted therapies, or "mito-organelle" approaches, are gaining attention for their role in reducing oxidative stress and restoring cellular energy balance. Nutraceuticals such as Plaqa Forte softgels, which contain polyenylphosphatidylcholine, are being explored for their neuroprotective and membrane-stabilizing properties in early-stage intervention strategies [7].

In 2019, dementia cost economies globally US\$1.3 trillion, with the Global Alzheimer's Disease Therapeutics Market size expected to be worth around USD 30.8 Billion by 2033 (Alzheimer's Disease International, 2022). This economic burden has intensified efforts to develop cost-effective interventions that can be implemented at scale. Prevention-focused strategies, including lifestyle modifications and risk factor management, are increasingly viewed as critical components of public health approaches to addressing the AD epidemic. The global nature of the AD challenge has fostered international collaborations and data-sharing initiatives that are accelerating research progress and therapeutic development.

Objectives

1. Present an overview of innovative and emerging non-pharmacological strategies for the management of AD, including interventions that extend beyond conventional drug-based treatments.
2. Highlight the role of cellular, mitochondrial, and peptide-based management in addressing underlying neurodegenerative mechanisms associated with AD.
3. Discuss the relevance and therapeutic potential of neuromodulatory techniques such as transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), hyperbaric oxygenation, ozone therapy, and virtual reality-based cognitive rehabilitation.
4. Explore the application of nutraceutical compound- polyenylphosphatidylcholine, and its potential to support neuroprotection and membrane integrity.
5. Emphasize the contribution of lifestyle-based modifications—including diet, sleep hygiene, social engagement, and cognitive training—to long-term brain health and AD risk reduction.

Methods

This article is presented as a commentary-style narrative review, drawing on the authors' expertise and a broad interpretation of the current literature on non-pharmacological and biologically innovative approaches to AD². The discussion integrates published research, emerging concepts, and practical perspectives on a wide range of alternative strategies.

The peer-reviewed studies, scientific reports, and key publications illustrating the promising trends and directions in AD management were selectively referenced. Emphasis was placed on non-pharmacological and adjunctive approaches, including neural stem cell therapy, mitochondrial-targeted strategies, nano-peptides, polyenylphosphatidylcholine, cognitive training, neuromodulation techniques (such as tDCS, TMS, and VR), dietary interventions, and lifestyle modification.

The included examples and references were chosen to represent innovation and therapeutic potential, reflecting the interpretation of relevance, novelty, and translational value. Product references related to the authors affiliated organization are discussed within this thematic framework, with attention to scientific rationale and application rather than promotional emphasis.

Discussion

The management of AD appears to be evolving toward integrative and non-pharmacological interventions, reflecting both the limitations of conventional drugs and a growing recognition of AD's multifactorial nature. Alternative approaches are being considered not only for symptom relief but also for their potential to modify disease processes and improve quality of life.

Neural cellular approach is currently being investigated as promising strategies, with evidence suggesting that transplanted neural cells may enhance neurogenesis, support synaptic connectivity, and reduce neuroinflammation in AD models [6,8].

Neural stem cell approach has emerged as a promising regenerative approach for AD, offering potential

to replace lost neurons and restore damaged neural networks. Human neural stem cells (hNSCs) have the capacity to substitute lost neurons in a functional manner, strengthen synaptic networks that have been compromised, and repair the damaged brain. Recent clinical trials have begun to evaluate the safety and efficacy of various stem cell approaches in AD patients. A randomized, double-blind, placebo-controlled, parallel-group phase 2a clinical trial tested the safety and efficacy of allogeneic mesenchymal stem-cell therapy, in slowing AD clinical progression [9]. The trial involved participants across ten centers in the United States and represents a significant advancement in translating stem cell research to clinical applications.

In a Stanford Medicine study, scientists transplanted stem cells into mice and found a reduction of brain abnormalities typical of AD [10]. These preclinical findings demonstrate the potential for stem cell therapy to address multiple aspects of AD pathology simultaneously, including neuroinflammation, amyloid pathology, and neuronal loss. The therapeutic mechanisms of neural stem cells in AD include direct neuronal replacement, secretion of neurotrophic factors, modulation of neuroinflammation, and promotion of endogenous neurogenesis [11]. Stem cell technology has the potential to revolutionize AD research. With the ability to self-renew and differentiate into various cell types, stem cells are valuable tools for disease modeling, drug screening, and cell therapy [14].

