Review Article

ALZHEIMER'S DISEASE (AD): MANAGING COGNITIVE IMPAIRMENTS AND BEHAVIORAL PROBLEMS

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ABSTRACT:
Alzheimer's disease being a common and multifactorial neurodegenerative disorder is one of the most challenging and emerging issues in clinical medicine these days. The current therapy includes anticholinesterases and NMDA antagonists - memantine only. Owing to the advancement in the knowledge of its pathophysiology, a lot of research is going on and many potential targets and alternative therapies including compounds acting on the pathological substrate of the disease have been proposed, which may be beneficial in prevention and treatment of this debilitating disease.

Key Words: Cognitive dysfunction, Therapeutics, Neurodegenerative disease, Problems behavioral

INTRODUCTION:

Alzheimer's disease (AD) is one of the major degenerative diseases affecting almost 35 million people globally. It is characterized by dementia: a persistent and progressive impairment in intellectual function, and at least one of the other cognitive deficits: apraxia, agnosia, aphasia and/or impaired executive function.[1] The disease may be of early-onset, occurring between 30-60 years of age whereas late-onset AD, after the age of 60 years, accounts for around 90% of cases. It's prevalence doubles every 5 years in the older population, reaching 30–50% at the age of 85.[2] The disease itself is becoming a slow pandemic and it is expected that by the year 2050, one person for every 85 individuals may have AD.[3] Almost all patients with AD are affected by neuropsychiatric symptoms at some point during their illness which includes depression occurring earlier in the course of disease followed by irritability, anxiety, aggression and delusions as the disease advances. Furthermore, behavioral problems such as hostility, sleep disturbances, and wandering have been identified.[4]

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Pathophysiology:

Amyloid Hypothesis: The pathological hallmarks of AD are extracellular amyloid plaques consisting of highly ordered fibrils of Amyloid Beta (Aβ) and intracellular neurofibrillary *tangles* composed of the microtubule-associated protein tau.[5] The mechanisms responsible for neuronal dysfunction and death may include direct impairment of synaptic transmission, oxidative stress, excitotoxicity and neuro-inflammation.[6]

Cholinergic Hypothesis: The most striking neurochemical disturbance in AD is a deficiency of Acetylcholine (Ach) due to atrophy and degeneration of subcortical cholinergic neurons which modulate cognition, learning, task, memory-related activities and maintain sleep-wake cycle as well.[7] AD, however, is a complex disorder and involves multiple neurotransmitters, including glutamate, serotonin, and neuropeptides.[8]

Genetic Relationship: Autosomal dominant AD is caused by mutations in the following three genes responsible for the formation of Aβ peptides: Amyloid Precursor Protein (APP), PSEN1 (Presenilin) and PSEN2.[9] β-secretase and γ-secretase generate Aβ by successive proteolytic cleavage of APP.[10]

Diagnosis:
For effective treatment, it is very important to get an early and accurate diagnosis of Alzheimer's disease. AD is diagnosed mainly clinically, based on the presence of memory impairment (especially short-term loss) and other cognitive impairments that are insidious, progressive, and not well explained by another disorder.[11]

Risk Factors.[12]

Non-Modifiable	Modifiable	Others
Age Genetics (APOE E_4, Presenilin) Down Syndrome (trisomy 21) Traumatic Brain Injury	Hypertension Diabetes Elevated Homocysteine, Cholesterol Environmental Factors (exposure to silicon, aluminum & other toxins, free-radicals, metals like Cu, Fe, Zn; etc.)	Inflammation Oxidative Stress Estrogens

Treatment:
The discovery of specific proteins that accumulate and aggregate in the AD has opened the door to new therapeutic approaches. To date, no approved therapy directly targets the disease proteins (Aβ, tau). However, there is intensive research going on to bring disease-modifying treatments into clinical care.[13] Many of the existing therapies are neurochemical, aiming to replace or compensate for damage to specific neurotransmitter systems that are selectively impaired.[14] The goal of the current review is to discuss possible therapies.

