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ALZHEIMER'S DISEASE: A REVIEW

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ABSTRACT

Alzheimer's disease is a brain disorder in which the patient eventually loss the memory and thinking skills. This makes it difficult for a patient to carry out the simple task. This is also one type of dementia with no known cause or cure. In this present review article, Pathology, Pathophysiology, symptoms and stages of the disease, diagnosis and FDA approved drugs for treatment of the disease have been explained neatly and legibly with proper tables which is easy to understand.

Key words: *Conyza sumatrensis*; Inflammation; *In-silico*; Cycloxygenase enzyme; Toxicity.

INTRODUCTION

Alzheimer's disease is a progressive neurodegenerative disorder of the brain that is characterised by the presence of beta-amyloid plaques in the brain[1]. An increased blood-to-brain influx and decreased brain-to-blood efflux across the bloob-brain barrier(BBB) can cause the accumulation of beta-amyloid plaques[2] .

The first case of AD was identified by Alois Alzheimer in 1906 in Germany[3]. Alzheimer's disease is the most common cause of dementia, AD is generally associated with the elderly because most cases present in persons older than age 65, but in about 5% of cases onset can be as early as age 40, resulting in the arbitrary age classifications of early-onset (ages 40 to 64 years) and late-onset (age 65 years and older).[4] Scientists estimate that around 35 million people now have Alzheimer's disease world-wide. In India one part of Indians are affected at present. For every 5-year age group beyond 65, the percentage of people with AD doubles. By 2050 107 million of people will be affected world-wide.[5] The prevalence of AD increases exponentially with respect to the age, affecting approximately 7% of 65-74 years of aged individuals, 53% of aged individuals b/w 75 to 84, and 40% of persons aged 85 years and older. AD shows its affect two times more as compared to men and family history increase the risk of inheriting AD by up to fourfold.Although genetic inheritance is a significant factor in its transmission, other factors may contribute. Factors determining age of onset and rate of progression remain largely undefined. Survival following AD onset is estimated to be 3 to 20 years, with an average of 8 years after the onset of symptoms.3 Approximately [10]0,000 individuals with AD die every year. AD is the eighth leading cause of death in United States. This is somewhat of a misrepresentation, as AD does not cause death directly, but indirectly by predisposing

patients to sepsis, pneumonia, choking and aspiration, nutritional deficiencies, and trauma. [4]

Alzheimer's disease clinical feature typically presents with early problems in memory and visuospatial abilities (eg, becoming lost in familiar surroundings, inability to copy a geometric design on paper), yet social graces may be retained despite advanced cognitive decline. Personality changes and behavioral difficulties (wandering, inappropriate sexual behavior, and agitation) may develop as the disease progresses. Hallucinations may occur in moderate-to-severe dementia. End-stage disease is characterized by near-mutism; inability to sit up, hold up the head, or track objects with the eyes; difficulty with eating and swallowing; weight loss; bowel or bladder incontinence; and recurrent respiratory or urinary infections.

"Subcortical" dementias (eg, the dementia of Parkinson's disease and some cases of vascular dementia) are characterized by psychomotor slowing, reduced attention, early loss of executive function, and personality changes, and benefit from cuing-in tests of memory.

Dementia with Lewy bodies may be confused with delirium, as fluctuating cognitive impairment is frequently observed. Rigidity and bradykinesia are the primary signs, and tremor is rare. Response to dopaminergic agonist therapy is poor. Complex visual hallucinations—typically of people or animals—may be an early feature that can help distinguish dementia with Lewy bodies from Alzheimer's disease. These patients demonstrate a hypersensitivity to neuroleptic therapy, and attempts to treat the hallucinations may lead to marked worsening of extrapyramidal symptoms.

Frontotemporal dementias are a group of diseases that include Pick's disease, dementia associated with amyotrophic lateral sclerosis, and others. Patients manifest personality change (euphoria, disinhibition, apathy) and compulsive behaviors (often peculiar eating habits or hyperorality). In contrast to Alzheimer's disease, visuospatial function is relatively preserved.

