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Recent treatment technologies for Alzheimer disease: a review

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ABSTRACT

Alzheimer disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, confusion, and behavioural changes. It primarily impairs brain function, leading to a gradual decline in cognitive abilities such as thinking, reasoning, and problem-solving. As the most common cause of dementia, AD reflects a deterioration in mental faculties severe enough to disrupt daily activities. The disease advances slowly and typically worsens over time. Currently available pharmacological treatments address only the symptoms of AD, largely due to the restrictive nature of the blood-brain barrier (BBB), which impedes the entry of therapeutic agents into the central nervous system. This review summarizes recent technological advances in AD treatment, focusing on monoclonal antibody (mAb) therapies, nanotechnology-based delivery systems, and gene-editing approaches. mAb therapies encompass passive immunotherapy and tau-targeting interventions aimed at mitigating pathological protein accumulation. Nanotechnology-based strategies for AD include the use of nano-carriers, nano-polymers, dendritic nanoparticles, liposomes, and exosomes. These platforms have demonstrated enhanced drug delivery across the BBB with minimal adverse effects. Furthermore, gene-editing techniques target specific genetic variants, such as apolipoprotein E4 (*ApoE4*), which are implicated in both early- and late-onset forms of AD. Gene-editing is emerging as a promising therapeutic modality for correcting dominant mutations associated with AD pathogenesis. Despite these advances, further research and clinical trials are essential in order to develop and validate novel treatment strategies for AD.

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1. Introduction

Alzheimer disease (AD) is a progressive neurodegenerative disorder that advances through preclinical, early, moderate, and ultimately late stages. Initial symptoms typically involve general cognitive impairment, most notably memory loss. As cognitive decline progresses, physical disabilities (such as difficulties with walking, eating, and sitting) signal the transition to the advanced stages of the disease. The aetiology of AD is multifactorial and not yet fully understood. While the accumulation of amyloid-beta (Aβ) and tau proteins is considered central to AD pathogenesis, numerous additional factors may contribute to it, including neuroinflammation, acetylcholine deficiency, glutamate imbalance, autophagy dysfunction, mitochondrial impairment, disrupted cholesterol homeostasis, oxidative stress, and insulin resistance. Although several theories have been proposed to explain the pathophysiology of AD, a unified hypothesis remains elusive.

AD is currently incurable, and available treatments primarily aim at alleviating symptoms and at modestly improving cognitive function. Therapeutic limitations stem from two major challenges: first, the disease progresses *via* multiple pathogenic pathways that are difficult to delineate; second, the blood-brain barrier (BBB) significantly impedes drug delivery to the central nervous system, thereby restricting therapeutic efficacy.

2. Therapeutic techniques of AD

Various therapeutic approaches have been explored over the past decades, yet existing pharmacological agents predominantly target symptoms rather than underlying disease mechanisms. These drugs have not demonstrated consistent efficacy in improving cognition, quality of life, functional capacity, or overall behavioural outcomes. The development of novel therapeutic modalities is essential for the advancement of the understanding of AD pathophysiology and enhancing treatment outcomes. To date, only two classes of drugs have been approved by the US Food and Drug Administration (FDA) for symptomatic treatment: cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate receptor modulators. ChEIs such as galantamine, donepezil, and rivastigmine are indicated for mild to moderate AD and offer temporary symptomatic relief. More recently, two monoclonal antibodies (mAbs) – lecanemab and aducanumab – have been approved for targeting Aβ plaque accumulation in the AD brain. Conventional therapies are limited by low efficacy, hepatotoxicity, gastrointestinal side effects, and poor BBB penetration[1]. This review aims to highlight recent technological advances in AD treatment.

