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FORMULATION AND ADVANCEMENT OF NEW POTENTIAL THERAPIES FOR ALZHEIMER'S DISEASE

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and behavioural changes. Despite significant advancements in understanding the pathology of AD, effective therapies remain limited. This paper explores the formulation and advancement of new potential therapies for AD, focusing on innovative drug discovery, novel therapeutic targets, and emerging treatment strategies. Recent research highlights the development of compounds that address key pathological features of AD, including beta-amyloid plaque accumulation, tau protein hyper phosphorylation, and oxidative stress. We discuss the integration of multidisciplinary approaches, including the synthesis of novel chemical entities, the use of advanced nanotechnology, and the application of personalized medicine. Additionally, we review preclinical and clinical trial data to evaluate the efficacy, safety, and potential of these emerging therapies. Our analysis underscores the importance of continued research and innovation in the quest to develop effective treatments for AD, offering hope for improved patient outcomes and quality of life.

Key words: Alzheimer's disease (AD), Neurodegenerative disorder, Cognitive decline, Novel therapeutic targets, Beta-amyloid plaques, Tau protein

Introduction

Alzheimer's disease (AD) represents a major challenge in modern medicine due to its complex and progressive nature. Characterized by a gradual decline in cognitive functions, memory loss, and significant behavioural changes, AD poses a significant burden on affected individuals and their families. Despite substantial progress in understanding its underlying mechanisms, current therapeutic options remain inadequate, highlighting the urgent need for innovative treatments. AD's pathology is marked by the accumulation of beta-amyloid plaques and neurofibrillary tangles, primarily composed of hyper phosphorylated tau proteins, contributing to neuronal dysfunction and loss. While existing treatments offer symptomatic relief, they do not halt or reverse disease progression. Recent advancements in drug discovery have led to the development of new chemical entities designed to target specific aspects of AD pathology, including beta-amyloid and tau protein abnormalities, as well as oxidative stress and inflammation. Additionally, researchers are exploring alternative therapeutic targets such as neuroinflammatory pathways, synaptic dysfunction, and mitochondrial health, which may offer new strategies for mitigating disease progression. The integration of multidisciplinary approaches, including innovations in nanotechnology and personalized medicine, is enhancing the precision and efficacy of new therapies. These advancements facilitate better targeting of drug delivery and individualized treatment plans. Comprehensive evaluations of preclinical and clinical trial data are essential for assessing the efficacy and safety of emerging therapies. Ongoing trials provide critical insights into the potential of new treatments to address the diverse aspects of AD pathology, offering hope for more effective and durable therapeutic options. The future of AD therapy lies in continued research and innovation, with collaborative efforts across scientific disciplines and advancements in technology crucial for developing effective treatments [1, 2].

Alzheimer's disease (AD) was first identified by German scientist Dr. Alois Alzheimer in 1907, who described it as a "neurodegenerative disease," indicating a continuous deterioration of the neuronal system. The disease is marked by a gradual decline in cognitive abilities and severe behavioral issues, including restlessness, irritability, disorientation, depression, and anxiety. It was later defined as a "progressive neurodegenerative disorder leading to irreversible loss of neurons in the cerebral cortex and hippocampus," characterized by memory loss, confusion, impaired intellect, social withdrawal, and poor judgment [3].

Alzheimer's disease is the most prevalent type of dementia, currently affecting over 50 million people globally. If no cure or preventive measures are discovered, this number is projected to increase to 152 million by 2050. The prevalence of Alzheimer's disease increases significantly with age, rising from about 2-3% among individuals aged 70-75 to 20-25% among those aged 85 and older. There is insufficient data to determine whether the prevalence of AD continues to rise or stabilizes. Notably, women are more likely to be affected by AD than men, largely due to age-adjusted risk factors. Additionally, studies have shown that the overall prevalence of AD varies widely across countries, influenced by social and economic factors [4].

The reduction of acetylcholine (ACh) levels in the synapse, the buildup of extracellular beta-amyloid (Aβ) plaques[11] and the formation of intraneuronal tangles made up of tau protein[12] are some key hallmarks associated with Alzheimer's diseaseLow levels of acetylcholine (ACh) are linked to impairments in normal thinking and memory. Aβ plaques can interfere with signal

transmission between neurons, leading to cell death, while tau tangles obstruct the transport of nutrients and other essential substances within neurons. In the early stages of Alzheimer's disease, the brain can initially adapt, allowing the individual to function normally. However, as nerve cells become damaged, the brain's ability to compensate diminishes, leading to a subtle decline in cognitive abilities. Over time, plaques and tangles appear not only in regions associated with cognitive function but also in other brain areas. Eventually, the damage to nerve cells becomes severe enough that individuals experience noticeable cognitive decline, such as memory loss or confusion about place and time. Social symptoms may also arise, including depression, personality changes, and a loss of interest in previously enjoyed activities. In later stages, basic physical functions, such as swallowing, can be impaired [5, 6].

