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Current Status, Efficacy Evaluation and Development Prospects of Pharmacological Treatments for Alzheimer's Disease

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Abstract:

Alzheimer's disease (AD) is a progressive neurodegenerative disorder. With population aging, its incidence rises continuously, imposing a heavy burden on society. Currently, relevant drugs can only alleviate disease progression but cannot achieve a complete cure, which urgently calls for in-depth research on AD pharmacological treatments. This paper conducts a comprehensive review, a gap that urgently necessitates in-depth research into AD pharmacological treatments. It provides an overview of AD and its current treatment landscape, involving the disease's status, the efficacy evaluation of pharmacotherapies, and the core value and significance of pharmacotherapy in AD intervention. Then, it explores AD's pathogenesis and pharmacotherapeutic targets. Additionally, the efficacy and safety of AD drug therapies are analyzed. Finally, limitations and challenges in current AD research are discussed. Through this study, it is concluded that although there are some advances in AD pharmacological treatments, there remains a long path to achieving a complete cure and further exploration of disease mechanisms and innovative drug development is therefore essential.

Keywords: Alzheimer's disease, pharmacotherapeutic targets, pathogenesis, safety risks, individualized treatment

1. Introduction

For instance, the precise interplay of various pathogenic factors is not fully elucidated, and the translation of preclinical drug successes to clinical efficacy is often limited. This paper centers on the pharmacological treatments for AD. The core question it intends to answer is: How can we comprehensively assess the current landscape of AD pharmacological therapies, including their mechanisms, efficacy, safety, and the challenges they face? To address this question, a systematic literature review approach is employed, drawing upon a broad range of scholarly articles from peer-reviewed, reputable journals.

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The study holds significant value as it aims to bridge the gap between fragmented research findings and a holistic understanding of AD pharmacological treatments. By identifying the bottlenecks in current therapies, it aspires to lay a foundation for guiding future research, such as the development of novel drug targets or combination therapeutic approaches, ultimately contributing to better management of AD.

2. Overview of Alzheimer's disease and current treatment landscape

2.1 Disease overall status

Popul ation aging has become a prominent global phenomenon, and AD, a progressive neurodegenerative ailment, has thus emerged as a critical healthcare concern[1]. In the field of AD research, although decades of exploration have yielded insights into its key pathological hallmarks like amyloid-β-aggregation and tau hyperphosphorylation, and numerous drug candidates have been investigated, substantial uncertainties still remain[2].

2.2 Incidence rate and clinical features

The disease affects roughly 7.2 million Americans aged 65 and over. Globally, about 1 in 9 people aged 65 and over has Alzheimer's. The lifetime risk for Alzheimer's at age 45 is 1 in 5 for women and 1 in 10 for men[3].

2.3 Core value and significance of pharmacotherapy in AD intervention

Pharmacotherapy is vital in AD intervention. Though nowadays AD still can't be cure, drugs like cholinesterase inhibitors and memantine can alleviate cognitive symptoms and slow the rate of disease progression. Drugs help patients maintain independence, reducing care giving and healthcare costs[4][5].