3. Monoclonal antibody therapies

Several passive immunotherapy agents have entered clinical trials for AD. Anti-amyloid mAbs represent the first disease-modifying treatments that slow clinical decline by targeting core biological mechanisms. Cummings *et al.*[1] have reported trials demonstrating a 15%–25% reduction in measurable Aβ plaques and an approximately 30% decrease in cognitive decline, which is considered clinically meaningful for preserving cognitive function and delaying disease progression. The approval of these agents marks a paradigm shift in AD treatment. Hong[2] has evaluated the efficacy, safety profiles, and adverse effects of aducanumab and lecanemab across different stages of AD, reporting improved therapeutic outcomes. Further research[3] has introduced a chimeric peptide, D20, which selectively promotes tau dephosphorylation. A single dose of D20 significantly reduced phosphorylated tau at multiple AD-relevant sites and lowered total tau levels, suggesting its potential as a therapeutic candidate for AD and related tauopathies.

4. Nanotechnology techniques for AD treatment

Ongoing research explores the use of nanotechnology and nanoparticles (NPs) for targeted drug delivery in AD, aiming to minimize adverse effects. Nanotechnology has emerged as a promising strategy for enhancing therapeutic efficacy.

A prior study[4] has reported the development of

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biodegradable and biocompatible dendrimeric delivery systems to transport flurbiprofen (FP; a drug with limited brain penetrability) across the BBB and release it at targeted sites. The conjugation of FP to dendrimeric poly(epsilon-lysine) macromolecules significantly improved BBB permeability.

In another study[5] researchers have synthesized a nanoscale cobalt/niacin metal–organic framework (Co/Niacin-MOF). *In vitro* and molecular docking analyses of acetylcholinesterase inhibitors (AChEIs) identified two compounds – 4-(1H-benzo[d]imidazol-2-yl)phenyl 4-methylbenzene sulfonate and 4-(benzo[d]thiazol-2-yl)phenyl benzoate – as promising candidates compared to donepezil.

Further research[6] has investigated FP–peptide delivery systems featuring an apolipoprotein E (ApoE)-mimicking peptide in order to facilitate receptor-mediated transcytosis across the BBB. The successful synthesis and attachment of FP to lysine-terminal molecular branches has demonstrated enhanced delivery without cytotoxicity.

Khope *et al.*[7] have emphasized that nanocarriers can deliver therapeutic agents directly to targeted regions of the central nervous system; a strategy particularly relevant for neurodegenerative and malignant conditions. *In vivo* studies have shown promising results for AD nanomedicines, including curcumin-loaded solid NPs, quercetin-loaded exosomes, and resveratrol delivered *via* non-metal inorganic NPs[8].

While nanomedicine holds substantial promise for AD treatment, further research is needed in order to evaluate the safety and efficacy of these emerging therapies.

5. Gene-editing technology for AD treatment

The clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) technology offers a transformative approach to AD therapy by targeting specific genes, such as apolipoprotein E4 (*ApoE4*), which are implicated in both early- and late-onset AD. This method also addresses challenges related to therapeutic delivery.

One study[9] has employed the CRISPR-Cas9 system derived from *Streptococcus pyogenes* to deactivate the *PSEN1M146L* allele in human fibroblasts, resulting in reduced extracellular Aβ levels and decreased presenilin (PSEN) expression. These findings underscore the potential of CRISPR-Cas9 to selectively mitigate AD-associated phenotypes. Additionally, Chen *et al.*[10] have introduced a gene-clustering framework using convolutional neural networks, termed Dual-Stream Subspace Clustering Network (DS-SCNet). This method has effectively identified biologically meaningful gene clusters from large-scale single-cell RNA sequencing data and has outperformed conventional clustering techniques across multiple evaluation metrics.

6. Conclusion

This review has outlined recent technological innovations in AD treatment, including monoclonal antibody therapies, gene-editing strategies, and nanotechnology-based delivery systems. Monoclonal antibody therapies encompass passive immunotherapy and tau-targeting approaches, while nanotechnology has demonstrated enhanced drug transport across the BBB with minimal adverse effects. Gene-editing techniques targeting specific genes, offer promising avenues for addressing dominant mutations associated with AD onset. Nonetheless, continued research and clinical validation are essential for the development of effective and safe therapeutic strategies.

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Conflicts of interest

None exist.

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