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Review Article

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A Review on Recent Approaches in Pharmacotherapy for management of Alzheimer's Disease

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ABSTRACT

It is a Neuro degenerative disease in which structural and functional ability of neuron is impaired. It is slowly starts with age progress. the alteration in the neuro transmitters levels in the brain. The neuro fibrillary tangles, neurotic plaques are responsible for the progression of disease. The alterations in the serotonergic systems raphae of the nucleus and cholinergic pathways in the brain is responsible for the loss of memory. The hyper-activation of glutamate levels in the brain is responsible for the progression of amnesia. The apolipoprotein E is responsible for the developing the disease. The oxidative stress, mitochondrial dysfunction affects the energy levels depletion in the brain affects the neuronal functions in the brain. It is caused by genetic involvement and environmental, life style factors plays a major role. The symptoms include aphasia, agnosia, apraxia, dementia, behavioural disturbances. It can diagnosed through MRI, CT scans, EEG examination were needed. The early diagnosis of the symptoms we can suppress the disease complications. The management of disease through medications and cognitive behavioural therapy to the patient.

Keywords: memory. MRI, CT scan, neuro-fibrillary tangles, neurotic plaques.

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1. Introduction

Oral controlled drug delivery systems represent the most Alzheimer's disease (AD), also known as Alzheimer International Journal of Medicine and Pharmaceutical Research

disease, or just Alzheimer's, accounts for 60% to 70% of cases of dementia. It is a chronic neurodegenerative disease

that usually starts slowly and gets worse over time. The most common early symptom is difficulty in remembering recent events. As the disease advances symptoms can include problems with language, disorientation, mood swings, loss of motivation, not managing self-care, and behavioural issues. Alzheimer's disease is caused by parts of the brain wasting away (atrophy), which damages the structure of the brain and how it works. It is not known exactly what causes this process to begin, although people with Alzheimer's disease have been found to have abnormal amounts of protein (amyloid plaques), fibres (tau tangles) and a chemical called acetylcholine in the brain [2].

Etiology

Most people with Alzheimer's disease have the late-onset form of the disease, in which symptoms become apparent in their mid-60s. The apolipoprotein E (APOE) gene is involved in late-onset Alzheimer's [1]. This gene has several forms. One of them, APOE 4, increases a person's risk of developing the disease person will definitely develop Alzheimer's disease, and people with no APOE 4 may also develop the disease.

Health, environmental and lifestyle factors

Heart disease, stroke, and high blood pressure, as well as metabolic conditions such as diabetes and obesity.

Age

Age is the single most significant factor in the development of Alzheimer's disease. The likelihood of developing the condition doubles every five years after you reach 65 years of age. However, it is not just older people who are at risk of developing Alzheimer's disease. Around 1 in 20 people with the condition are under 65. This is called early-onset Alzheimer's disease and it can affect people from around 40 Years of age.

- Family history
- Down's syndrome
- Head Injuries
- Cardiovascular disease
- Smoking
- Obesity
- Diabetes
- High blood pressure
- High cholesterol

Epidemiology:

The World Health Organization estimated that in 2005, 0.379% of people worldwide had dementia, and that the prevalence would increase to 0.441% in 2015 and to 0.556% in 2030. Other studies have reached similar conclusions. Another study estimated that in 2006, 0.40% of the world population (range 0.17–0.89%; absolute number 26.6 million, range 11.4–59.4 million) were afflicted by AD, and that the prevalence rate would triple and the absolute number would quadruple by 2050 [3].

Stages of Alzheimer's Disease

Early symptoms

- Forgetting about recent conversations or events
- forget the names of family members and places and objects
- repeating themselves regularly, such as asking the same question several times

- show poor judgment [4]
- become unwilling to try out new things or adapt to change
- There may also be some early signs of mood changes, such as increasing anxiety or agitation, or periods of confusion.