Dementia in association with motor findings, such as extrapyramidal features or ataxia, may represent a less common disorder (eg, progressive supranuclear palsy, corticobasal ganglionic degeneration, olivopontocerebellar atrophy).[6]

Classification of Dementia[4]

- Dementia of the Alzheimer's type.
- Vascular dementia.
- Dementia due to human immunodeficiency viral disease.
- Dementia due to head trauma.
- Dementia due to Parkinson's disease.
- Dementia due to Huntington's disease.
- Dementia due to Pick's disease.
- Dementia due to Creutzfeldt-Jakob disease.
- Dementia due to other general medical condition (e.g, normal-pressurehydrocephalus, hypothyroidism, brain tumor, vitamin B12 deficiency,intracranial radiation).
- Substance-induced persisting dementia (e.g., alcohol, inhalant,sedative, hypnotic, anxiolytic, or other substance).
- Dementia due to multiple etiologies.

Pathogenesis and Pathophysiology:[4,7]

Genetics:

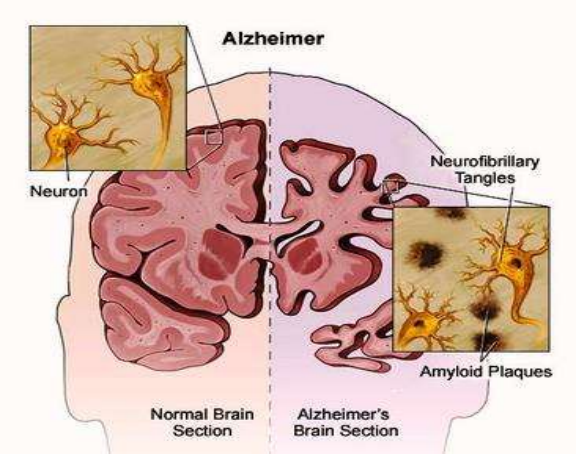
Genetic factors have been investigated in both early- and late onset AD [4]. Several genetic factors play important roles in the pathogenesis of at least some cases of AD. One is the *APP* gene on chromosome 21. Adults with trisomy 21 (Down's syndrome) consistently develop the typical neuropathologic hallmarks of AD if they survive beyond age 40[7]. Almost all early-onset cases of AD can be attributed to alterations on chromosomes 1, 14, or 21. The majority and most aggressive early-onset cases are attributed to mutations of an Alzheimer's gene located on chromosome 14, which produces a protein called presenilin 1. Similar in structure to presenilin 1 is a protein produced by a gene on chromosome 1 called presenilin 2. Presenilin 2 is responsible for early-onset AD in a family of Germans living in Russia's Volga Valley.8 Both presenilin 1 and presenilin 2 encode for membrane proteins that may be involved in amyloid precursor protein (APP) processing. Only a small number of early-onset familial AD cases have been associated with mutation in the APP gene, resulting in overproduction of beta-amyloid protein (βAP) [4].

Genetic susceptibility to late-onset AD is thought to be primarilyinfluenced by the apolipoprotein E (apo E) genotype [4]. Apo E gene on chromosome 19 in the pathogenesis of late onset familial and sporadic forms of AD. Apo E is involved in cholesterol transport and has three alleles: 2, 3, and 4. The Apo E4 allele has a strong association with AD in the general population, including sporadic and late-onset familial cases [7]. Humans inherit one copy of the apo E gene from each parent. Apo E3 is the most common type, occurring in 40% to 90% of the population, with apo E2 and apo E4 occurring less frequently. However, rather than being causative, the apo E4 allele is a risk factor for development of AD [4].

Inheritance of the apo E4 isoform increases risk for late-onset AD; however, the degree of risk depends on such factors as the number of apo E4 copies, age, ethnicity, and gender. Overall, about 40% of patients with late-onset AD have at least one copy of apo E4. Individuals homozygous for apo E4 are at increased risk, and as many as 90% of persons inheriting two copies of apo E4 will develop AD by age 80 years. Moreover, onset of symptoms occurs at a relatively younger age as compared to patients having zero or only one copy of apo E4 in their genotype. In Caucasians, inheriting a single copy of apo E4 increases AD risk, whereas inheriting the apo E2 allele may protect against AD.Differences also exist with regard to gender; inheriting one copy of apo E4 increases risk in females more than in males. However, genetic causes of AD have been associated with only a small percentage of Alzheimer's patients, and the exact cause of AD remains unknown [4].

