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"ALZHEIMER'S DISEASE IN YOUNG GENERATION"

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia, accounting for 60–80% of cases and affecting nearly 50 million people worldwide, with projections rising to 139 million by 2050. First described in 1907 by Alois Alzheimer in his patient Auguste Deter, AD is a progressive neurodegenerative disorder marked by cognitive decline, memory loss, impaired language, and executive dysfunction, ultimately leading to loss of independence and mortality. Early-onset cases, though rare, have been documented, including the youngest reported diagnosis at 19 years of age in China. Pathophysiologically, AD is characterized by amyloid-β (Aβ) plaque accumulation, neurofibrillary tangles of hyperphosphorylated tau protein, hippocampal atrophy, oxidative stress, and neuroin flammation mediated by microglial activation. Clinical progression occurs in three stages: mild (memory lapses, poor judgment), moderate (disorientation, impaired recognition, hallucinations), and severe (loss of speech, recognition, and body function control). Major risk factors include advanced age, APOE ε4 genotype, female sex, and family history, while protective variants such as APOE ε2 and klotho genes reduce susceptibility. Epidemiologically, AD prevalence doubles every decade after age 65, with up to 50% of individuals affected by age 85. Current management combines pharmacological approaches—primarily cholinesterase inhibitors and memantine—with non-pharmacological interventions such as physical exercise, music, sleep regulation, and oxygen therapy to slow progression and improve quality of life. Despite advances, AD remains a major cause of disability, dependence, and mortality, highlighting the urgent need for preventive strategies, novel therapeutics, and comprehensive care models to address its rising global burden., the amyloid cascade, tau pathology, oxidative stress, and mitochondrial

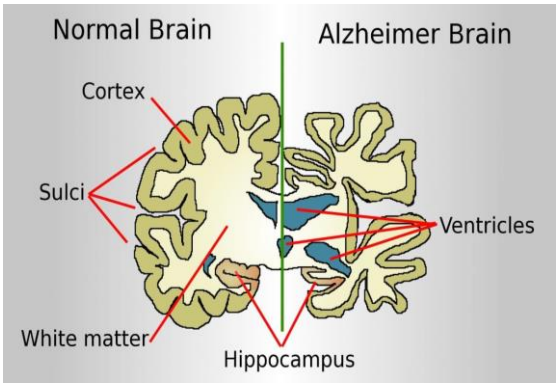
dysfunction are among the hypotheses. Clinically, AD develops in mild, moderate, and severe phases, culminating in total.

KEYWORDS: Pathophysiologically, AD is characterized by amyloid-β (Aβ) plaque accumulation, neurofibrillary tangles of hyperphosphorylated tau protein, hippocampal atrophy, oxidative stress, and neuroin flammation mediated by microglial activation.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disease that currently accounts for 60–80% of all cases of dementia. It is estimated that 50 million people worldwide suffer from some form of dementia; however, due to an increase in life expectancy, it is projected that 139 million people worldwide will have some form of dementia by 2050, which will have significant effects on the socioeconomic and health systems. Early in the 20th century, German psychiatrist and neuropathologist Alois Alzheimer made the initial diagnosis of Alzheimer's disease. Dr. Alzheimer presented his research on a patient named Auguste Deter in 1906. The patient had alterations, memory loss, and linguistic issues. Although Alzheimer's disease is usually associated with elderly adults, there are early onset variants that can occur in those under 65. A 19-year-old Chinese man who started having memory issues at the age of 17 was the youngest person to be diagnosed with Ad. Since Alzheimer's usually affects older persons, this case published in the journal of AD is noteworthy.

The hallmark of dementia is a progressive decline in cognitive function, mostly in memory but also in language, praxis, visual perception, and most especially executive function. Most of the reasons of this illness are progressive, but not inevitably so. As cognitive function deteriorate, there is growing interference with the patients' daily activities leading to loss of independence and finally for some the need for nursing home care. The patients normally survive 5–10. These pathophysiological Changes include the accumulation of hazardous Species of amyloid-b (Ab), the creation of Neurofibrillary tangles of hyperphosphorylated Tau protein, and neurodegeneration that may Result from uncontrolled activation of microglia In the brain leading to production of neurotoxins And inflammatory factors.