Although these approaches remain in the early stages of clinical development, they may eventually offer regenerative avenues for addressing neurodegeneration. Ongoing preclinical studies continue to refine protocols for cell delivery, integration, and safety. Some studies have shown that neural stem cells can modulate microglial activation, potentially influencing the inflammatory milieu in AD [13]. The ability of these cells to secrete neurotrophic factors such as BDNF and NGF adds the additional mechanism of therapeutic relevance. Moreover, transplanted neural stem cells may promote endogenous repair processes by stimulating resident progenitor populations [16]. Recent work also highlights the potential of induced pluripotent stem cell (iPSC)-derived neural cells to model patient-specific pathology and assess therapeutic responses [17]. While challenges remain—such as ensuring targeted delivery and avoiding tumorigenicity—strategies involving encapsulation or biomaterial scaffolds are being explored to improve safety and efficacy [15]. In addition, combining cellular therapies with neurorehabilitation or pharmacological agents may enhance functional recovery through synergistic effects [14]. In light of these developments, neural cell-based strategies are increasingly being positioned as part of a broader regenerative medicine approach for neurodegenerative diseases. Nonetheless, large-scale randomized clinical trials will be essential to determine clinical benefits and establish therapeutic guidelines.

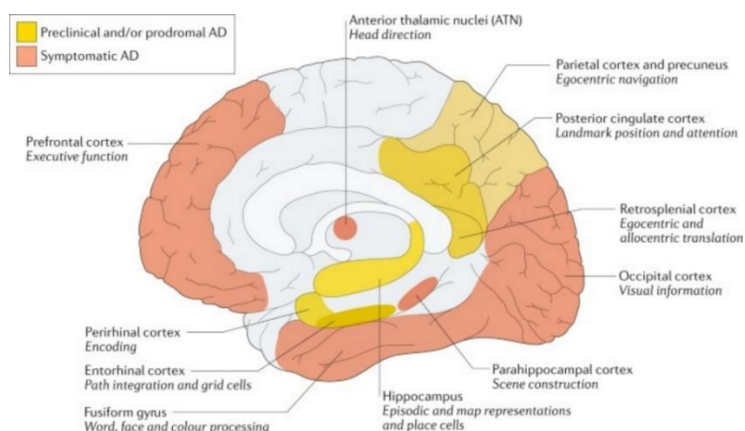


Figure 2: Anatomical illustration of AD-related neuropathological changes. Yellow areas are brain areas affected by Alzheimer's disease (AD) pathophysiology in preclinical and prodromal stages of the disease; red areas are brain areas affected in symptomatic stages of the disease. Source: Vann SD, Aggleton JP, Maguire EA. (2009) What does the retrosplenial cortex do? *Nat Rev Neurosci.* 10:792-802.

The hippocampus, a brain region central to memory formation and spatial navigation, is among the earliest and most severely affected structures in AD. One of the hallmark pathological changes observed in this region includes extensive **neuronal death**, attributed primarily to the accumulation of amyloid-beta plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein [18,17]. According to the research paper, the application of **hippocampal-derived stem cells** has demonstrated a potential to replenish neuronal populations and stimulate endogenous regeneration, offering a promising avenue for mitigating cell loss in preclinical models [6,13]. The approach using the **Targeted Brain Specific Precursor Stem Cells** of the hippocampus has incredible potential and plays an essential role in the clinical outcomes and progression of AD. As the disease advances, **hippocampal volume reduction** becomes increasingly evident, often correlating with the severity of memory impairment. Experimental interventions involving neural stem cell transplantation have suggested that volumetric increases in the hippocampus may be achievable, potentially reversing some structural degeneration [14,15]. Additionally, AD disrupts **functional connectivity** between the hippocampus and cortical regions, contributing to deficits in memory consolidation and cognitive flexibility. Preliminary findings indicate that restoring network integrity through cellular therapies may yield improvements in learning and communication [16]. Notably, **impairments in encoding new information** often represent the earliest clinical symptom of AD, reflecting the hippocampus's central role in short-term memory processes [19]. Efforts to preserve or augment the function of non-degenerated hippocampal neural precursors may enhance memory performance, particularly in early-stage interventions. Moreover, **hippocampal atrophy** has gained recognition as a **neuroimaging biomarker** for AD diagnosis, often used alongside cerebrospinal fluid and PET-based markers to increase diagnostic accuracy [2]. These findings collectively underscore the relevance of hippocampal-targeted regenerative cellular strategies such as the implementation of **Targeted Brain Specific Precursor Stem Cells** of the frontal lobe, hippocampus, whole brain and other required and damaged structures.