ENVIRONMENTAL AND OTHER FACTORS: A number of environmental factors have been associated with an increased risk of AD, including stroke, alcohol abuse, small head circumference, repeated or severe head trauma, Down syndrome, and lower levels of education. In particular, traumatic head injury in combination with the apo E4 genotype has been associated with an increased risk of AD [4].

Deposition of Amyloid: Deposition of a form of amyloid, derived from breakdown of APP, is a consistent feature of AD. The breakdown product, known as beta amyloid (Aβ) is a prominent component of the senile plaques found in the brains of AD patients and it is usually present within the walls of cerebral blood vessels as well.



The Aβ peptides are derived through processing of APP. APP is a protein of uncertain cellular function that is synthesized with a single transmembrane domain and expressed on the cell surface. A soluble form of APP can be released from the cell surface by proteolytic cleavage, by an enzymatic activity termed α-secretase; at least three distinct enzymes have been shown to have α-secretase activity.

Molecules of APP that have undergone this cleavage cannot give rise to the Aβ fragment (see However, surface APP can also be endocytosed and may then undergo processing to generate Aβ peptides that are less soluble and tend to aggregate into amyloid fibrils. These are generated through cleavage at a site N-terminal to the start of the transmembrane domain by an enzyme called β-secretase (BACE-1) and cleavage within the transmembrane domain by γ-secretase. This process is constitutively active in cells, and γ-secretase appears to perform other important intramembranous proteolysis events, including cleavage of Notch, a cell fate-determining molecule. The cleavage of Notch results in release into the cell of a portion of the molecule that is involved in cell signaling and transcriptional regulation. Both by inference and by direct experimentation, it has been suggested that a similar function can be attributed to a fragment of the C-terminal portion of APP that is generated by the same cleavages that generate Aβ.

Several gene loci have been identified for familial Alzheimer disease. The first of these was the gene for APP on chromosome 21. The pathogenic mutations in the APP gene all result in increased generation of Aβ. Furthermore, the development of Alzheimer disease in individuals with trisomy 21 has been related to a gene dosage effect with increased production of APP and subsequently Aβ. Two other genetic loci linked to early-onset familial Alzheimer disease have been identified on chromosomes 14 and 1; these probably account for the majority of early-onset familial Alzheimer disease pedigrees. The genes on these two chromosomes encode highly related intracellular proteins, presenilin-1 (PS1) and presenilin-2 (PS2). Even before these genes were cloned, it was recognized that the cellular phenotype of these mutations was an increased level of Aβ generation, particularly $A\beta_{42}$. It has now become clear from studies of knockout mice, from directed mutatagenesis of PS1 and PS2, from pharmacologic studies, and from biochemical purifications that the presenilins are a component of γ-secretase and possibly are the portion of a multiprotein complex containing the active proteolytic site. Thus, the genetic evidence strongly supports the notion that the underlying pathogenetic event in AD is the accumulation of Aβ [8].

Hyperphosphorylation of the protein tau: NFTs and neuritic plaques are considered the signature lesions of AD; without them AD does not occur. NFTs are comprised of paired helical filaments that aggregate in dense bundles. Paired helical filaments are formed from tau protein.Tau protein provides structural support to microtubules, the cell's transportation and skeletal support system[4]. The presence of Aβ also leads neurons to hyperphosphorylate the microtubule binding protein tau.

With this increased level of phosphorylation, tau redistributes within the neuron from the axon into dendrites and cell body and aggregates into tangles. This process also results in neuronal dysfunction and cell death. The anatomic distribution of these changes, which occur roughly in parallel, are responsible for the clinical signs and symptoms; they appear to develop well in advance of clinical presentation.[8]

Neuritic plaques (also termed amyloid or senile plaques) are extracellular lesions found in the brain and cerebral vasculature (amyloid angiopathy). Plaques are comprised of *β*AP, and an entwined mass of broken neurites (axon and dendrite projections of neurons). Manyof these broken neurites contain neuropil filaments made up of the abnormally phosphorylated tau protein found in NFTs.7,13 Two types of glial cells, astrocytes and microglia, are also found in plaques.Among other functions, glial cells secrete inflammatory mediators and serve as scavenger cells, which may be important in causing the inflammatory processes that occur in the development of AD[4].

