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Current Pharmacotherapeutic Approaches for Management of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease with insidious onset which involves irreversible worsening modifications in cognitive behavior and other principal mental functions. Alzheimer's disease is considered the most common type of dementia, which probably begins with mild memory deficits and possibly leads to a consequential decline in basic mental abilities such as losing the capacity for recognizable speech and failing to process new information. The pathophysiology of Alzheimer's disease is characterized by the accumulation of extracellular amyloid-β plaques, neurofibrillary tangles formed due to hyperphosphorylated tau proteins in the intracellular environment, and neuroinflammation. Nevertheless, no neuroprotective or neuro-regenerative drug is available at present that targets the treatment of AD. Current treatment for AD predominantly involves mitigating the symptoms in patients suffering from Alzheimer's disease. Thus, multiple target strategies have been initiated, aiming at multiple targets involved in developing Alzheimer's disease. In the pharmacotherapeutic approaches to AD, the drugs that are approved by the FDA and are currently available for management and treatment include- Acetylcholinesterase (AChE) inhibitors, N-methyl D-aspartate (NMDA) receptor antagonists, β site amyloid precursor protein cleavage enzyme 1 (BACE1) inhibitors, and monoclonal antibodies, which mainly enhances the Aβ and tau pathology that boosts acetylcholine levels and inhibits hyperphosphorylation of tau proteins. Therefore, this review summarizes and briefly analyzes the current strategies in therapeutic approaches for the management of Alzheimer's disease.

Keywords: Alzheimer's Disease; Dementia; Amyloid-B Plaques; Neurofibrillary Tangles; Hyperphosphorylated Tau Proteins; Neuroinflammation; Aβ Pathology; Tau Pathology; Acetylcholinesterase Inhibitors; N-Methyl D-Aspartate Receptor Antagonists; Monoclonal Antibodies

Abbreviations: AD: Alzheimer's Disease; FDA: Food and Drug Administration; NMDA: N-methyl-D-aspartate; ARIA-E: Alzheimer's Related Imaging Abnormality-Edema/Effusion; CNS: Central Nervous System; AV block: Atrioventricular Blockage; NFT: Neurofibrillary Tangles; PHF: Pair Helical Filaments; AVs: Autophagic Vacuoles; CAA: Cerebral Amyloid Angiopathy; EAL: Endosomal-Autophagic-Lysosomal.

Introduction

Alzheimer's disease is a chronic brain disorder disabling senile dementia, which leads to loss of memory, reasoning, and a decline in cognitive ability. AD globally ranks as the seventh leading cause of death, after ischemic heart disease, stroke, and cancers. Alzheimer's disease is considered a

common type of dementia (de-MEN-she-a; de=away from; -mentia=mind) a permanent or progressive general loss of intellectual abilities including impairment of memory, judgment, and personality changes. The cause of most AD cases remains unknown so far but typically starts in the entorhinal cortex and hippocampus parts of the brain which are responsible for the formation of memory, it later affects the cerebral cortex which is essential for language, reasoning, and social behavior eventually, other areas of the brain are also affected [1].

Shreds of evidence suggest that AD is inherited in an autosomal dominant pattern and is caused by a combination of genetic factors, lifestyle/environmental factors, and other aging factors. It is identified that genetics plays a supreme role in the onset of both early and late Alzheimer's disease by mutations in three different genes [coding for presenilin-1(PSEN-1), presenilin-2(PSEN-2), and amyloid precursor protein (APP)] [2]. Trisomy 21 is a risk factor for early onset of dementia. Increasing age is also the most important risk factor for Alzheimer's disease. An estimated 6.7 million Americans aged 65 years, and about 8.8 million Indians older than 60 years are victims of Alzheimer's disease and dementia until now [3].

Physiopathology of Alzheimer's Disease

Alzheimer's is a neurocognitive disorder marked by impairment of episodic memory that significantly interferes with cognitive impairment in areas such as semantic memory, visuospatial abilities, and behavioral and social skills where consciousness is not affected. The median survival time of a patient suffering from Alzheimer's disease ranges from 7 to 10 years after being diagnosed. The lifespan of the patient who is subjected to AD depends imperatively on the age of the patient when AD is diagnosed [4].