Hippocampal Targeted Brain Specific Precursor Stem Cells

1. Hippocampal stem cell therapy in Mild Cognitive Impairment (MCI) may offer therapeutic benefits for addressing key structural and functional changes observed in MCI. While most patients with mild cognitive impairment transition to AD, others develop non-AD dementia, remain in the MCI state, or improve indicating a critical window for therapeutic intervention [20]. Hippocampus Stem Cells in MCI might be helpful to reduce following structural changes: a) atrophy: early signs of MCI may include slight atrophy in the hippocampus, detectable with neuroimaging techniques such as MRI; b) memory decline: individuals with MCI may specifically report problems with memory that are greater than normal for their age, which corresponds to the hippocampal dysfunction; c) predictor of AD: hippocampal atrophy in MCI is considered a significant risk factor for the development of AD.
2. Hippocampus Stem Cells in AD: a) can present new cells into the region as well as help to regenerate own cells; b) might be helpful to regain the volume reduction as the hippocampus volume might be possible to increase by the introduction of new cells; c) disrupted connectivity: connections between the hippocampus and other brain regions deteriorate in AD, which can be restored to a certain extent and reflect on the compounding problems with memory, learning, and communication d) early symptom indicator: since the hippocampus is critical for memory, one of the earliest symptoms of AD is often difficulty remembering new information. The enhanced presence of not impaired hippocampus stem cells might lead to the positive outcomes in formation of a new memory; e) biomarker in diagnosis: because hippocampus atrophy is relatively specific to AD, it's used as a biomarker for diagnosing the disease, often in conjunction with other indicators.

Whole Brain Targeted Brain Specific Precursor Stem Cells

The ultimate goal of whole brain stem cell therapy is functional improvement. Whole brain stem cell therapy offers the potential to replace lost or damaged neurons in multiple regions affected by AD, including the hippocampus, cortex, basal forebrain, and amygdala. This broader application may address not only memory deficits but also language, executive function, and behavior. AD involves widespread neuroinflammation. Whole brain stem cell application may reduce systemic inflammation through the secretion of anti-inflammatory cytokines like IL-4 and TGF- β . Stem cells can activate resident neural stem or progenitor cells in different brain areas, encouraging intrinsic repair processes across the whole brain. They also have been shown to enhance the clearance of amyloid-beta and phosphorylated tau, both of which accumulate diffusely throughout the AD brain. Whole brain stem cell integration may help re-establish lost connections across multiple brain networks, essential for cognitive processing.

The Targeted Brain Specific Precursor Stem Cells could be from any part of the brain that has been involved in the AD process causing different clinical symptoms. For example, they might include the following impaired in AD regions:

- The **entorhinal cortex** is among the first regions to exhibit pathological changes, with early damage disrupting the transmission of information to and from the hippocampus [19].
- The cerebral cortex as progressive degeneration of this region, particularly in the temporal and

parietal lobes, is associated with deficits in language, sensory integration, and reasoning.

- The prefrontal cortex as involvement in later stages is linked to impairments in planning, decision-making, and judgment [21].
- Other association areas across various lobes, responsible for integrating sensory and cognitive information, also show functional decline, leading to difficulties in executing complex tasks.

Additionally, the **basal forebrain**, which includes cholinergic nuclei, undergoes degeneration that contributes to cognitive symptoms through diminished acetylcholine signaling.

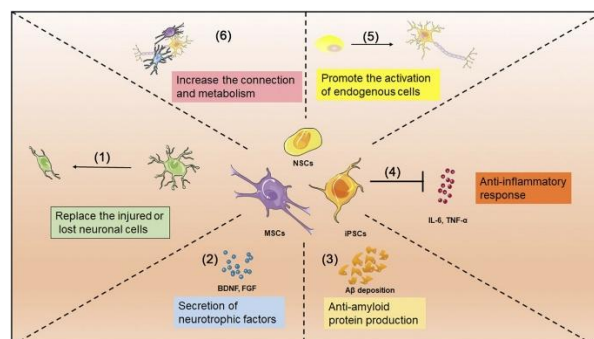


Figure 3: Stem cell mechanisms of action to treat AD. 1) Replacement of the injured or lost neuronal cells. 2) Secretion of neurotrophic factors [BDNF and fibroblast growth factor (FGF)]. 3) Anti-amyloid protein production. 4) Anti-inflammatory response [interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α)]. 5) Promotion of the activation of endogenous stem cells. 6) Improvement of the metabolic activity of neurons in the brain. Source: Si Zizhen. (2021) Stem Cell Therapies in Alzheimer's Disease: Applications for Disease Modeling. *J Pharmacol Experimental Thera.* 377(2):207-17.