Inflammatory mediators and other immune system constituents are present near areas of plaque formation, suggesting that the immune system plays an active role in the pathogenesis.Cholinergic pathways, especially a large system of neurons located at the base of the forebrain in the nucleus basalis of Mynert, are profoundly damaged. Cholinergic cell loss appears to be a result of the disease pathology rather than the disease-producing event.

Serotonergic neurons of the raphe nuclei and noradrenergic cells of the locus ceruleus are also lost, whereas monoamine oxidase type B (MAO-B) activity is increased.Glutamate and other excitatory amino acid neurotransmitters have been implicated as potential neurotoxins in AD.Elevated cholesterol levels in brain neurons may alter cell membrane functioning and result in the cascade leading to plaque formation.Estrogen interacts with nerve growth factor, which may explain its ability to promote synaptic growth. Estrogen also acts as an antioxidant and may help maintain normal cholinergic transmission[4].

Diagnosis: [4].

NINCDS-ADRDA Criteria and Diagnostic Work-Up for Probable Alzheimer's Disease

I. History of progressive cognitive decline of insidious onset
- In-depth interview of patient and caregivers

II. Deficits in at least two or more areas of functioning

III. No disturbance of consciousness
- Confirmation with use of dementia rating scale (e.g., Mini-Mental Status Exam [MMSE] or Blessed Dementia Scale)

IV. Age between 40 and 90 years (usually >65 years)

V. No other explainable cause of symptoms
- Normal laboratory tests including hematology, full chemistries, B12 and folate, thyroid function tests, Venereal Disease Research Lab test (to rule out venereal disease or syphilis)
- Normal electrocardiogram and electroencephalogram
- Normal physical exam, including thorough neurologic exam
- Neuroimaging: CT or MRI scanning: No focal lesions signifying other possible causes of dementia are present. Abnormalities which are common, but not diagnostic for AD include general cerebral wasting, widening of sulci, widening of the ventricles, and lesions of white matter surrounding the ventricle deep in the brain.

The Mini-Mental Status Exam is a commonly used scale that measures orientation, recall, short-term memory, concentration, constructional praxis, and language. The MMSE is scored from 0 to 30, with a score of 10–26 typical of mild to moderate Alzheimer's disease.

National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA).

Stages of Cognitive Decline: The Global Deterioration Scale (GDS)

Stage 1	Normal	No subjective or objective change in intellectual functioning.
Stage 2	Forgetfulness	Complaints of losing things or forgetting names of acquaintances. Does not interfere with job or social functioning. Generally a component of normal aging.
Stage 3	Early confusion	Cognitive decline causes interference with work and social functioning. Anomia, difficulty remembering right word in conversation, and recall difficulties are present and noticed by family members. Memory loss may cause anxiety for patient.
Stage 4	Late confusion (early AD)	Patient can no longer manage finances or homemaking activities. Difficulty remembering recent events. Begins to withdraw from difficult tasks and to give up hobbies. May deny memory problems.
Stage 5	Early dementia(moderate AD)	Patient can no longer survive without assistance. Frequently disoriented with regard to time (date, year, season). Difficulty selecting clothing. Recall for recent events is severely impaired; may forget some details of past life (e.g., school attended or occupation). Functioning may fluctuate from day to day. Patient generally denies problems. May become suspicious or tearful. Loses ability to drive safely.
Stage 6	Middle dementia (moderately severe AD)	Patients need assistance with activities of daily living (e.g., bathing, dressing, and toileting). Patients experience difficulty interpreting their surroundings; may forget names of family and caregivers; forget most details of past life; have difficulty counting backward from 10. Agitation, paranoia, and delusions are common.
Stage 7	Late dementia	Patient loses ability to speak (may only grunt or scream), walk, and feed self. Incontinent of urine and feces. Consciousness reduced to stupor or coma.

TREATMENT:

DESIRED OUTCOME.

The primary goal of treatment in AD is to maintain patient functioning as long as possible. Secondary goals are to treat the psychiatric and behavioral sequelea[4].

The management of AD is challenging and gratifying, despite the absence of a cure or a robust pharmacologic treatment. The primary focus is on long-term amelioration of associated behavioral and neurologic problems.