Through this review, we aim to provide a comprehensive overview of the current landscape and future directions in AD treatment, underscoring the importance of sustained investment in research to improve patient outcomes and quality of life.

Epidemiology

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and ranks as the sixth leading cause of death in the United States. Although AD pathology can begin in midlife, clinical symptoms typically emerge after age 65. The incidence of AD is rising rapidly, primarily due to the increasing number of individuals aged 65 and older worldwide. The elderly population in the Americas is projected to grow from 63 million in 1997 to 137 million by 2050. Similarly, Africa's elderly population will expand from 18 to 38 million, Europe's from 113 to 170 million, and Asia's from 172 to 435 million [7].

In the U.S., the Aging, Demographics, and Memory Study (ADAMS) found that 14% of individuals aged 71 and older have dementia, with AD accounting for 70% of these cases. Additionally, 22% of people in this age group (approximately 5.4 million Americans) experience cognitive impairment without overt dementia [8].

Age is the primary risk factor for AD, but it alone does not cause the disease. Other significant risk factors include having one or more apolipoprotein E4 (APOE4) alleles, lower educational and occupational levels, a family history of AD, moderate or severe traumatic brain injuries, and cardiovascular issues. Gender also influences AD prevalence, with nearly two-thirds of AD patients being women. According to ADAMS, 16% of women and 11% of men over 71 years of age have dementia. This disparity is partly due to genetic, hormonal, and societal factors, including historical differences in education and career opportunities [9].

Racial disparities in AD prevalence are evident as well. Older African Americans and Hispanics have higher rates of AD compared to Caucasians, partly due to lower education levels and higher rates of cardiovascular conditions. Other genetic and societal factors also contribute to these differences.

Clinical Presentation of Alzheimer's disease (AD)

Recognizing the clinical features and symptoms of Alzheimer's disease (AD) is crucial for diagnosis and management, despite the increasing availability of biomarker tests such as amyloid PET imaging that detect underlying neuropathology. Identifying symptoms of cognitive decline, behavioural changes, functional impairment, and conducting cognitive testing are essential for diagnosing and staging AD [10].

Cognitive Decline

Memory impairment is the most prevalent symptom of AD. While non-memory cognitive issues such as aphasia, executive dysfunction, apathy, or personality changes can appear early and sometimes be the initial signs, memory decline generally remains the primary symptom. Initially, recent episodic memories are most affected, while long-term memories are usually preserved. As the disease advances, all aspects of episodic memory are impacted. In contrast, working memory and semantic memory tend to be affected only in later stages of the disease.

Language disturbances, such as difficulty finding words, often occur early but are usually mild. A slight decline in visuospatial skills is also observed in the early stages and worsens as the disease progresses. Executive dysfunction, however, can begin even before dementia develops and, like other cognitive domains, deteriorates over time [11, 12].

Neuropsychiatric Symptoms

AD patients often exhibit a range of neuropsychiatric symptoms. These behavioural symptoms can worsen over time but may fluctuate and not be present during every visit. Addressing these symptoms is crucial as they significantly impact caregiver burden and are a leading cause of institutionalization. Early neuropsychiatric symptoms include apathy, anxiety, and irritability, often triggered by challenging situations. Mild to moderate depressive symptoms are also common early on. In later stages, disturbances in appetite, sleep, disinhibition, and perceptual changes (such as hallucinations) or thought disturbances (such as delusions) become more prevalent. Anosognosia, or lack of insight into one’s condition, often appears early and presents management challenges.

Among the neuropsychiatric symptoms, irritability, agitation, sundowning, psychosis, and diminished insight are particularly pressing due to the emotional and physical strain they impose on families and caregivers [13, 14].

Neurologic Examination

Apart from mental status assessments, neurologic examinations in AD patients are often normal. Parkinsonian symptoms may develop in later stages, but if such symptoms appear early (within a year of cognitive issues) and are accompanied by cognitive fluctuations and early-onset psychosis, dementia with Lewy bodies should be considered. In the advanced stages of AD, pathologic reflexes such as grasp, root, and suck reflexes may emerge. Patients progressively become more impaired, ultimately becoming mute, incontinent, and bedridden. At this final stage, complications like aspiration, malnutrition, immobility-related issues, deep venous thrombosis, and infections often lead to death [15, 16].

