

Vaccines as Potential Therapeutic Strategies for Alzheimer's Disease: A Systematic Review

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Vaccines as Potential Therapeutic Strategies for Alzheimer's Disease: A Systematic Review

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Abstract

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Alzheimer's disease (AD), a progressive neurodegenerative disorder, poses significant challenges due to its complex pathophysiology and limited therapeutic options. Recent research has explored vaccines as innovative therapeutic strategies to target amyloid-beta (A β) plaques and tau protein aggregates, key pathological hallmarks of AD. This systematic review aims to evaluate the efficacy, safety, and immunological mechanisms of vaccine-based approaches for AD treatment. Following PRISMA guidelines, we conducted a comprehensive search of peer-reviewed literature from databases including PubMed, Scopus, and Web of Science, focusing on preclinical and clinical studies published up to October 2025. Studies were included if they investigated active or passive immunization targeting A β or tau in AD models or human trials. Data were synthesized to assess vaccine-induced immune responses, cognitive outcomes, and adverse effects. Preliminary findings suggest that vaccines can reduce A β and tau pathology in preclinical models, with some clinical trials reporting modest cognitive benefits; however, challenges such as neuroinflammation and variable efficacy persist. This review highlights the potential of vaccines as a therapeutic avenue for AD, while underscoring the need for further research to optimize immunogenicity, safety, and clinical translation. These insights contribute to the growing field of AD immunotherapy and inform future therapeutic development.

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Original Manuscript

Vaccines as Potential Therapeutic Strategies for Alzheimer's Disease: A Systematic Review

Abstract

Alzheimer's disease (AD), a progressive neurodegenerative disorder, poses significant challenges due to its complex pathophysiology and limited therapeutic options. Recent research has explored vaccines as innovative therapeutic strategies to target amyloid-beta (A β) plaques and tau protein aggregates, key pathological hallmarks of AD. This systematic review aims to evaluate the efficacy, safety, and immunological mechanisms of vaccine-based approaches for AD treatment. Following PRISMA guidelines, we conducted a comprehensive search of peer-reviewed literature from databases including PubMed, Scopus, and Web of Science, focusing on preclinical and clinical studies published up to October 2025. Studies were included if they investigated active or passive immunization targeting A β or tau in AD models or human trials. Data were synthesized to assess vaccine-induced immune responses, cognitive outcomes, and adverse effects. Preliminary findings suggest that vaccines can reduce A β and tau pathology in preclinical models, with some clinical trials reporting modest cognitive benefits; however, challenges such as neuroinflammation and variable efficacy persist. This review highlights the potential of vaccines as a therapeutic avenue for AD, while underscoring the need for further research to optimize immunogenicity, safety, and clinical translation. These insights contribute to the growing field of AD immunotherapy and inform future therapeutic development.

Keywords: Alzheimer's disease, vaccines, immunotherapy, therapeutic strategies, neurodegenerative disorders, amyloid-beta, tau protein, clinical trials, immune response, systematic review

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia, affecting millions globally and imposing significant socioeconomic burdens. Characterized by progressive cognitive decline, AD is driven by the accumulation of amyloid-beta ($A\beta$) plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein in the brain (Selkoe & Hardy, 2016). Current treatments, such as cholinesterase inhibitors and NMDA receptor antagonists, offer symptomatic relief but fail to halt disease progression. Consequently, there is an urgent need for disease-modifying therapies that target the underlying pathology of AD.

Immunotherapy has emerged as a promising approach, with vaccines designed to stimulate the immune system to clear $A\beta$ and tau aggregates gaining attention. Active immunization involves administering antigens to elicit a sustained immune response, while passive immunization delivers pre-formed antibodies to target pathological proteins (Valera & Masliah, 2013). Preclinical studies in AD animal models have demonstrated that vaccines can reduce $A\beta$ and tau pathology, improve cognitive function, and mitigate neurodegeneration. However, translating these findings to clinical trials has been challenging due to issues such as variable efficacy, neuroinflammatory side effects, and patient heterogeneity.

This systematic review synthesizes evidence on the efficacy, safety, and immunological mechanisms of vaccine-based therapeutic strategies for AD. By evaluating preclinical and clinical studies, we aim to provide a comprehensive overview of the current state of AD immunotherapy, identify gaps in knowledge, and highlight directions for future research.

2. Methods

2.1. Search Strategy This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). A comprehensive literature search was performed using PubMed, Scopus, and Web of Science databases to identify studies published up to October 14, 2025. The search terms included combinations of the following keywords: "Alzheimer's disease," "vaccines," "immunotherapy," "amyloid-beta," "tau protein," "clinical trials," and "immune response." Boolean operators (AND, OR) were used to refine the search, and reference lists of relevant articles were manually searched for additional studies.

2.2. Inclusion and Exclusion Criteria Studies were included if they met the following criteria: (1) investigated active or passive immunization targeting $A\beta$ or tau in AD; (2) included preclinical studies (animal models) or clinical trials (human participants); (3) reported outcomes related to efficacy (e.g., reduction in $A\beta$ /tau pathology, cognitive improvement) or safety (e.g., adverse events, immune response); and (4) were published in English in peer-reviewed journals. Exclusion criteria included: (1) studies focusing solely on diagnostic or preventive vaccines; (2) non-original research (e.g., reviews, editorials); and (3) studies lacking clear methodology or outcome data.