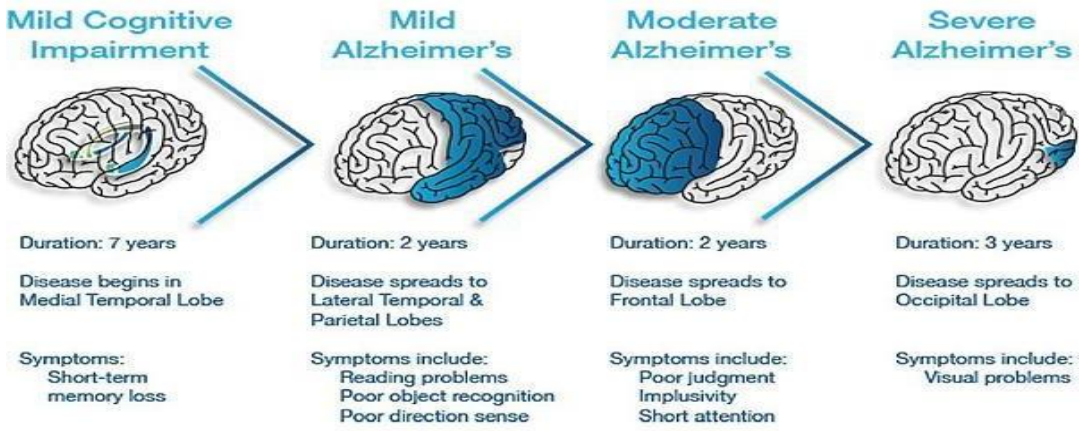


Historical Background

Alois Alzheimer, a German physician, reported the first instance of Alzheimer's disease in 1907. He first saw Auguste Deter, a 51-year-old woman, in 1901. Auguste's husband Karl committed her to a psychiatric hospital when she began exhibiting peculiar behavior, including hiding objects, threatening neighbors, and accusing her husband of adultery. She also lost the capacity to undertake daily duties such as cooking and housework. Auguste came under Alzheimer's treatment at a mental hospital in Frankfurt. There he watched and recorded her behavioral patterns: she could speak but not write her own name, she could name objects such as a pencil but not the meal she was eating, she was courteous sometimes but loud and obnoxious at other times. He diagnosed Auguste with "presenile dementia" The young man's brain scans showed" shrink age in the hippocampus, a region crucial for memory and his cerebrospinal fluid contained biomakers consistent with AD. While early-onset Alzheimer's (occurring before a 65) is rare, it can account for up to 10% of all diagnosis.

Hippocampus: The hippocampus, a seahorse-shaped region of the brain found in the temporal lobe, is essential for learning, memory formation, and spatial navigation. It is in charge of transforming short-term memories into long-term ones and is a fundamental part of the limbic system. Significant memory loss and trouble navigating familiar situations can result from hippocampal damage. In the Modern Era, French physician Philippe Pinel (1745–1826) first recognized dementia as a diagnosis in 1797.

Stages



1. **Stage 1 (mild stage):** It is the first stage and lasts for two to four years. In addition to feeling less energetic, the patient also experiences mild memory loss and mood swings, is slow to learn and react, finds it difficult to complete daily tasks, becomes confused and makes poor decisions regarding written material, takes longer than usual to complete daily tasks, and has trouble handling money or paying bills.

2. **Stage 2 (moderate type):** It is the longest stage, and the patient experiences symptoms for two to ten years. The brain regions in charge of language, perceptions, reasoning, and consciousness are harmed in moderate AD. Becomes incapacitated and forgets their past and current circumstances. Difficulties speaking, reading, and writing; difficulty identifying familiar faces; increased disorientation and detachment from reality; confusion between recollections of the distant past and the present; and increased memory loss uncertainty, trouble identifying relatives or friends, a failure to pick up new skills. Difficulty completing multi-stage tasks, including dressing, and trouble replicating in novel circumstances impulsive actions, delusions, paranoia, or hallucinations.