Current Role of Biomarkers in Alzheimer Disease Diagnosis

Biomarkers play a crucial role in diagnosing Alzheimer's disease (AD), complementing clinical assessments and aiding in the differential diagnosis of dementia. According to the American Academy of Neurology (AAN) guidelines, physicians are advised to perform structural imaging on all patients exhibiting objective cognitive decline. This recommendation is based on evidence indicating that 5% of patients with cognitive issues may have a nondegenerative lesion, such as a slow-growing brain tumor, subdural hematoma, or normal pressure hydrocephalus. Structural imaging, such as CT or MRI, can also reveal ischemic changes, prompting further investigation and potentially initiating treatments to address vascular risk factors or make behavioural adjustments [17].

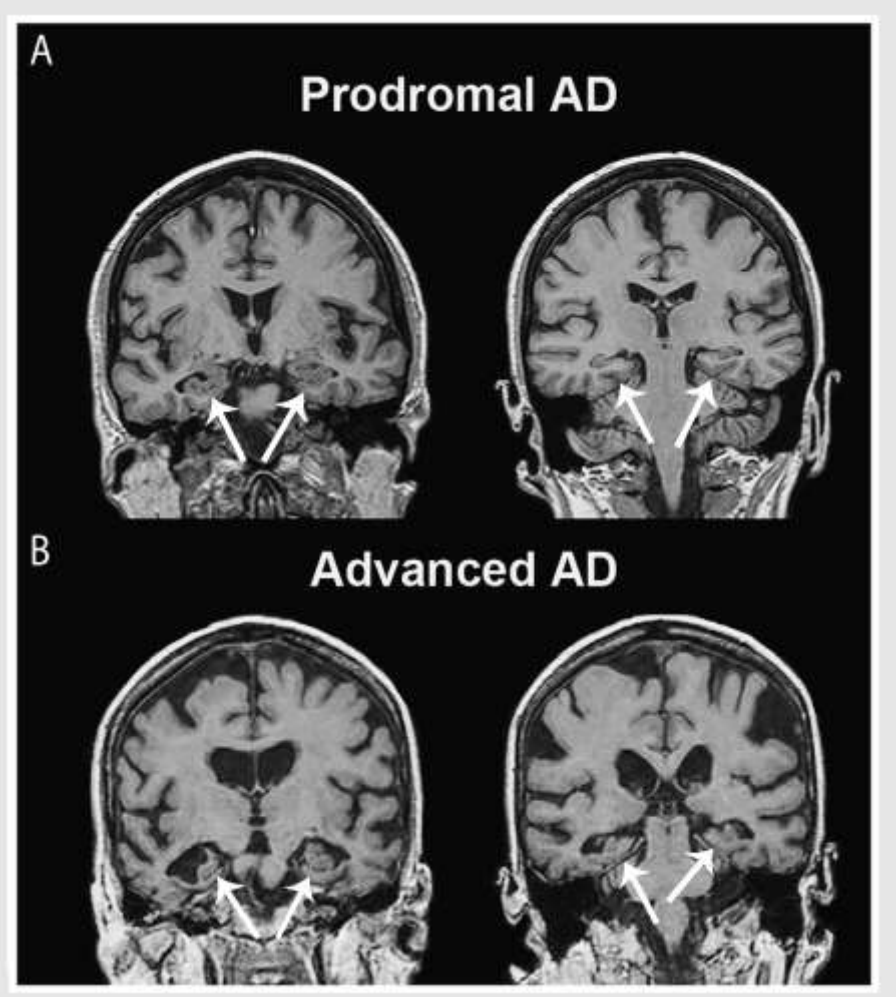

Figure 1: Coronal T1-weighted MRI slices with findings suggestive of Alzheimer disease (AD) pathology show mesial temporal atrophy (A, B, arrows) and, in the more advanced stages, global brain atrophy with pronounced ventricular enlargement.

MRI is particularly valuable due to its higher resolution, which allows better distinction between normal and mildly affected AD patients. MRI findings indicative of AD include

mesial temporal atrophy and, in advanced stages, global brain atrophy with enlarged ventricles. Cortico-subcortical microhemorrhages, visible on gradient echo MRI sequences, suggest vascular amyloidosis [18].

Functional imaging techniques like SPECT and PET are used to identify specific patterns associated with AD. These include temporoparietal hypoperfusion and hypometabolism. Recent advancements in arterial spin-labeling MRI have also shown promise in detecting perfusion abnormalities. However, while SPECT and PET generally offer high sensitivity, their specificity is lower, leading to a higher risk of false-positive diagnoses. Currently, Medicare only covers FDG-PET and SPECT for distinguishing AD from frontotemporal dementia [19].

Amyloid PET imaging, which detects amyloid deposition in the brain, holds potential for improving AD diagnosis. Despite its high sensitivity and specificity, its clinical use is limited due to high costs and insurance coverage issues. Concerns include the lack of disease-modifying therapies and the potential psychological impact of detecting asymptomatic brain amyloidosis. To address these issues, guidelines have been established for appropriate use, recommending amyloid PET imaging for specific scenarios such as amnestic mild cognitive impairment, atypical AD, and early-onset cases [20].