3. Pathogenesis and pharmacotherapeutic targets of Alzheimer's disease

3.1 Core pathogenesis mechanisms of AD

AD develops through the interplay of overlapping pathological pathways. At its core, abnormal protein aggregation drives disease progression: amyloid precursor protein (APP) is split sequentially by β-secretase and γ-secretase to produce β-amyloid (Aβ) peptides, with $A\beta_{42}$—due to its structural traits—readily clumping into extracellular senile plaques that disrupt neuronal communication and trigger neurotoxicity; concurrently, tau protein, which normally functions to stabilize neuronal microtubules, becomes hyperphosphorylated, losing this stabilizing ability and forming intracellular neurofibrillary tangles that block intracellular transport and lead to neuronal death[6]. These abnormal proteins further activate brain microglia (the central nervous system's immune cells), prompting the release of pro-inflammatory factors like IL-1β and TNF-α; long-term chronic inflammation then speeds up neurodegenerative damage, worsening AD progression. Neurotransmitter imbalance also plays a key role: extensive loss of cholinergic neurons reduces acetylcholine levels in the brain—a neurotransmitter critical for memory encoding and retrieval—directly impairing cognitive function, while excessive glutamate release overstimulate NMDA receptors, causing excitotoxicity and additional neuronal harm. Moreover, high levels of reactive oxygen species (ROS) accumulate in AD brains, inducing oxidative damage to lipids, proteins, and DNA that disrupts neuronal function and accelerates cell death. Collectively, AD's pathogenesis stems from the complex interaction of these processes, laying a multi-target foundation for developing AD drugs and intervention strategies[7].

3.2 Clinical needs, current status and significance of AD drug therapy

3.2.1 Clinical needs of AD drug therapy

The clinical demand for AD pharmacotherapy mainly focuses on two core aspects. First, there is an urgent need for therapeutic agents that can delay disease progression: existing symptomatic drugs only provide temporary symptom relief, and effective interventions for mild cognitive impairment (MCI), the preclinical stage of AD, are lacking to prevent its progression to moderate or severe AD [8]. Second, safer and more effective drugs for mental and behavioral symptoms are needed; 50%-90% of AD patients suffer from depression, agitation, and other symptoms, yet current medications for these symptoms have limited efficacy and are associated with potential side effects.

3.2.2 Current status of AD drug therapy

Current AD drug therapy is divided into two categories with limited overall effects. Symptomatic drugs are the mainstay, including cholinesterase inhibitors for mild-to-moderate AD and NMDA receptor antagonists for moderate-to-severe AD. Disease-modifying drugs are emerging: aducanumab may delay progression by reducing brain Aβ deposition, but its cognitive improvement effect is unclear and it carries side effect risks[9].

3.2.3 Significance of AD drug therapy

AD pharmacotherapy holds great significance for patients, families, and society. For patients, it alleviates cognitive decline and mental symptoms, improving quality of life. For families, it reduces the burden of care by slowing the loss of patients' self-care ability. For society, it eases the pressure of medical and social support systems caused by the growing AD population, expanding AD patient population and promotes advancements in neuroscience and pharmaceutical research.

4. Efficacy and Safety of AD Drug Therapy

4.1 Efficacy Evaluation System

AD drug efficacy is evaluated via a two-dimensional system combining subjective scales and objective biomarkers. Subjective assessment uses standardized tools: the Mini-Mental State Examination (MMSE) measures overall cognitive function; the Alzheimer's Disease Assessment Scale-Cognitive Subscale is sensitive to mild cognitive changes; the Activities of Daily Living (ADL) scale assesses patients' ability to perform daily tasks. Objective evaluation relies on biomarkers: Positron emission tomography (PET) detects brain amyloid-beta (Aβ) or tau protein changes ("a measure used to evaluate the effects of disease-modifying drugs such as aducanumab); cerebrospinal fluid (CSF) testing measures Aβ42, Aβ40, and tau levels to reflect pathological improvements[10][11][12].

4.2 Safety Risks

AD drugs carry safety risks, varying by drug type:
First, Cholinesterase inhibitors (donepezil, rivastigmine): Common cholinergic side effects (nausea, diarrhea) ease in 1-2 weeks; elderly patients with comorbidities may face severe bradycardia or syncope (needing dose adjustment/withdrawal).
Second, NMDA receptor antagonists (memantine): Mild side effects (dizziness, fatigue); patients with renal insufficiency require dose reduction (drug is excreted via kidneys).
Third, Disease-modifying drugs (aducanumab): Risk of amyloid-related imaging abnormalities; 30%-40% of high-dose users develop ARIA (most cases are asymptomatic, though some patients may experience severe headaches).