3. **Stage3 (severe type):** Severe circumstances are absorbed at this final level. Plaques and tangles are found throughout the brain in severe AD, which causes the brain tissue to shrink significantly. The patient may be unable to feed themselves, have severely impaired speech, lose the ability to recognize people, have uncontrollable bodily functions (such as swallowing or bowel and bladder control), be unable to communicate, be dependent on others for care, and be unable to leave bed all or most of the time. Memory power worsens or becomes nearly nonexistent during this stage, and the patient frequently sleeps, murmurs, or complain.

Epidemiolog

Dementia:- One of the main causes of dependence, disability, and death is acquired progressive cognitive impairment that affects activities of daily living. According to current estimates, 44 million individuals worldwide suffer with dementia. As the population ages, this is expected to more than triple by 2050, when the yearly cost of dementia in the US alone might surpass $600 billion. Dementia is the most common cause of mortality in England and Wales, making up 11.6% of all recorded deaths in 2015.

Incidence and prevalence—According to Alzheimer's Disease International, the prevalence of dementia is anticipated to be 50 million worldwide in 2018 and is expected to quadruple by 2050, with two-thirds of those affected residing in low- and middle-income nations. According to the latest recent research, the prevalence of dementia in Europe is expected to quadruple by 2050. 1 Gathering proof indicates that there may be a decrease in the prevalence of dementia in high-income nations, although the evidence for this is not as strong. The prevalence of AD rises exponentially with age, from 3% among those aged 65 to 74 to over 50% among those aged 85 and above. Russ et al. conducted a thorough analysis of the regional differences in AD incidence and prevalence.

Mortality—Although research on death do not support this theory, a protracted disease duration may account for the relatively steady prevalence despite declining incidence. Survival times of three to four years were observed in a US-based study assessing survival following a dementia diagnosis in nearly 60,000 individuals. This estimate is consistent with a multicenter study that provided estimates of the length of the prodromal (mild cognitive impairment) and preclinical stages of Alzheimer's disease in addition to the dementia stage. The preclinical, prodromal, and dementia stages of Alzheimer's disease are estimated to last 10, 4, and 6 years, respectively, for a person 70 years of age. The prevalence of scientifically defined Alzheimer's disease is three times higher than that of clinically characterized Alzheimer's disease at age 85, according to a first attempt to estimate prevalence based on a biological (rather than clinical) definition.

According to pooled data from population-based studies conducted in Europe, the age-standardized prevalence of dementia and AD among individuals 65 years of age and older is 6.4% and 4.4%, respectively.

Risk factors for dementia and Alzheimer's disease—The two biggest risk factors for

Alzheimer's disease are having at least one APOE ε4 allele and being older than 65, albeit this is not a set definition. Additionally, women are more likely than men to get Alzheimer's, particularly after the age of 80. Despite having a similar amyloid β burden, women are also more likely to have a larger tau load. The U.S. National Institutes of Health recently released an impartial state-of-the-science conference report in 2010 to give patients, healthcare professionals, and the general public an evaluation of the facts currently available on cognitive decline and Alzheimer's disease prevention. One continuous but unchangeable risk factor for dementia is a family history of the disease. It is also evident that those with MCI have a higher chance of developing dementia. With 10–15% developing dementia annually as opposed to 1%–2% of healthy individuals. Clinical samples had greater conversion rates (12–17% annually) than community-based research (4–15% annually).

Genetics

Causative and risk genes—According to twin studies, heritable variables account for 60–80% of the risk of Alzheimer's disease. The heritability of Alzheimer's disease is somewhat explained by the common APOE ε4 allele, but not entirely.