As AD progresses, widespread atrophy becomes more pronounced, with general loss of brain volume and enlargement of the ventricles due to the reduction in cortical and subcortical tissue. These anatomical changes correlate with worsening clinical symptoms, including profound memory loss, personality alterations, and a diminishing ability to perform activities of daily living [1]. Understanding the pattern and progression of regional brain involvement provides a framework for targeting interventions and monitoring disease trajectory.

Mitochondrial-targeted interventions, often referred to as "mito-organell" therapies, aim to restore cellular energy production and reduce oxidative damage. Given that mitochondrial dysfunction contributes to AD pathophysiology, these interventions have shown encouraging results in preclinical studies and may help delay progression by supporting bioenergetic stability [22,23]. In experimental models, compounds enhancing mitochondrial dynamics—such as fission and fusion processes—have demonstrated neuroprotective effects [8]. These therapies may also influence mitophagy, a mechanism essential for clearing dysfunctional mitochondria, which is often impaired in AD [23]. Some molecules aim to enhance mitochondrial biogenesis by activating pathways such as PGC-1 α , which supports overall cellular resilience [25]. In parallel, antioxidant therapies targeting mitochondrial reactive oxygen species (ROS) have shown potential to reduce oxidative damage in neuronal cells [24]. Approaches involving coenzyme Q10, MitoQ, and SS-31 peptides have entered early clinical exploration due to their ability to

localize within mitochondria and mitigate damage.

Mito-Organells of the whole brain in AD are one of the great examples of mitochondrial-targeted interventions which includes:

1. **Enhanced Brain-Wide Energy Metabolism**

Neurons depend heavily on adenosine triphosphate (ATP) generated by mitochondria to support synaptic transmission and cognitive processes. Restoring mitochondrial function across different brain areas may help sustain global neuronal activity and cognitive resilience [22].

2. **Reduction of Systemic Oxidative Stress**

Mitochondrial dysfunction contributes to the overproduction of reactive oxygen species (ROS), which damage lipids, proteins, and DNA. Supporting mitochondrial antioxidant defense mechanisms throughout the brain may limit oxidative injury and slow neurodegenerative changes.

3. **Preservation of Synaptic Plasticity**

Synaptic function relies on localized mitochondrial activity, especially in high-demand regions like the hippocampus and prefrontal cortex. Enhancing mitochondrial health can help preserve synaptic plasticity, which underpins learning and memory [25].

4. **Regulation of Calcium Homeostasis**

Mitochondria are involved in buffering intracellular calcium, which is critical for neural excitability and synaptic function. Whole-brain mitochondrial support may help prevent calcium dysregulation, which is frequently observed in AD and contributes to neuronal damage [23].

5. **Mitigation of Neuroinflammation**

Mitochondrial dysfunction can activate innate immune responses in the brain, exacerbating inflammation. Improved mitochondrial function may reduce the release of pro-inflammatory signals and help modulate microglial activity across brain regions.

6. **Facilitation of Neurogenesis and Repair**

Healthy mitochondria are necessary for the proliferation and differentiation of neural progenitor cells. Enhancing mitochondrial activity in neurogenic zones such as the hippocampus and subventricular zone may support endogenous repair mechanisms [14].

7. **Potential Synergy with Other Therapeutics**

Mitochondrial-targeted strategies may enhance the effectiveness of other interventions, such as cognitive training, stem cell therapy, or neuromodulation, by improving neuronal energy availability and reducing cell stress.

Mito-Organelles of Frontal Lobe in AD

In AD, mitochondrial dysfunction is increasingly recognized as a contributing factor to neuronal degeneration and cognitive decline. The frontal lobe—particularly the prefrontal cortex—is responsible for executive functions such as reasoning, planning, attention, and working memory, all of which are commonly affected in AD. Therapeutic strategies that support or restore mitochondrial function in this region may provide several potential advantages.

1. **Support for Executive Functions**

The frontal lobe has high energy demands due to its complex cognitive tasks. Mitochondrial dysfunction in this region has been associated with impairments in attention, decision-making, and task switching. Therapies aimed at enhancing mitochondrial energy production may contribute to improved performance in these domains.

2. **Reduction in Oxidative Stress**

Mitochondria are a major source of reactive oxygen species (ROS), which contribute to oxidative damage in neurons. Interventions that target mitochondrial ROS production may help protect frontal lobe neurons from oxidative injury, which is prominent in AD pathology.