Alzheimer's disease is associated with brain atrophy and localized cholinergic neuron degeneration, particularly in the frontal cortex and extending from the subcortical areas such as the nucleus basalis of Meynert (NBM). The NBM was identified as the cholinergic center in the brain with neurons providing cholinergic inputs to the neocortex (the largest part of the cerebral cortex, and approximately makes up half of the total volume of the human brain). As the NBM is considered an enormous source of cholinergic innervations widespread throughout the subcortical areas, the degeneration of neurons in these areas causes AD and other neurodegenerative disorders [5].

On autopsy, the brains of AD victims showed three characteristic features, which are considered pathological hallmarks of Alzheimer's disease-

- Extracellular beta-amyloid plaques.
- Intracellular neurofibrillary tangles.
- Loss of neurons (neuronal loss) [6].

Beta-Amyloid Pathology: Senile plaques are a definitive neuropathological feature in AD- affected brains. The parenchymal amyloid-β peptide (Aβ) is essential, as the biochemical alteration of the Aβ cycle remains the fundamental biomarker of Alzheimer's disease. Aβ is a 4kDa fragment of amyloid precursor protein (APP), an extensive precursor molecule widely produced by the brain's neurons. It is also a 39-48 amino acid peptide which is derived from β-APP. The two sequential proteolytic cleavages of APP by β-secretase [β-APP cleaving enzyme-1(BACE-1)] at ectodomain and γ-secretase at the intramembrane site. The mutations in the APP peptide or the β-secretase enzyme may contribute to or accelerate the onset of amyloidogenic pathology in enhancing AD. β-CTF – a fragment of 99 amino acids is rapidly cleaved by γ-secretase to generate amyloid-β peptide [7].

As amyloid-β deposition and accumulation of autophagic vacuoles (AVs) are pathological features in Alzheimer's disease. Dysregulation of the endosomal-autophagic-lysosomal (EAL) pathway shows the earliest changes and is a prominent neuropathological feature in Alzheimer's disease. However accurate role of the EAL pathway in neurodegeneration remains vague. Aβ deposition has a crucial position in triggering a cascade of degenerative processes. Aβ deposition occurs at the vascular level as cerebral amyloid angiopathy (CAA-a cerebrovascular disorder). In the amyloidogenic pathway, the APP is cleaved by β-secretase to generate a C-terminal fragment (β-CTF begins with N-terminal aspartyl residue of Aβ)[8]. This C-terminal fragment is then cleaved by γ-secretase to produce amyloid beta peptide (Aβ). The accumulation of Aβ manifests a deleterious effect, yet the amyloid precursor protein derived C-terminal fragment (APP-CTF) contributes to this pathology.

β-secretase is a transmembrane aspartyl protease involved in the pathogenesis of AD, the one that cleaves APP and its other substrates. There are two prime forms of enzymes are- BACE-1 and BACE-2 [9]. BACE-1 is tremendously expressed in the brain but is found at lower levels in other peripheral tissues/organs in contrast to BACE-2. β-secretase activity is regarded as the rate-limiting step in amyloid pathology, due to their indispensable role in generating Aβ. γ secretase is known as a multi-subunit enzyme that comprises proteins- APH1, PEN2, nicastrin, and presenilin (PSEN1 and PSEN2) both β and γ secretase are considered major target sites for the development of new anti-AD drugs [10].