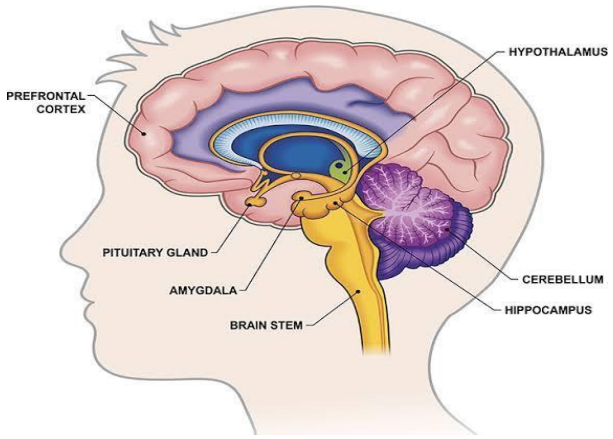
Numerous genome-wide association studies have been conducted to find novel genetic variants in Alzheimer's disease. The most recent study to date examined approximately 150,000 individuals with Alzheimer's disease and age-matched controls, as well as more than 300,000 individuals with a proxy phenotype of Alzheimer's disease (parental history of Alzheimer's disease) and controls (no parental history of Alzheimer's disease). This increased the number of risk alleles linked to Alzheimer's disease to over 40. Only 2% to 5% of all Alzheimer patients have early-onset familial AD, which is frequently brought on by autosomal dominant mutations (such as those in the amyloid precursor protein, presenilin-1, and presenilin-2 genes). Most AD cases are sporadic and exhibit significant variation in terms of neuropathological characteristics and risk factor profiles. Compared to the general population or relatives of people without dementia, first-degree relatives of Alzheimer patients have a greater lifetime chance of getting AD.

Protective genes— Interest in finding protective genetic variants has increased because risk-increasing genetic variants have been identified (figure 3C). The lifetime risk of Alzheimer's disease is expected to be two times lower in carriers of the protective APOE ε2 allele. In comparison to non-arrivers, homozygous APOE ε2 allele carriers have a remarkably low risk of Alzheimer's disease. A similar impact was linked to variations in the klotho longevity

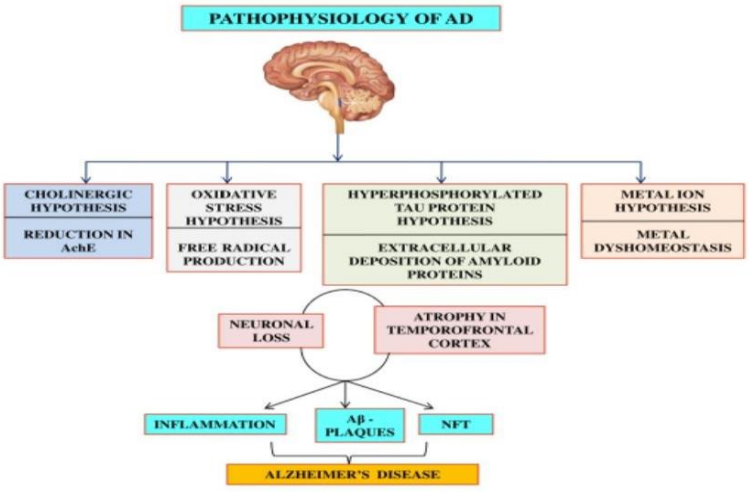
gene.

Pathophysiology

On a broad scale, the pathophysiology of Alzheimer's disease (AD) can be described as the progressive loss of brain tissue. Neurons gradually perish in a certain pattern as the illness worsens. Memory loss, especially short- term recall, is one of the first symptoms of AD. The cortex, particularly the hippocampus, is one of the brain regions involved in remembering. Brain atrophy, including hippocampal atrophy, and cognitive decline are strongly correlated with tau protein accumulation.



Alzheimer's disease's neuropathology includes neuronal loss and atrophy in the temporofrontal cortex, which results in inflammation, the deposition of amyloid plaques, an aberrant cluster of protein fragments, and tangled bundles of fibers. As a result, the cerebral cortex has more monocytes and macrophages, as well as activated microglial cells in the parenchyma.