3. **Preservation of Synaptic Function**

Synaptic plasticity in the frontal cortex is energy-dependent and relies on mitochondrial regulation of calcium signaling. By stabilizing mitochondrial dynamics and transport, therapeutic approaches may help maintain synaptic function and support communication between neurons [25].

4. **Modulation of Neuroinflammation**

Mitochondrial dysfunction can promote neuroinflammatory responses by releasing pro-inflammatory molecules. Therapies that improve mitochondrial health may assist in reducing inflammatory signaling in the frontal cortex, which has been linked to progression of cognitive symptoms.

5. **Improved Neuronal Survival**

The restoration of mitochondrial function in the frontal lobe may enhance neuronal resilience and delay cell loss. This may be particularly relevant in early stages of AD, where frontal lobe metabolism and connectivity begin to decline [22].

6. **Promotion of Mitochondrial Biogenesis**

Certain therapeutic agents and lifestyle interventions, such as physical activity or mitochondrial-targeted compounds (e.g., PQQ, CoQ10), have been studied for their capacity to stimulate mitochondrial biogenesis, which may benefit frontal lobe metabolism in AD [26].

Furthermore, the interplay between mitochondrial health and calcium homeostasis also represents an emerging area of interest, as calcium dysregulation is a known contributor to neurodegenerative pathology [27]. In addition to energy production, mitochondria play a role in apoptosis regulation, and modulating these pathways may support neuronal survival. Clinical trials investigating mitochondrial enhancers are ongoing and may offer insights into safety, tolerability, and long-term benefits in AD populations [22]. Integrating mitochondrial-targeted therapies with other interventions such as cognitive training or neurostimulation may yield synergistic outcomes. Moreover, biomarkers of mitochondrial function are being explored to guide patient stratification and monitor therapeutic response [28,22]. These insights collectively support the relevance of mitochondria as a therapeutic target and highlight the need for continued translational research in this area.

Nano-peptides are also being explored for their ability to cross the blood-brain barrier and modulate pathological protein aggregation. In addition to this targeted mechanism, the peptide formulations may exhibit anti-inflammatory and neuroprotective properties, suggesting a broad therapeutic potential [29].

Nano Organo Peptides of Frontal Lobe are one of the great examples of this technology and approach that potentially benefits in following:

1. **Targeted Delivery Across the Blood–Brain Barrier (BBB):** One of the major advantages of nano-formulated peptides is their ability to cross the BBB and accumulate in specific brain regions, including the frontal lobe. Nanocarriers (e.g., liposomes, polymeric nanoparticles) enhance bioavailability and localization of peptides with neuroprotective properties [30].
2. **Modulation of Frontal Lobe Synaptic Activity:** Nano-organopeptides can influence neurotransmitter systems and synaptic plasticity mechanisms involved in prefrontal functions. Some peptides mimic growth factors or signaling molecules, potentially supporting synaptic maintenance and cognitive flexibility.
3. **Reduction of Local Neuroinflammation:** Peptide-based agents with anti-inflammatory properties can reduce glial activation and cytokine release in the frontal cortex. This may help mitigate executive dysfunction associated with chronic neuroinflammation. As evidence, the nano-peptides targeting NF- κ B and IL-1 β pathways have shown regional specificity in reducing cortical inflammation.
4. **Improvement in Executive and Behavioral Symptoms:** By supporting cellular signaling and reducing oxidative stress, nano-organopeptides may improve behaviors mediated by the frontal lobe, including mood regulation, planning, and inhibitory control.
5. **Neuroprotection and Anti-Apoptotic Effects:** Some nano-peptides function by preventing apoptosis through mitochondrial membrane stabilization and caspase inhibition in cortical neurons. This effect is particularly relevant to slowing neuronal loss in AD.

Nano Organo Peptides of Thalamus in AD:

Targeting the thalamus with **nano-organopeptides**—small biologically active peptides delivered via nanocarriers—represents an emerging approach in neurotherapeutics that may offer unique advantages in AD treatment.