CSF biomarkers, particularly amyloid-β (Aβ) and tau proteins, are well-established in AD diagnosis. Aβ deposition in the brain is an early marker of AD and is associated with reduced CSF Aβ levels. Increased levels of total and phosphorylated tau in CSF occur later in the disease and correlate with cognitive decline. Although CSF Aβ and tau testing is covered by most U.S. insurance plans, it is not routinely used due to the invasive nature of lumbar punctures and associated risks. However, CSF biomarkers can be particularly useful in challenging diagnostic cases or atypical presentations [21].

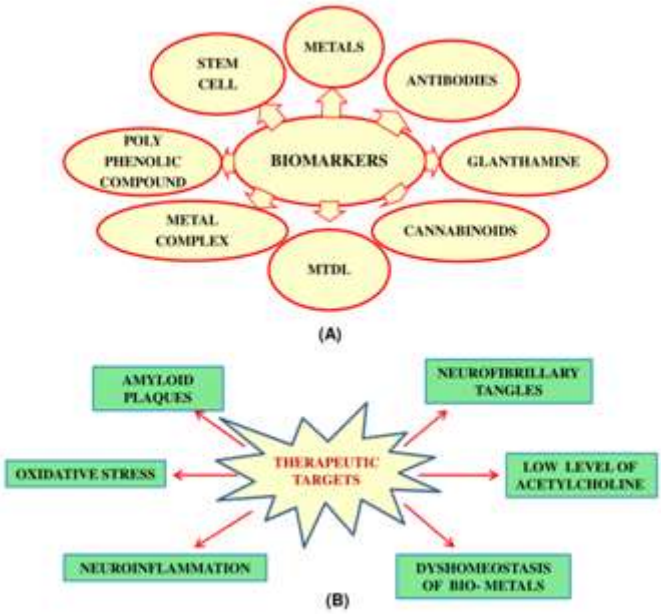

Figure 2: Alzeimer disese: Biomarkers and therapeutic targets

Treatment

The clinical management of Alzheimer's disease (AD) dementia involves several key tasks. Patients should receive both diagnostic and prognostic counseling, alongside an optimized medication regimen. Managing any coexisting behavioural and non-neurological conditions is crucial. Coordinating care among physicians, nurse practitioners, and social workers is essential, and appropriate safety measures should be taken for patients with functional impairments and poor judgment. Encouraging social engagement, participation in adult day care centers, exercise programs, and support groups for both patients and caregivers is also important [22, 23].

For medication, there are two main classes approved for AD: acetylcholinesterase inhibitors (AChEIs) and the NMDA receptor antagonist memantine. AChEIs, including donepezil, rivastigmine, and galantamine, are used for patients with mild to moderate AD. They have shown some benefits in cognitive functions like memory and concentration but are mainly symptomatic. Gastrointestinal side effects are common during dose escalation, and bradycardia or heart block may occur, particularly in patients with existing cardiac issues or those on certain medications. If one AChEI causes intolerable side effects, another should be tried [24].

Memantine, an NMDA receptor antagonist, is used in addition to AChEIs for moderate to severe AD stages. It has shown beneficial effects on cognition, behavior, daily living activities, and overall function, though side effects like confusion and dizziness are rare. The initiation of cholinesterase inhibitors and memantine therapy can be controversial, and recent analyses have questioned their effectiveness in mild cognitive impairment and mild AD [25, 26].

Non-pharmacologic interventions are the first line of treatment for behavioural symptoms of AD. Creating a familiar, well-lit environment can help reduce disorientation. Aggressive behavior should be managed with positive reinforcement. Depressive symptoms can be treated with selective serotonin reuptake inhibitors (SSRIs) due to their low risk of anticholinergic effects, and SSRIs like citalopram may help with agitation. For agitation or disruptive behavior, atypical antipsychotic medications may be used cautiously. These include quetiapine, risperidone, and olanzapine, which should be administered in low doses and with careful monitoring. Antipsychotic medications carry risks such as increased cardiovascular and cerebrovascular events, and all antipsychotics come with a black box warning for increased risk of death in older adults with dementia [27, 28].

CONCLUSION:

Alzheimer's disease (AD) is an irreversible neurodegenerative condition impacting more than 5 million people in the U.S. While early and even presymptomatic diagnosis of AD is now possible, effective preventative or disease-modifying treatments that can change its progression are still lacking. The impact of AD on patients, their families, and caregivers is profound and devastating. As the number of AD patients continues to rise, the strain on families, caregivers, the healthcare system, and society at large will increase unless a cure is found.

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