The Cholinergic Hypothesis: The first and most researched theory explaining AD pathophysiology at the molecular level is the cholinergic hypothesis. More than 30 years ago, it was described as a primary degenerative process that can specifically harm cholinergic neuron groups in the hippocampus, frontal cortex, amygdala, nucleus basalis, and medial septum—regions and structures that play crucial functional roles in conscious awareness, attention, learning, memory, and other mnemonic processes. In mild to moderate AD, cholinergic receptor binding is decreased in particular brain areas and is associated with neuropsychiatric symptoms.

Reduced receptor binding may be linked to reduced processing speed in healthy older persons. Binding in vivo may give a possible molecular therapeutic target and uncover connections to other significant brain alterations linked to AD and aging. For more than 20 years, medications that tend to normalize the level of acetylcholine transmitters, like donepezil and cholinesterase inhibitors (ChEIs), have been the cornerstone of symptomatic treatment for AD. The clinical decline is linked to a significant loss of cholinergic neurons formed in the forebrain nuclei (medial) and a corresponding decline in acetylcholine- mediated neurotransmission.

Hyperphosphorylated tau protein and amyloid β Hypothesis:-The development of Senile plaques (SP), which is brought on by amyloid beta (Aβ) deposition, is one of the primary pathogenic characteristics of AD. Typically, ß-secretase, β-secretase, and γ-secretase split the precursor protein of amyloid (APP) to create soluble tiny peptides known as Aβ.

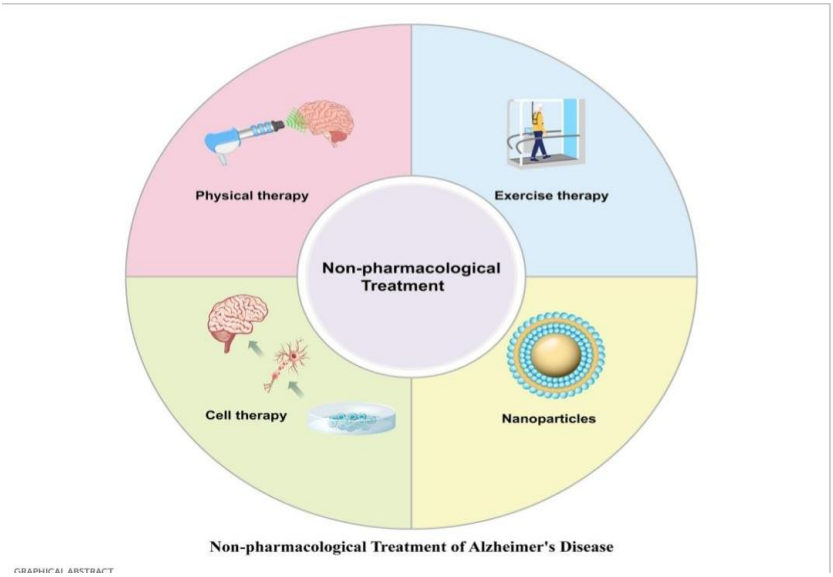
Depending on the degree of oligomerization, the imbalance between the synthesis and clearance of B-amyloid (Aβ) results in several forms of toxic oligomeric, including protofibrils, fibrils, and plaques. The sequence, concentration, and stability conditions of Aβ are significant determinants, although the cause of its creation is yet unknown. Numerous factors, including oxidative stress/mitochondrial dysfunctions, amyloid/tau toxicity, and cholinergic dysfunction, are linked to the etiology of Alzheimer's disease.

The Tau (τ) Protein

The etiopathogenesis of AD is not fully explained by the amyloid cascade hypothesis, which views the production and buildup of amyloid beta peptide as the start of the disease process. According to this theory, the τ protein develops as a secondary pathogenic event that leads to neurodegeneration.