Building rapport with the patient, family members, and other caregivers is essential to successful management. In the early stages of AD, memory aids such as notebooks and posted daily reminders can be helpful. Common sense and clinical studies show that family members should emphasize activities that are pleasant and deemphasize those that are unpleasant. Kitchens, bathrooms, and bedrooms need to be made safe, and eventually patients must stop driving. Loss of independence and change of environment may worsen confusion, agitation, and anger. Communication and repeated calm reassurance are necessary [7].

Donepezil, rivastigmine, galantamine, memantine, and tacrine are the drugs presently approved by the Food and Drug Administration (FDA) for treatment of AD. Due to hepatotoxicity, tacrine is no longer used [7].

The pharmacologic action of donepezil, rivastigmine, and galantamine is inhibition of cholinesterase, with a resulting increase in cerebral levels of acetylcholine [7].

Anticholinergic drugs such as anticholinesterase inhibitors (Rivastigmine, Physostigmine, Neostigmine and Pyridostigmine) has shown good efficacy in improving the cognitive function in Alzheimer type dementia.some studies have demonstrated mild transitory improvement in memory following physostigmine treatment. Their use is limited because of short half-life and systemic cholinergic actions. If the decline in MMSE score is more than 2 to 4 points after treatment for 1 year with the initial agent, it is reasonable to change to a different cholinesterase inhibitor. Otherwise, treatment should be continued with the initial medication throughout the course of the illness.[4,5,9].

All the cholinesterase inhibitors are relatively easy to administer, and their major side effects are gastrointestinal symptoms (nausea, diarrhea, cramps), altered sleep with bad dreams, bradycardia (usually benign), and sometimes muscle cramps[7].

FDA-Approved Drugs for Alzheimer's Disease[10]

Generic Drug and Mechanism	Dosage Form and Dosage	Indication and Effect	Adverse effects	others
Donepezil HCl Reversibly inhibits acetyl-cholinesterase, primarily in CNS	5, 10 mg tablets 5 mg daily, usually at bed-time Dose may be increased to 10 mg after 4–6 weeks	Symptomatic treatment of mild to moderate AD Small improvements in cognition and function occur within 12–24 weeks; benefits may last for at least 2 years	Cholinergic effects,particularly affecting the GI tract (nausea, anorexia, diarrhea); headache; bradycardia may occur	Completely bioavailable and may be given as a single daily dose due to long half-life (70 hr) Metabolized by CYP3A4 isoenzymes
Galantamine HBr Reversibly inhibits acetylcholinesterase, primarily in CNS; also stimulates nicotinic receptors at a site distinct from that of acetylcholine	4, 8, 12 mg tablets 4 mg twice daily, with food Dose may be increased every 4–6 weeks in 4 mg BID increments, to a maximum dose of 12 mg BID	Symptomatic treatment of mild to moderate AD. Small improvements in cognition and function occur within 12-24 weeks. Benefits may last for more than 1 year.	Cholinergic effects, particularly affecting the GI tract (nausea, anorexia, diarrhea); headache; bradycardia may occur	Highly bioavailable. Initial dose is not therapeutic; slow titration increases tolerability. Metabolized by CYP2D6 and CYP3A4 isoenzymes.
Rivastigmine tartrate Reversibly inhibits acetyl-cholinesterase and butyrylcholinesterase, primarily in CNS	1.5, 3, 4.5, 6 mg tablets 1.5 mg twice daily, with food. Dose may be increased every 4–6 weeks in 1.5 mg BID	Symptomatic treatment of mild to moderate AD. Small improvements in cognition and function occur within 12-24 weeks. Benefits	Cholinergic effects, particularly affecting the GI tract (nausea, anorexia, vomiting, diarrhea); headache; bradycardia may occur	Highly bioavailable. Therapeutic effect greatly exceeds biologic half-life (1 hr), allowing for twice daily dosing. Metabolized by