Symptomatic Treatment

i. Cholinesterase inhibitors (ChEIs). They constitute the current first-line therapy for symptomatic treatment of cognitive impairments in mild to moderate AD. The FDA-approved ChEIs used for AD are rivastigmine, galantamine, and donepezil. Their adverse effects have been attributed to excessive peripheral cholinergic stimulation.[15] Tacrine was approved by the FDA in 1993, but the extent of alanine aminotransferase elevation and hepatotoxicity limited its use.[16] Although these drugs are not curative and don't alter the pathology of AD whereas the magnitude of evidence demonstrates that they delay the deterioration in cognitive function, behavioral manifestations and thus improve the overall well-being of the patients.[17]

ii. Non-Competitive N-methyl-D-aspartate (NMDA) Antagonist: Memantine. It is either used as an adjunct or an alternative to anti-cholinesterases, generally in later stages of AD. Its long-term functional outcomes have yet to be demonstrated.[18]

Disease-Modifying Interventions

i. Cerebrolysin. It has neurotrophic effects similar to that of endogenous nerve growth factors, which may play a role in AD pathogenesis by preserving neuronal function.[19]
ii. Ferulic Acid. It is a new therapeutic agent, which inhibits the Aβ - aggregation in experimental models.[20]
iii. Posiphen. It may slow the onset of disease or delay its progression by inhibiting the production of APP.[21]
iv. Agmatine. It activates antioxidant signaling pathways and thus may be a promising agent for improving cognitive decline and attenuating apoptosis in AD.[22]
v. Aducanumab. It may be beneficial in early diagnosed disease, by preserving memory and improving skills that could slow the disease progression.[23]
vi. Tramiprosate. It is an anti-amyloid aggregation agent and may help to treat mild to moderate form of AD.[24]
vii. Tarenflurbil and Semagacestat. They decrease Aβ formation by inhibiting γ secretase and thus may delay the progression of AD.[25]

Invasive Therapies

i. Deep Brain Surgery (DBS). It modulates the neurobiological activity and

improves cognitive function in patients with AD.[26]

ii. Memory Prosthetics. An artificial hippocampal system implanted in the rats' brain restored long-term memory. These findings open up amazing possibilities for ameliorating brain damage caused by AD.[27]

iii. Transcranial Magnetic Stimulation. Studies have shown that repetitive transcranial magnetic stimulation of the prefrontal lobes produce a significant improvement in the patients' ability to understand spoken language.[28]

Non-Pharmacologic Strategies

Behavioral problems in patients with AD are often best managed non-pharmacologically. Communication with the patients should be in simple language and their daily activities must be broken down into simple component tasks. Concealing doorways and encouraging movement under supervision may limit wandering. Additionally, minimizing daytime naps, limiting bedtime, cognitive behavior therapy and bright light therapy may be beneficial to the patients having sleep disturbances.[29]

Pharmacologic Approaches

Pharmacologic treatment should be reserved for patients who pose an imminent danger to others or themselves or when symptoms are substantially distressing to the patient.

Pharmacological options

Atypical Antipsychotics. The atypical antipsychotic agents: olanzapine, quetiapine, risperidone, and aripiprazole are increasingly becoming the first choice for agitation and psychosis in AD because of their better safety profile compared to typical agents (haloperidol) but must be used with caution in patients with vascular risk factors due to an increased risk of stroke.[30]

Benzodiazepines can be used occasionally for acute agitation. However, their adverse effects on cognition don't make them a better choice for long-term management.[31]

Antidepressants. They are used to combat symptoms of agitation and depression in patients with AD. Citalopram (a SSRI) has shown promising effects in clinical trials.[32]

Cholinergic agonists. Tacrine also resulted in the reduction or stabilization of delusions and xanomeline resulted in a greater reduction in episodes of delusion, suspiciousness, fearfulness, agitation, or wandering than the placebo.[33]

Electroconvulsive therapy (ECT). ECT has been adopted for depression, agitation and psychosis due to AD, but is mainly reserved for life-threatening or pharmacologically-unresponsive conditions.[34]

Emerging Therapeutic Approaches/ Novel Research Targets.

Future trends include the use of multiple drugs acting by different mechanisms such as antioxidant and anti-inflammatory action and inhibiting the formation of ß-amyloid plaques and fibrillary tangles.