Oxidative stress hypothesis: Both reactive nitrogen species (RNS) and reactive oxygen species (ROS) are produced in both normal and abnormal human processes. They serve both beneficial purposes in cellular signaling pathways and toxic ones that can cause damage to cellular structures (such as cell membranes, lipids, proteins, and DNA). The brain is especially susceptible to oxidative stress due to its high oxygen consumption, which is 20% higher than that of other mitochondrial respiratory tissues. The brain's basic functioning unit, the neuron, is rich in polyunsaturated fatty acids. It can interact with ROS to trigger molecular apoptosis and the lipid peroxidation reaction. Oxidative stress injury can also be caused by neurons having less glutathione.

Non-pharmacological therapy of AD



Non-pharmacological therapies (NPTs) can improve the quality of Life (QOL) of people with Alzheimer’s disease.

1. **Physical therapy:** Physical therapy offers the benefits of being non-invasive and extremely safe. It mainly uses stimuli like electricity, magnetic fields, sound, and light for treatment (Shen et al., 2023). One effective therapeutic approach for AD may be physical therapy. Both direct and indirect biological elements that impact brain health have been connected to physical and cognitive activity. Details on the kind, intensity, duration, and mix of therapies will need to be investigated in future studies.

2. **Music therapy:** The behavioral and psychological symptoms of dementia may be treated non-pharmacologically using music therapy, but while some trials have shown promise,

the majority are small and uncontrolled. For people with moderately severe and severe AD, music therapy is a safe and efficient way to alleviate agitation and anxiety.

3. **Sleep:** Sleep disturbance appears to be a contributing factor in the pathogenesis of Alzheimer's disease. Inadequate sleep causes an early build-up of amyloid-β (A β). Numerous studies have revealed that sleep patterns can directly or indirectly impact Alzheimer's disease, which may lead to memory loss and eventually develop into AD. Non-rapid-eye-movement (NREM) sleep disturbance, Aβ, and AD are associated and have a plausible explanation. A novel element connecting cortical Aβ to poor hippocampal-dependent memory consolidation is disruption of NREM sleep. As people age, getting enough sleep appears to be a new treatment goal that offers therapeutic and anticipatory compensation. NREM sleep and Aβ pathology have a reciprocal, causative relationship that may increase the risk and progression of Alzheimer's disease. NREM sleep disruption serves as a novel biomarker for AD. A novel mechanism by which cortical Aβ hinders hippocampus-dependent memory consolidation could be the disturbance of NREM sleep. In the form of a non-invasive biomarker of Aβ pathology, AD risk, and AD pathophysiological development, the disturbance of NREM sleep physiology offers potential diagnostic relevance. There is evidence that sleep disturbances are both a cause and an effect of AD progression; these disturbances are changeable and may be prevented or treated therapeutically.

4. **Exercise therapy:** Exercise therapy contributes to the improvement of AD symptoms in addition to physical therapy. Exercise can slow the development of clinical symptoms by enhancing executive and cognitive abilities.

5. **Oxygen therapy:** In AD patients, hypoxia can exacerbate Aβ, tau, and neuroinflammatory disease by causing neurodegeneration. In AD mice, oxygen therapy specifically improves cognitive function, lessens mitochondrial damage, relieves impairment in protein synthesis, and increases proteins linked to antioxidant defense.