1. **Support for Cognitive Integration and Sensory Processing:** The thalamus facilitates communication between distant brain regions. By stabilizing synaptic transmission and enhancing neurotransmitter signaling, nano-organopeptides may help maintain thalamocortical connectivity, which is often disrupted in AD. Studies suggest thalamic hypoactivity contributes to disorganized cortical signaling in AD, and peptide modulation of GABAergic and glutamatergic transmission may normalize these circuits.
2. **Reduction of Neuroinflammation in Thalamic Nuclei:** Neuroinflammation affects thalamic relay nuclei and is associated with attentional deficits in AD. Nano-peptides with anti-inflammatory properties can be selectively delivered to these nuclei using targeted nanocarriers.
3. **Restoration of Thalamic Atrophy and Connectivity:** Structural MRI studies have shown that thalamic atrophy correlates with disease progression in AD. Nano-organopeptides that promote neurotrophic signaling (e.g., BDNF or NGF analogs) may support neuronal survival in thalamic subregions.
4. **Targeted Delivery Across the Blood–Brain Barrier:** Advanced nano-formulations can be

engineered to deliver peptides directly to deep-brain regions like the thalamus, overcoming one of the primary limitations in peptide therapy.

5. **Potential Modulation of Consciousness and Sleep–Wake Cycles:** The thalamus is involved in arousal and circadian rhythm regulation. Some nano-peptides may influence thalamocortical oscillations, potentially benefiting sleep quality and alertness—both of which are frequently disturbed in AD.

Recent advances in peptide chemistry and drug delivery technologies have facilitated the design of peptide-based approach with enhanced stability and bioavailability. These compounds often mimic the endogenous molecules while incorporating modifications that extend their half-life and reduce degradation. Importantly, peptide therapeutics may be tailored to target synaptic loss, mitochondrial dysfunction, and chronic inflammation—hallmarks of AD pathology [18]. Preclinical investigations have shown that certain neuroprotective peptides can reverse learning and memory deficits in transgenic mouse models. Their targeted mechanism of action allows for high specificity, reducing off-target effects commonly observed in traditional small molecule drugs. Advanced delivery systems such as liposomes and nanoparticles further enhance brain penetration and controlled release. Some peptides might have the ability to interfere directly with amyloid-beta or tau aggregation, offering a potential for disease modification. Emerging data also support their role in supporting neurotrophic signaling and neuronal survival. While clinical translation remains in early stages, the peptide-based approach represents a growing field that integrates molecular precision with therapeutic versatility [31].

Nutraceuticals such as polyenylphosphatidylcholine (PPC) (for example in the form of **Plaqx Forte softgels**) are of interest due to their role in maintaining membrane fluidity and supporting cholinergic function. This compound has been associated with protective effects against oxidative stress and inflammation, and may contribute to neuronal resilience [32]. PPC has been studied for its role in hepatic and neuronal membrane repair, offering potential cross-benefits for systemic and neurological health [35]. It adds fluidity and promotes stability and function of transmembrane proteins, including the membranes of energy-producing mitochondria, neuronal and intestinal cell membranes. Plaqx Forte also has antioxidant, cytoprotective and fluid-regulating effects [36]. It is known to support lipid metabolism and modulate membrane-bound enzyme activity, which may be relevant in neurodegenerative conditions [37]. Some studies have indicated that long-term supplementation with phosphatidylcholine can attenuate age-related cognitive decline and maintain attention and memory performance. Clinical studies have suggested that PPC supplementation may improve cognitive function in patients with mild cognitive impairment and early-stage dementia through multiple mechanisms, including enhanced membrane integrity, improved mitochondrial function, and reduced inflammation. The compound's ability to cross the blood-brain barrier and incorporate into neuronal membranes makes it particularly relevant for neurodegenerative conditions [26]. The compound's amphiphilic structure allows it to integrate into cell membranes, potentially improving synaptic function and signal transduction [38]. There is also emerging interest in its antioxidant properties, particularly in reducing lipid peroxidation in neuronal membranes [39]. Evidence from preclinical models suggests that it may influence neurotransmitter levels, including acetylcholine and dopamine, which are commonly dysregulated in AD. Furthermore, phosphatidylcholine may support mitochondrial function by enhancing membrane integrity and electron transport processes.

Its tolerability profile appears favorable, with minimal reported side effects in clinical use for other indications. Although further validation is warranted, the product's safety profile and mechanistic basis support its inclusion in adjunctive care discussions.

Non-pharmacological interventions continue to play an important role in holistic care. Cognitive training and rehabilitation programs have demonstrated benefits in preserving or enhancing cognitive function, particularly when these interventions are tailored to individual profiles [5]. These programs may focus on specific domains such as attention, working memory, or language, depending on the individual's cognitive profile. Emerging evidence supports the use of adaptive training algorithms that adjust task difficulty based on real-time performance [40]. Digital platforms have made it feasible to deliver such interventions remotely, increasing accessibility for patients in diverse settings. Cognitive interventions may also promote structural brain changes, including increased cortical thickness and hippocampal volume in some studies [41]. Group-based cognitive stimulation activities, including social and recreational tasks, have shown promise in enhancing mood and engagement alongside cognition [42]. Longitudinal studies suggest that regular engagement in mentally stimulating activities may contribute to cognitive reserve, potentially delaying the onset of clinical symptoms [3]. Multimodal programs combining cognitive tasks with physical activity or mindfulness practices are also under investigation for their synergistic effects. Overall, cognitive interventions represent a flexible and increasingly evidence-based component of comprehensive AD care.