i. Omega-3 Fatty Acids: DHA and EPA; Natural antioxidants; vitamin D_3 and E; and phosphatidylserine (a phospholipid) play a pivotal role as modulators of neuronal function, cognition, immune response and oxidative stress mechanisms in the brain. Hence, may be beneficial in the prevention and treatment of AD.[35]

ii. Selegiline. It is a monoamine oxidase inhibitor with antioxidant properties.[36]

iii. GABAergic Modulation. Etazolate, a $GABA_A$ modulator, α-secretase and phosphodiesterase-4 inhibitor, was proved beneficial in a recent trial, but the effectiveness and long-term benefits are yet to be determined.[37]

iv. Serotonin Receptor Modulation. Many serotonergic drugs (MAOIs and SSRIs) are under consideration as monotherapy or with ChEIs for their cognitive enhancing capacities.[38]

v. Histaminergic Modulation. Selective H_3 antagonists have shown positive effects on attention and memory, but their therapeutic role is not clear yet.[39]

vi. Adenosine receptor modulation. In vivo studies have shown the neuroprotective role of an adenosine 2A blocker.[40]

Preventive Treatments

The anticipated rise in the vulnerability of an older population to AD has led to the consideration of preventive therapy that will require the development of safe treatments or interventions that could be used in a large number of susceptible individuals. [(2)] Non-steroidal anti-inflammatory drugs, estrogen-replacement therapy, and an anti-amyloid vaccine are a few potential preventive therapies under consideration.[41]

Alternative Therapy

Phytotherapy enhances the brain's ability to function, and therefore, provides stability when used consistently.

Neuroprotective Mechanisms of Plant Extracts.[42] - Cholinesterase Inhibition: Achyroclinetomentosa, Eupatorium viscidum, Ruprechtiaapetala, Zanthoxylum coco, Salvia officinalis, Trichoclinereptans, Angelica archangelica, Poncirus trifoliate, Treculiaobovoidea, Cassia obtisufolia, Desmodiumgangeticum, Huperzia Serrata. Modification of Monoamines: Moringa oleifera. Antioxidant activity: Desmodiumgangeticum, Ginkgo biloba, Salvia officinalis. Antiamyloid aggregation effect: Ginkgo Biloba.

Neuroprotective Effect of Traditional Plant Extracts.

Japanese-Chinese Medicines**:** Research demonstrated their probable axonal extension activity against amyloid β induced axonal atrophy; improving memory impairment.[43] European Plant extracts: S.triloba and Teucrium polium have shown effectiveness in managing mild to moderate AD by amelioration of cognition.[44] Ayurvedic Herbs: Ashwagandha, Shankhpushpi, Guggulu, Gotu Kola, Curcuma longa and Bacopa monnieri may help in improving the symptoms and progression of AD.[45]

Nutritional therapy. Studies in recent decades demonstrated the role of nutrition in treating dementia. Healthy dietary changes, in particular switching to a diet composed of whole grains, fish, nuts, fruits, vegetables, low-fat dairy, healthy oils, and eliminating white sugar reduce cognitive decline and prevent the early onset of AD. Although, its effectiveness varies from person to person but it's likely to be beneficial.[46]

Lifestyle Changes. Studies show that physical activity can slow down and even prevent the progression of cognitive decline in AD. Gardening, walking, yard work, and even dancing may help.[47]

Social Interaction: Psychosocial intervention is a great approach to improve cognition and overall wellness in patients with AD. There are many ways to improve the quality of life and possibly dementia symptoms through social activities such as talking about events from the past, taking part in group activities to improve memory, problem-solving skills, and doing everyday tasks.[48]

Acupuncture: Recent clinical trials have shown that not only is acupuncture a safe option that improves cognitive ability, but improves pain and insomnia too.[49]

Reflexology: Massages improve quality of life by reducing pain and distress in patients.[50] Aromatherapy: It has positive effects on the reduction of behavioral and psychiatric symptoms of AD, enhancement of cognitive functions and improving quality of life.[51]

Prognosis

Life expectancy after a diagnosis of AD is reported to be 3–15 years. Hospital care is usually preferable for patients with end-stage disease.[1]

CONCLUSION:

Alzheimer's disease (AD) is a multifactorial neuro-degenerative disorder. Although a lot of research and clinical trials are going on but despite all the scientific efforts, no pragmatic curative therapies have been found yet. The three anti-cholinesterases; donepezil, rivastigmine and galantamine along with memantine, constitute current mode of therapy. Additionally,

antipsychotics and antidepressants are used to ameliorate the behavioral problems associated with the disease. Treatments under research include compounds modifying the pathological substrates of the disease: Aβ, APP and tau protein.

Author's Contribution:

SA: Conception of work, design and supervision
MP: Acquisition of data and substantial contribution in design
MN: Drafting article
AF: Reference writing
SJ: Reviewing article critically

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