Tau Pathology: Other neuropathological characteristic features of AD are hyperphosphorylated, flame-shaped neurofibrillary tangles (NFT) of microtubules bound by tau proteins [11]. Tau is a transient and highly soluble protein isoform resulting from alternative splicing from gene MAPT, their chief role is maintaining and stabilizing the internal skeleton (cytoskeleton) of neurons. Tauopathies are neuro-disorders that are associated with the accumulation of insoluble tau proteins. In normal adult human brain, tau contains 2-3 moles phosphate/ mole of tau protein. Hyperphosphorylation of tau proteins depresses the biological activity of tau proteins [12]. In Alzheimer's diseased brain- tau is three to four-fold hyperphosphorylated proteins were found, this state of hyperphosphorylation is tightly polymerized into twisted pair helical filaments (PHF). PHF-tau hyperphosphorylation is then admixed with straight filaments (SF) leading to the formation of insoluble neurofibrillary tangles (NFT). Abnormal hyperphosphorylation of tau can be found as intraneuronal deposits, forming filamentous tau aggregates, as these tau aggregates accumulate in the hippocampus first and then can be seen in the cerebral cortex, lower concentrations can be seen in the soma, proximal segment of axon, and dendrites. Many studies revealed that the deposition of tau proteins in patients proportionally increases with aging, duration, and severity of the disease [13].

Neuronal Loss: Synaptic loss is depicted as an indicator of neuronal dysfunction moreover in general, it is accepted that tau dysfunction is the ultimate reason for neuronal loss in AD. Advanced studies have demonstrated that Alzheimer's disease is associated with an increased rate of brain and hippocampal atrophy [14]. Cholinergic neurons are majorly damaged in patients suffering from AD. A substantial decline in the concentration of acetylcholine in the AD brain is also known based on the 'choline hypothesis'. Alzheimer's disease predominantly targets the cholinergic neurons in the basal forebrain, including the neurons that form the nucleus basalis of Meynert. Nevertheless, in addition to abnormal hyperphosphorylation of tau, the formation of senile plaques, neuroinflammation, and oxidative stress also plays a detrimental role in neurodegeneration by damaging different cellular elements [15].

Management for Alzheimer's Disease: Despite of increasing number of cases in the recent past, no cure exists for Alzheimer's disease. However, effective treatment and management strategies are used to slow down the progression of AD. To date, only six drugs have been approved by the U.S. Food and Drug Administration (FDA)- donepezil, rivastigmine, galantamine, aducanumab, and memantine. These drugs focus on the cholinergic system and antagonism of N-methyl-D-aspartate receptors. Out of these aducanumab is the only drug that is used in the clearance of Aβ plaques. Lately, in 2023 the U.S. Food and Drug Administration (FDA) approved a new drug lecanemab which helps target the protein beta-amyloid complexes and reduces the amyloid plaques [16].

Acetylcholinesterase Inhibitors (Ache): Cholinesterase inhibitors enhance the cholinergic functions of the brain by inhibiting the activity of cholinesterase enzymes as these enzymes break down acetylcholine, an excitatory neurotransmitter that has wide involvement in various functions of the brain which includes memory and, learning thereby AChE inhibitors increase the availability of ACh to stimulate the nicotinic and muscarinic receptors present in the brain to enhance their cognitive behavior. The acetylcholinesterase inhibitors that are typically prescribed for the treatment of AD [17].

- Tacrine
- Rivastigmine
- Donepezil
- Galantamine

Tacrine: Tacrine was the first drug approved by the FDA in the year 1993. It acts as a central inhibitor of acetylcholinesterase, by increasing levels of acetylcholine in various regions of the brain. However, the drug was used widely, but its effectiveness of tacrine was questioned as it resulted in various side effects such as palliative effects observed in patients suffering from mild to moderate dementia. A large number of adverse effects such as nausea, vomiting, diarrhoea, blurred vision, as well as hepatotoxicity have been reported due to safety concerns the use of tacrine was withdrawn in 2013 [17].

Rivastigmine: One of the main drugs that came into formulation in the year 1985 was rivastigmine, which was approved by the FDA in 1997. Rivastigmine is indicated in the treatment of mild to moderate dementia of Alzheimer's disease and mild to moderate Parkinson's dementia. Rivastigmine is a reversible inhibitor of both acetylcholinesterase and butyrylcholinesterase enzymes they act by binding to anionic and stearic sites of AChE. Rivastigmine is formulated as oral capsules, oral liquids, and transdermal patches. It is the first AD therapy that is available as skin patches that deliver the drug continuously for 24 hours. The initial dosing of the drug is 1.5mg twice a day, the dose may be increased to 3mg, subsequently increased to 4.5mg, and then 6mg twice a day. The maximum dose on oral administration is 12mg per day and transdermally is 13.3mg daily. Side effects of rivastigmine were consistent and they mostly included abdominal pain, nausea, vomiting, and loss of appetite. Overdosing with the drug can cause various symptoms such as irregular heartbeat, chest pain, convulsions, or shock [18].