Transcranial direct current stimulation (tDCS). Recent clinical trials have demonstrated that tDCS delivered twice daily over six weeks can improve cognitive function in patients with AD, establishing it as a promising therapeutic intervention. tDCS works by applying low-intensity electrical current to specific brain regions, modulating neuronal excitability and potentially enhancing synaptic plasticity [43]. The mechanism of tDCS involves subthreshold modulation of neuronal membrane potentials, with anodal stimulation generally increasing excitability and cathodal stimulation decreasing it [44,45]. In AD, tDCS is typically applied to regions showing early pathological changes, such as the temporoparietal cortex and prefrontal regions [30].

tDCS has also shown efficacy in reducing depression and anxiety symptoms in older adults, addressing important comorbidities that frequently accompany AD [46]. The ability to simultaneously target cognitive symptoms and mood disturbances makes tDCS particularly attractive for holistic AD management. Protocol optimization remains an active area of research, with studies investigating optimal electrode placement, current intensity, session duration, and treatment frequency [47,30]. Home-based tDCS systems are being developed to improve accessibility and allow for extended treatment protocols [48].

Transcranial magnetic stimulation (TMS). Transcranial magnetic stimulation (TMS) has emerged as a promising non-invasive brain stimulation technique for treating cognitive impairment in AD, though evidence regarding long-term efficacy remains limited [49]. Meta-analyses have demonstrated that repetitive TMS (rTMS) can significantly improve cognitive ability in patients with mild to moderate AD, with stimulation of multiple sites and long-term treatment showing better outcomes. A comprehensive systematic review revealed an overall medium-to-large effect size (0.77) favoring active rTMS over sham

stimulation in improving cognitive functions in patients with mild cognitive impairment and AD [50]. High-frequency rTMS targeted to the left dorsolateral prefrontal cortex (DLPFC) for over 20 sessions has been shown to induce the greatest cognitive improvement, with effects lasting for more than one month after the final treatment [51]. Recent large multisite double-blind randomized trials have investigated both short and long-term efficacy of rTMS applied to AD patients at mild to moderate stages using treatment durations of 2 or 4 weeks [52]. High-frequency left DLPFC stimulation and low-frequency right DLPFC rTMS may specifically improve memory function, while high-frequency right inferior frontal gyrus rTMS may enhance executive performance [50]. The treatment has shown significant improvements in cognition as measured by ADAS-cog scores, though effects on MMSE scores remain inconsistent across studies [33].

Novel interventional targets such as the precuneus may represent more effective stimulation sites for improving AD-associated cognitive performance. TMS utilizes magnetic fields to non-invasively stimulate targeted brain regions from outside the skull, making it a safer alternative to invasive procedures [53]. Despite promising results, researchers emphasize that more large-scale randomized controlled trials are needed to fully validate the therapeutic potential of rTMS in AD treatment.

Hyperbaric oxygenation therapy (HBOT) involves the administration of oxygen at higher-than-atmospheric pressures in a controlled chamber. HBOT has been suggested to improve mitochondrial function, reduce neuroinflammation, and enhance neurogenesis in preclinical AD models [54]. The therapeutic mechanism of HBOT is thought to involve increased oxygen dissolution in plasma, which can reach tissues with compromised vascular supply that are typically hypoxic in AD. Studies have demonstrated that repeated HBOT sessions may promote angiogenesis and improve blood-brain barrier integrity, potentially facilitating better nutrient delivery and waste clearance from neural tissue. Preliminary clinical data indicate that HBOT may improve cerebral perfusion and cognitive performance, although more controlled trials are needed to confirm efficacy and long-term safety.

Ozone therapy, which delivers a mixture of ozone and oxygen, has been investigated for its potential anti-inflammatory and antioxidant effects. Some studies report that ozone may modulate oxidative stress and cytokine levels, contributing to neuroprotective outcomes [55]. The proposed mechanisms of ozone therapy in neurodegeneration include the activation of antioxidant enzyme systems such as superoxide dismutase, catalase, and glutathione peroxidase, which may help counteract the oxidative damage characteristic of AD. Ozone administration methods vary considerably, including intravenous ozone-oxygen mixtures, rectal insufflation, ozonated water consumption, and topical applications, each with different bioavailability and systemic effects. The therapy is thought to induce a controlled oxidative stress response that subsequently upregulates endogenous antioxidant defenses, a phenomenon known as hormesis or oxidative preconditioning. Although data in AD populations remain limited, ozone therapy continues to be explored within integrative and experimental frameworks.