Pharmacological management

1. Cholinesterase Inhibitors

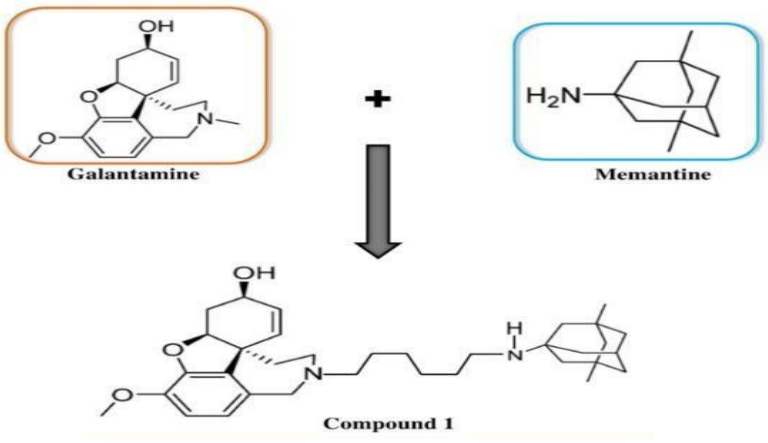
The only approved medications for the primary treatment of AD are acetylcholinesterase inhibitors (AChEI). Numerous randomized controlled studies and significant independent evaluations, such as the American Academy of Neurology's dementia management

guidelines, a UK National Institute of Clinical Excellence appraisal, and Cochrane meta-analyses.

Table 1. Pharmacological characteristics of cholinesterase inhibitors.

Drug	Mechanism of action	Half-life	Protein-binding capacity	Metabolism
Donepezil	Selective reversible noncompetitive inhibitor of AChE*	58–90 hours	96%	CYP 2D6, CYP 3A4‡
Rivastigmine	Pseudo-irreversible inhibitor of AChE and BChE†	2 hours	40%	Non-hepatic, metabolized by AChE and BChE
Galantamine	Reversible inhibitor of AChE, presynaptic modulator of nicotinic AChE	5–7 hours	18%	CYP 2D6, CYP 3A4

Combination of Galantamine and Memantine: Biochemical research has suggested that glutamatergic cell activity is dysfunctional in AD. Additionally, the cholinergic system and their mutual failure play a crucial role in the pathophysiology of Alzheimer's. Therefore, the current standard of care for people with AD is thought to be CTs that simultaneously target the glutamatergic and cholinergic systems. However, by using a variable-length polymethylene linker to join two therapeutic molecules, new hybrid compounds were created using a dual-binding method (compound 1, Figure 1). Compounds with a hexamethylene spacer are thought to exhibit the most favorable characteristics in this class. The ideal distance to enable simultaneous interaction with the catalytic active site and the peripheral anionic binding site on AChE was provided by a 6-methylene spacer.



Guidelines for prescribing cholinesterase inhibitors in Alzheimer's disease:- Get a precise diagnosis of Alzheimer's from a psychiatrist or specialist physician. 2. Evaluate the severity of the illness: AChEIs are only recommended for mild to severe Alzheimer's disease. 3. Examine your overall health (taking AChEIs is strictly prohibited if you have bradycardia,

heart block, asthma, or an active peptic ulcer). 4. If at all possible, stop taking anticholinergic medications 5.

Establish treatment objectives and advise the patient and family on reasonable expectations of benefit and risk. 6. Verify adherence 7. Conduct a baseline cognitive evaluation: • MMSE <10 and clinically mild-moderate Alzheimer's disease: CIBIS/CIBIC (for non-English speaking, low education, visual/hearing impairment, and intellectually handicapped); • MMSE >24: ADAS-Cog required; • MMSE 10–24: qualified for PBS subsidy 8. Obtain a written PBS authority script for the first six months of treatment. 9. A review at one, three, and six months by a specialist or general practitioner.

CONCLUSION

The youngest individual to be overdiagnosed with AD was a 19-year old Chinese male who began experiencing memory problems at the age of 17. This instance that was published in the journal of AD is remarkable because Alzheimer's disease often affects elderly people. AD has a significant negative impact on patients' quality of life, and its prevalence is progressively increasing annually. Despite the identification of a number of common pathological alterations in AD, treatment strategies aimed at these alterations have either not produced the best outcomes or are linked to serious consequences. The historical backdrop, phases, epidemiology, pathophysiology, non-pharmacological management, pharmaceutical management, and advancements in physical therapy, exercise therapy, cell therapy, and nanoparticle- based treatments for AD are all included in this review. These non-pharmacological methods can either treat AD directly or act as supplemental treatments, providing patients with extra advantages.

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