	increments, to a maximum dose of 6 mg BID	may last for more than 1 year		hydrolysis. Initial dose is not therapeutic; administration with food and slow titration are necessary to increase tolerability
Tacrine Reversibly inhibits acetyl-cholinesterase and butyrylcholinesterase, in CNS and periphery.	10, 20, 30, 40 mg tablets Initially 10 mg QID, with increases of 10 mg QID every 4 weeks; maximum dose is 40 mg QID	Symptomatic treatment of mild to moderate AD Small improvements in cognition and function occur within 12–24 weeks	Cholinergic effects, particularly affecting the GI tract (nausea, anorexia, vomiting, diarrhea); abdominal pain; headache; bradycardia may occur. Increases in ALT levels require frequent monitoring	Poor bioavailability, further reduced by giving with food Adverse effects limit patient tolerability Multiple daily doses require frequent dosing Metabolized by CYP1A2, CYP2D6 Initial dose is not therapeutic

Others:

Memantine:

Excitotoxic reactions and cell death due to the release of glutamate in the CNS has led to research into the use of N-methyl-D-aspartate (NMDA) antagonists to treat AD and other neurodegenerative disorders. Memantine is an amantadine derivative appears to act by blocking overexcited N-methyl-D-aspartate (NMDA) channels. It is indicated for treatment of moderate to severe AD. It is usually well tolerated, and side effects include constipation, confusion, dizziness, headache, coughing, and hypertension. It is used as monotherapy and in combination with cholinesterase inhibitors. It is initiated at 5 mg/day and increased weekly by 5 mg/day to the effective dose of 10 mg twice daily. Dosing must be adjusted in patients with renal impairment[4,5,7,10].

Estrogen:[5,7,10]

Estrogen has several beneficial effects on the brain, including improved cerebral blood flow, increased glucose transport and metabolism, and facilitated repair of damaged neurons. The beneficial effects of Estrogen controversial in a prospective observational study, the use of estrogen replacement therapy appeared to protect—by about 50%—against development of AD in women. This study seemed to confirm the results of two earlier case-controlled studies. Sadly, a prospective placebo-controlled study of a combined estrogen-progesterone therapy for asymptomatic postmenopausal women increased, rather than decreased, the prevalence of dementia. This study markedly dampened enthusiasm for hormone treatments for the prevention of dementia. Additionally, no benefit has been found in the treatment of AD with estrogen. Research work shows that postmenopausal hormone therapy increases the risk of dementia in healthy women. In these circumstances estrogen after administration improves the cognitive function.In this case raloxifene which is a selective estrogen receptor modulator reduces the risk of dementia in Alzheimer's disease (Research approach from University of Wisconsin). The National Institute of aging also prescribed regarding the estrogen patch which is a sustained release to reduce the risks of Alzheimer's disease.

Antioxidants:[5,7]

The brain has high oxygen consumption rate and abundant poly unsaturated fatty acids in the neuronal cells. If the neuronal cells get free radical damage, it results in cognitive decline and neurodegenerative diseases (Alzheimer's disease). In this case the antioxidants α-tocopherol (vitamin E),monoamino oxidase inhibitor (selegiline), phenolics (curcumin), tannins (gallic acid) and polyphenolics (ferulic acid) reduce the free radical formation and prevents the cognitive syndromes, slowed institutionalization and progression to death. Because vitamin E has less potential for toxicity than selegiline and is cheaper, the doses used in this study of 1000 IU twice daily are offered to many patients with AD. However, the beneficial effects of vitamin E remain controversial, and most investigators no longer give it in these high

doses because of potential cardiovascular complications.

Vaccination: [5, 7.]

Several vaccines are under development to reduce the cognitive symptoms due to Alzheimer's disease. These vaccines stimulate the immune system to produce antibodies against the pathogens which create the problem. The vaccine is injected in the form of β-amyloid that clear the plaques and physical signs of Alzheimer's disease. Vaccination against beta amyloid$_{42}$ has proved highly efficacious in mouse models of AD; it helped to clear amyloid from the brain and prevents further accumulation of amyloid. However, in human trials this approach led to life-threatening complications, including meningoencephalitis. Modifications of the vaccine approach using passive immunization with monoclonal antibodies are currently being evaluated in phase 3 trials. Another experimental approach to the treatment of AD has been the use of and secretase inhibitors that diminish the production of beta amyloid$_{42}$.One of the developed vaccines administered by intramuscular route is AN-1792 which produces nonfatal inflammation, improvement and recovery from symptoms of Alzheimer's disease. Another one is developed in the modified form of amyloid protein administered by nasal route.