Virtual reality (VR)-based interventions offer immersive environments for cognitive training and behavioral engagement. In older adults and early-stage AD patients, VR has been shown to enhance spatial navigation, memory recall, and emotional well-being [56]. VR allows for personalized and adaptive interaction, which may increase engagement and motivation. Additionally, VR can be combined with

physical exercise or cognitive tasks for multimodal therapy delivery.

Systematic reviews have confirmed the efficacy of VR-based training programs for improving cognitive disorders in patients, with particular benefits observed in memory, attention, and executive function domains [57]. VR environments can simulate real-world scenarios, allowing patients to practice functional activities in a safe, controlled setting. The immersive nature of VR can enhance engagement and motivation, particularly important considerations for individuals with AD who may have difficulty with traditional cognitive training approaches [58]. VR also allows for precise control over environmental factors and the ability to gradually increase complexity as patients improve [59].

Applications include virtual environments for spatial navigation training, which specifically targets hippocampal function; virtual reality exposure therapy for addressing anxiety and behavioral symptoms [60], and social VR platforms that can help maintain social connections and reduce isolation [61].

Lifestyle factors such as diet, exercise, sleep hygiene, and social engagement are increasingly recognized as modifiable contributors to cognitive health. Adherence to Mediterranean-style dietary patterns and sustained physical activity have been associated with delayed onset and reduced progression of cognitive decline [62,4]. These strategies are frequently integrated into broader public health and prevention frameworks. Memory-enhancing diets, particularly those rich in polyphenols, omega-3 fatty acids, and antioxidants, have been associated with neuroprotective effects and improved cognitive outcomes [63]. Physical exercise represents one of the most well-established lifestyle interventions for cognitive health, with benefits that extend beyond cardiovascular fitness to include direct effects on brain structure and function [64]. Aerobic exercise has been shown to promote neurogenesis, enhance synaptic plasticity, and increase production of brain-derived neurotrophic factor (BDNF) [65]. Resistance training and multicomponent exercise programs that combine aerobic, strength, balance, and flexibility components have shown particular promise for older adults at risk for cognitive decline [66]. These programs address multiple aspects of physical and cognitive health simultaneously [67].

Good sleep hygiene, including consistent sleep routines and reduction of nighttime disturbances, supports memory consolidation and is linked to reduced amyloid deposition [68]. Regular social engagement may buffer against cognitive decline by enhancing emotional well-being and stimulating cognitive reserve [69]. Structured memory training exercises have shown efficacy in improving specific cognitive functions and may contribute to maintained independence in daily activities. Combining these lifestyle approaches appears to offer cumulative benefits and aligns with current recommendations for dementia risk reduction [1].

Taken together, the approaches discussed here reflect a growing interest in diversifying the therapeutic landscape for AD. Continued research and clinical evaluation will be essential to better understand how these interventions may be integrated, personalized, and scaled for meaningful patient outcomes.

Conclusion

AD remains a complex and multifactorial condition, requiring approaches that transcend conventional

pharmacological paradigms [1]. This commentary has highlighted a diverse array of innovative and emerging interventions that span cellular therapies [6,16], mitochondrial and peptide-based strategies [22,31], nutraceuticals [32], neuromodulation techniques [34], and lifestyle-based modifications [62,3]. The potential of neural stem cells, mito-organells, nano-peptides, Plaqx Forte and other alternative approaches, including tDCS, TMS, HBOT, ozone, diet, exercises, memory trainings gaining more attention as prospective and holistic application of innovative AD's management [36]. Each of these approaches targets different yet interconnected aspects of the disease process, offering opportunities for synergistic treatment models [18]. While many of these interventions are still in early stages of clinical validation, their potential for personalized application and low-risk integration into patient care strategies makes them worthy of continued exploration [14]. Importantly, these developments reflect a paradigm shift toward holistic, preventive, and mechanistically informed treatment frameworks [2]. As research advances, a clearer understanding of optimal timing, patient selection, and combined modality approaches will be essential [28,22]. Collaborative efforts between clinicians, researchers, and stakeholders will play a pivotal role in translating these promising innovations into effective, accessible care for individuals affected by AD [1].

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