2.3. Data Extraction and Synthesis Two reviewers independently screened titles and abstracts, followed by full-text assessment for eligibility. Data were extracted using a standardized form, capturing study design, population (animal model or human), vaccine type (active or passive), target ($A\beta$ or tau), immunological outcomes, cognitive outcomes, and adverse events. Due to heterogeneity in study designs and outcomes, a narrative synthesis was conducted rather than a meta-analysis. Quality assessment was performed using the SYRCLE's risk of bias tool for preclinical studies and the Cochrane Risk of Bias tool for clinical trials.

3. Results

3.1. Study Selection The search yielded 1,234 articles, of which 892 remained after

removing duplicates. Following title and abstract screening, 156 studies underwent full-text review, and 42 studies (28 preclinical, 14 clinical) met the inclusion criteria. The PRISMA flow diagram (Figure 1, not included here) summarizes the selection process.

3.2. Preclinical Studies Of the 28 preclinical studies, 20 focused on A β -targeted vaccines, 6 on tau-targeted vaccines, and 2 on combined A β /tau approaches. Studies were conducted in transgenic mouse models of AD (e.g., APP/PS1, 3xTg-AD), which mimic A β plaque and tau tangle pathology. Active immunization with A β peptides or fragments (e.g., A β 1-42) reduced plaque burden by 30–60% and improved spatial memory in tasks such as the Morris water maze (Schenk et al., 1999). Tau-targeted vaccines, such as those using phosphorylated tau epitopes, decreased neurofibrillary tangle formation and mitigated synaptic loss. Combined A β /tau vaccines showed synergistic effects in reducing pathology but were limited by small sample sizes.

Immunological outcomes included robust antibody production and microglial activation, which facilitated clearance of pathological proteins. However, some studies reported meningoencephalitis-like inflammation, particularly with A β vaccines, highlighting safety concerns. Adjuvants, such as CpG oligodeoxynucleotides, enhanced immune responses but increased the risk of neuroinflammation.

3.3. Clinical Studies Fourteen clinical trials (Phase I–III) were included, with 10 targeting A β and 4 targeting tau. Early A β vaccines, such as AN1792, showed promise in reducing plaque burden but were halted due to meningoencephalitis in 6% of participants (Orgogozo et al., 2003). Second-generation vaccines (e.g., CAD106, ACC-001) used modified A β epitopes and safer adjuvants, demonstrating improved safety profiles but modest cognitive benefits. For instance, CAD106 reduced A β levels in cerebrospinal fluid but did not significantly improve scores on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) (Winblad et al., 2012).

Tau-targeted vaccines, such as AADvac1, elicited antibody responses against pathological tau and showed preliminary evidence of slowed cognitive decline in Phase II trials. However, clinical efficacy was variable, with benefits primarily observed in early-stage AD patients. Adverse events included mild injection-site reactions and, in rare cases, neuroinflammatory responses. Patient heterogeneity and short trial durations limited the ability to detect robust cognitive improvements.

3.4. Safety and Immunological Mechanisms Both preclinical and clinical studies emphasized the importance of balancing immunogenicity and safety. Vaccines elicited Th2-biased immune responses to minimize pro-inflammatory Th1 responses, which are associated with neuroinflammation. Passive immunization with monoclonal antibodies (e.g., aducanumab, lecanemab) bypassed some safety concerns of active vaccines but required repeated dosing, increasing costs and logistical challenges. Microglial activation and antibody-mediated clearance were key mechanisms for reducing A β and tau pathology, though excessive microglial activation was linked to adverse effects.

4. Discussion

This systematic review synthesizes evidence on vaccine-based therapeutic strategies for AD, highlighting their potential to target A β and tau pathology. Preclinical studies demonstrate consistent reductions in plaque and tangle burden, accompanied by cognitive improvements in animal models. These findings underscore the mechanistic feasibility of immunotherapy, with vaccines leveraging the immune system to clear pathological proteins via antibody production and microglial activation.

However, clinical translation remains challenging. Early A β vaccines, such as AN1792, were limited by severe adverse events, prompting the development of safer second-generation vaccines. While these vaccines improved safety profiles, their cognitive benefits were

modest, likely due to the complexity of AD pathology and the advanced disease stage of trial participants. Tau-targeted vaccines show promise, particularly for early-stage AD, but require further validation in larger, longer-term trials. Combined A β /tau vaccines, though underexplored, may address the multifactorial nature of AD more effectively.

Safety remains a critical concern, with neuroinflammation and meningoencephalitis reported in both preclinical and clinical studies. Optimizing adjuvants and delivery systems could mitigate these risks while enhancing immunogenicity. Additionally, patient selection is crucial, as immunotherapy appears most effective in early AD, before extensive neurodegeneration occurs. Biomarker-driven approaches, such as amyloid and tau imaging, could improve trial design by identifying suitable candidates.

Limitations of this review include the heterogeneity of study designs, which precluded meta-analysis, and the limited number of clinical trials for tau and combined vaccines. Publication bias may also overrepresent positive findings. Future research should focus on optimizing vaccine formulations, conducting long-term trials, and exploring combination therapies that target both A β and tau. Personalized immunotherapy, tailored to individual pathology and immune profiles, may further enhance efficacy.

5. Conclusion

Vaccines represent a promising therapeutic strategy for AD, with preclinical studies demonstrating robust reductions in A β and tau pathology and clinical trials showing preliminary cognitive benefits. However, challenges such as variable efficacy, safety concerns, and patient heterogeneity must be addressed to realize their full potential. This systematic review underscores the need for continued research to optimize vaccine design, refine patient selection, and validate long-term outcomes. As immunotherapy evolves, vaccines may play a pivotal role in the development of disease-modifying treatments for AD, offering hope for millions affected by this devastating neurodegenerative disorder.