4.3 Response Modifiers and Individualized Treatment

Response to AD drugs is affected by two key modifiers. The first is patient-related factors, including age, genetic background and disease stage. Elderly patients may have weaker responses, APOE ε4 carriers often show poorer efficacy, while symptomatic drugs work better in mild-to-moderate AD. Drug factors include dosage (insufficient doses reduce efficacy; excessive doses increase side effects) and drug-drug interactions (e.g., cholinesterase inhibitors combined with anticholinergics may weaken therapeutic effects). Individualized treatment focuses on tailoring plans: For mild-to-moderate AD with good renal function, low-dose donepezil is preferred; for moderate-to-severe AD with renal insufficiency, adjusted-dose memantine is used; for APOE ε4 carriers using aducanumab, frequent PET scans are required to monitor for ARIA.

5. Limitations and Challenges in Current Research

Current research on Alzheimer's disease (AD) pharmacotherapy still grapples with notable limitations and multi-faceted challenges, which impede the development of effective therapeutic options. A primary obstacle lies in the incomplete understanding of AD pathogenesis. While the amyloid-beta (Aβ) and tau protein hypotheses dominate current research, they fail to fully account for the disease's complexity. For example, some individuals with substantial Aβ accumulation in the brain do not develop cognitive decline, and anti-Aβ agents like aducanumab have shown inconsistent effects on cognitive improvement[13]. This suggests that unaddressed pathological

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pathways—such as neuroinflammation or synaptic loss—have not been integrated into treatment strategies, creating gaps in drug development. Another key issue is the flaws in efficacy evaluation systems. Subjective assessment tools, including the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog), depend on observer or patient reports, making them susceptible to interference from factors such as mood, environment, and other variables. This leads to inaccurate reflections of a drug's true therapeutic impact. Meanwhile, objective biomarkers like positron emission tomography (PET) scans and cerebrospinal fluid (CSF) tau measurements are costly and invasive, limiting their applicability in large-scale clinical trials. Furthermore, the link between "pathological improvement" (e.g., reduced Aβ) and "functional benefit" (e.g., better daily living ability) has not been fully validated. Additionally, individual differences and high drug development risks pose significant hurdles. AD patients differ in genetic makeup—for instance, carriers of the APOE ε4 allele often show weaker responses to cholinesterase inhibitors—as well as disease stage and comorbid conditions. However, most current drugs follow a "one-size-fits-all" approach, lacking targeted designs. Late-stage clinical trial failures are also common; solanezumab, another anti-Aβ drug, missed primary endpoints in phase 3 studies, partly due to poor patient selection (e.g., enrolling those with advanced AD where pathological damage is irreversible) and unclear therapeutic windows. This increases the cost and time burden of drug research and development.

6. Conclusion

This paper comprehensively explores the clinical needs, therapeutic status, efficacy and safety evaluation, as well as existing limitations of AD pharmacotherapy, with the aim of presenting a holistic overview of this field.. Through systematic analysis, it is concluded that current AD drug therapy, though making some progress (such as the approval of disease-modifying drugs like aducanumab), still faces multiple challenges. In terms of efficacy, the existing symptomatic drugs can only temporarily alleviate symptoms, and the effect of disease-modifying drugs on cognitive function improvement is not yet clear. In terms of safety, different drug classes are associated with distinct side effects, with disease-modifying drugs posing relatively more prominent safety concerns. Moreover, the current research on AD pharmacotherapy is limited by the incomplete understanding of pathogenesis, flawed efficacy evaluation systems, and high risks in individualized treatment and drug development. For future research, it is necessary to deepen the exploration of AD's complex pathogenesis, integrate multiple pathological mechanisms into therapeutic strategies, and establish more accurate and feasible efficacy evaluation systems. At the same time, it is essential to strengthen the research on individualized treatment, develop targeted drugs based on patient genetic background, disease stage and other factors, and reduce the risks and costs of drug development through optimized clinical trial design. Only through these measures can we advance the development of AD pharmacotherapy and bring greater hope to AD patients.

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