Donepezil: Donepezil is a rapid central reversible cholinergic drug, a non-competitive inhibitor of acetylcholinesterase by increasing the availability of acetylcholine at synaptic vesicles. Moreover, donepezil causes inhibition of various aspects of glutamate excitotoxicity, decreases the response of inflammatory cytokines, and reduces oxidative stress-induced responses [19]. The FDA approved this drug for the treatment of mild to moderate, and severe Alzheimer's. Studies have indicated that donepezil can increase cognitive ability in patients suffering from vascular dementia. Donepezil is available in multiple formulations and is primarily metabolized in the liver, it can be administered in oral, transdermal, liquid, or jelly form. The initial recommended dose for donepezil is 5mg per day, subsequently increased to 10mg for 4-6 weeks. For the treatment of moderate to severe dementia, donepezil can be gradually increased to 23mg/daily. The available dosage for transdermal patches is 5mg/day but can be increased to 10mg daily. This drug shows good characterization in showing the least adverse effects, especially on the gastrointestinal tract which include-nausea, diarrhea, vomiting, and muscle cramps are often reported on higher doses [20].

Galantamine: Galantamine (also known as galanthamine) is a tertiary alkaloid in nature that is used in the treatment and management of Alzheimer's disease. Galantamine was approved by the FDA in 2001 for the treatment of mild to moderate Alzheimer's disease. The dose for the oral tablet is 4mg, 8mg, 12mg, and 24mg per day and the oral solution is 4mg/ml. A capsule extended-release form is available with different dose strengths of 8mg, 16mg, and 24mg. this leads to increased patient compliance with the treatment [21]. Galantamine has an interesting ability to act at the level of the central nervous system and also shows little activity in the peripheral nervous system. Although this drug has good tolerability and is safe and sound it also gives side effects such as sinus bradycardia, induced generalized seizures, and atrioventricular blockage (AV block). The patients on high administration of galantamine dosing up to 24mg/day are at risk related to gastrointestinal system involving weight loss, anorexia, nausea, vomiting, and diarrhoea. Hence, weight monitoring is necessary during galantamine therapy [22].

N-methyl -D-Aspartate (NMDA) Receptor Antagonist: N-methyl-D-aspartate (NMDA) receptor antagonists are a class of drugs that block the activity of NMDA receptors in the central nervous system. NMDA receptors play a crucial role in synaptic transmission and are involved in processes like learning and memory. These receptors are ionotropic glutamate receptors, meaning they respond to the neurotransmitter glutamate. The absorption of NMDA receptor antagonists depends on the route of administration [23]. For example, ketamine can be administered intravenously, intramuscularly, or orally. The rate and extent of absorption can vary based on the specific drug. NMDA receptor antagonists distribute throughout the body, including the central nervous system (CNS), due to their lipophilic nature. The distribution into the CNS is particularly relevant, as these drugs exert their effects on NMDA receptors in the brain. Metabolism of NMDA receptor antagonists occurs primarily in the liver. For instance, ketamine is metabolized by cytochrome P450 enzymes to various metabolites, including norketamine. The elimination half-life of NMDA receptor antagonists varies. For ketamine, it is relatively short, typically around 2-3 hours. The elimination. The NMDA-receptor antagonists have a significant impact on the development of tolerance to opioid analgesics. Consequently, NMDA-receptor antagonists may represent a new class of analgesics and may have potential as coanalgesics when used in combination with opioids [24].