Nonsteroidal anti-inflammatory agents and statins:[4,7,10.]

The recognition that acute-phase inflammatory proteins are present in neuritic plaques has led to the investigation of nonsteroidal anti-inflammatory drugs (NSAIDs) for the treatment or prevention of AD.Several retrospective studies suggest that nonsteroidal anti-inflammatory agents and statins (HMG-CoA reductase inhibitors) Pravastatin and lovastatin, but not simvastatin, were associated with a lower prevalence of AD and may have a protective effect on dementia, and controlled prospective studies are being conducted. Similarly, prospective studies with the goal of lowering serum homocysteine levels are underway, suggesting an association of elevated homocysteine with dementia progression based on epidemiologic studies. Finally, there is now a strong interest in the relationship between diabetes and AD, and insulin-regulating studies are being conducted. However, because of limited prospective data and the potential for side effects, NSAIDs are not recommended for general use in prevention or treatment of AD.

Implanting Healthy Neurons:[5]

Cognitive problems are stem from low levels of acetylcholine. Transplanting healthy cholinergic neurons (cholinoceptors) into the brain would be a direct way to restore acetylcholine levels. Stem cells having cholinoceptors is also produce healthy levels of acetylcholine which prevents neurodegenerative diseases (Alzheimer's disease).

PHARMACOTHERAPY OF NONCOGNITIVE SYMPTOMS:

Mild to moderate depression is common in the early stages of AD and responds to antidepressants or cholinesterase inhibitors. Selective serotonin reuptake inhibitors (SSRIs) are commonly used due to their low anticholinergic side effects. Generalized seizures should be treated with an appropriate anticonvulsant, such as phenytoin or carbamazepine. Agitation, insomnia, hallucinations, and belligerence are especially troublesome characteristics of some AD patients, and these behaviors can lead to nursing home placement. The newer generation of atypical antipsychotics, such as risperidone, quetiapine, and olanzapine, are being used in low doses to treat these neuropsychiatric symptoms. The few controlled studies comparing drugs against behavioral intervention in the treatment of agitation suggest mild efficacy with significant side effects related to sleep, gait, and cardiovascular complications. All of the antipsychotics carry a black-box warning and should be used with caution. However, careful, daily, nonpharmacologic behavior management is often not available, rendering medications necessary[7].

Antipsychotics

- Risperidone (Risperdal) has been studied in clinical trials and used in practice for psychotic symptoms or behavioral disturbances associated with dementia. The recommended initial dose is 0.25 mg daily, titrated in 0.25- to 0.5-mg increments up to 1 mg daily. If response is inadequate, further titration to 2 mg daily may be attempted if tolerated.
- Olanzapine (Zyprexa) has been shown to be beneficial in controlled trials. However, it has anticholinergic effects, raising concern about its utility for the treatment of AD.
- Quetiapine (Seroquel) has been evaluated only in open-label studies. It may be a reasonable alternative for patients who respond inadequately to or cannot tolerate risperidone or olanzapine.
- Aripiprazole (Abilify) and ziprasidone (Geodon) require further study before they can be recommended in this population[4].

Antidepressants

- Depression and dementia have many symptoms in common, and the diagnosis of

depression can be difficult, especially later in the course of AD.

- The selective serotonin reuptake inhibitors (SSRIs) citalopram and sertraline have been recommended as first-line agents because of demonstrated efficacy in placebo-controlled trials. Fluoxetine and paroxetine, as well as the serotonin/norepinephrine reuptake inhibitors venlafaxine and mirtazepine may be alternatives[4].

Miscellaneous Therapies

- Carbamazepine, mean dose 300 mg/day, and citalopram, 10 to 20 mg/day, have been shown to improve psychosis and behavioral disturbance in AD patients.
- Oxazepam and other benzodiazepines have been used to treat anxiety, agitation, and aggression, but they generally show inferior efficacy compared with antipsychotics.
- Buspirone has shown benefit in treating agitation and aggression in small studies with minimal adverse effects.
- Selegiline may decrease anxiety, depression, and agitation[4].

CONCLUSION

This present review article gives the overview of the Alzheimer's disease.

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