Memantine: Memantine is an N-methyl-D-aspartate (NMDA) receptor antagonist used in the treatment of Alzheimer's disease. Alzheimer's disease is a neurodegenerative disorder characterized by the progressive loss of memory and cognitive function. Memantine works by modulating the activity of glutamate, the major excitatory neurotransmitter in the brain. It acts as an uncompetitive, low-affinity NMDA receptor antagonist, meaning it binds to the receptor in a voltage-dependent manner and blocks excessive activation without completely inhibiting normal neurotransmission [25]. Memantine blocks the effects of excessive glutamate stimulation on NMDA receptors, preventing excitotoxicity. It helps to regulate glutamate activity and maintain the balance of neurotransmission. It is typically prescribed in combination with other medications, such as acetylcholinesterase inhibitors like donepezil, which work through a different mechanism to enhance cholinergic neurotransmission. Oral memantine is completely absorbed with an absolute bioavailability of ≈100% [26]. Steady-state plasma concentrations, achieved after about 2 weeks of memantine 20 mg/day, range from 70 to 150 gmg/L, while the steady-state area under the plasma concentration-time curve from time 0 to 24 hours is ≈1800 gmg • h/L after 4 weeks of treatment [27]. The elimination half-life of memantine is relatively long, ranging from 60 to 100 hours [28].

Monoclonal antibodies: Recent studies have shown that monoclonal antibodies targeting amyloid beta protein, such as Crenezumab and Aducanumab, have failed to provide significant clinical benefit in the treatment of Alzheimer's disease. However, it is important to note that there may be other factors contributing to the lack of efficacy, such as the timing and dosage of antibody administration, as well as the heterogeneity of patients and disease progression. Additionally, Lecanemab, a monoclonal antibody directed against aggregated soluble and insoluble forms of amyloid

beta, has shown limited cognitive benefit [29].

Aducanumab: Aducanumab, a monoclonal antibody targeting beta-amyloid plaques, has been granted accelerated approval by the U.S. Food and Drug Administration (FDA) for the treatment of Alzheimer's disease [30]. Aducanumab was found to be well-tolerated up to a dosage of 30 mg/kg [31]. In patients who received ≤ 30 mg/kg, the 3 most reported symptoms were headache, diarrhoea, and upper respiratory tract infection. Alzheimer's related imaging abnormality-edema/effusion (ARIA-E) was the most severe side effect and was present in the few patients who received the 60 mg/kg dose [32].

Lecanemab: Lecanemab is still in the investigational stage or has recently received approval, information from clinical trial databases or recent research articles may provide insights into the recommended dosage and efficacy [33]. Recent study shown that Lecanemab treatment resulted in significant reduction in amyloid plaques and a slowing of clinical decline [34,35].

Conclusion

The management of Alzheimer's disease has witnessed advancements in pharmacotherapy aimed at addressing cognitive decline, behavioral symptoms, and enhancing the quality of life for affected individuals. While current medications, such as acetylcholinesterase inhibitors (e.g., donepezil) and N-methyl-D-aspartate (NMDA) receptor antagonist (e.g., memantine), have demonstrated symptomatic benefits, they do not represent a cure and have limitations in modifying the underlying disease progression.

In recent years, there has been notable attention given to monoclonal antibody therapy, exemplified by Aducanumab, targeting beta-amyloid plaques in the brain. The accelerated approval of Aducanumab by the U.S. Food and Drug Administration (FDA) has sparked discussions about its potential impact on the course of Alzheimer's disease. However, challenges exist, including controversies surrounding trial data and the need for further post-approval studies to confirm its clinical benefit.

The multifactorial nature of Alzheimer's disease necessitates a comprehensive approach, involving not only pharmacotherapy but also non-pharmacological interventions, lifestyle modifications, and ongoing research to identify novel therapeutic targets. Moreover, the importance of early diagnosis and personalized treatment plans tailored to individual patient profiles is increasingly recognized.

As the field continues to explore new avenues, including the investigation of emerging drugs and therapeutic strategies, healthcare professionals face the ongoing challenge of balancing symptomatic relief with disease-modifying interventions. Collaborative efforts among researchers, clinicians, and regulatory bodies are crucial for advancing our understanding of Alzheimer's disease and developing effective, targeted therapies to improve patient outcomes.

It is recommended to consult the latest scientific literature and healthcare professionals for the most up-to-date information on Alzheimer's disease pharmacotherapy and management strategies.

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