Middle stage symptoms

As Alzheimer's disease develops, memory problems will get worse and someone with the condition may find it increasingly difficult to remember the names of people they know and may struggle to recognise their family and friends [5].

Other symptoms may also develop, such as:

- Increasing confusion and disorientation – for example, not knowing where they are and walking off and getting lost
- obsessive, repetitive or impulsive behaviour
- delusions (believing things that are untrue)
- problems with speech or language (aphasia)
- disturbed sleep
- changes in mood, such as frequent mood swings, depression and feeling increasingly anxious, frustrated or agitated
- difficulty performing spatial tasks, such as judging distances
- problems with eyesight, such as poor vision or hallucinations
- They may need help eating, washing, getting dressed and using the toilet.

Later symptoms

- In the later stages of Alzheimer's disease, the symptoms become increasingly severe and distressing for the person with the condition, as well as their carers, friends and family[6].
- Hallucinations and delusions will often become worse and the person with the condition may start to become violent, demanding and suspicious of those around them.
- Difficulty eating and swallowing (dysphagia)
- Difficulty changing position or moving around without assistance considerable weight loss (although some people eat too much and put on weight). unintentional passing of urine (urinary incontinence) or stools (bowel incontinence)
- gradual loss of speech[7]
- short- and long-term memory

2. Pathophysiology

- It includes extracellular amyloid plaques, intracellular NFTs, synaptic deterioration, and neuronal death. Granulovascular degeneration in the hippocampus and amyloid deposition in blood vessels it causes damage to the tissues.
- The "amyloid cascade" hypothesis reveals that amyloid plaques interfere with synaptic activity and initiate a series of downstream effects that cause increasing inter- and intraneuronal dysfunction and, ultimately causes the cell death.

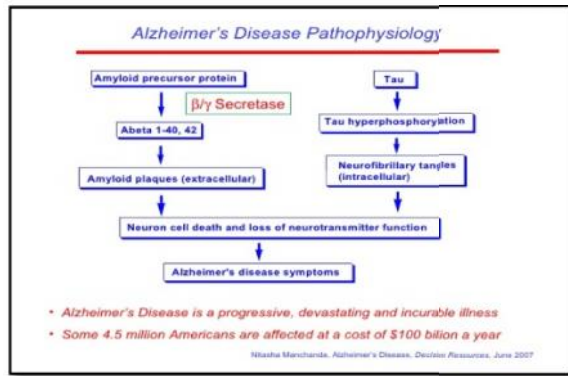


Figure1: Pathophysiology of Alzheimers Disease

Signs and Symptoms

- Language dysfunction (e.g., searching for words) may occur as an early feature in AD dementia, and can interfere considerably with communication as the patient's vocabulary and comprehension become impoverished.

- Spatial disorientation leads to lost objects and difficulty navigating. Acalculia may manifest as inability to maintain a checkbook or household accounts.
- Apraxia is an inability to carry out practiced motor tasks, such as brushing teeth or using a remote control. Although these classic AD symptoms are attributable to posterior cerebral dysfunction, AD dementia usually causes some frontal (executive) dysfunction even early in the disease course.
- Depression, sleep disturbance, and/or apathy may be present early. Psychotic symptoms, psychomotor agitation, verbal and physical aggression, and inappropriate sexual behavior tend to appear during later stages of dementia [9].

Diagnosis test:

Computerized tomography (CT) scan – where several X-rays of brain [9] magnetic resonance imaging (MRI) scan[10] where a strong magnetic field and radio waves are used to produce detailed images of the inside of brain [10].

Table 1: Signs and Symptoms Helpful in Differential Diagnosis of Dementia

	History	Examination	Testing
Alzheimer disease	Gradual, insidious onset Repeating questions, statements, and stories Decline in IADLs	Memory affected out of proportion to other cognitive functions	Failure of encoding on memory testing Disproportionate atrophy of mesial temporal lobes and/or parietal lobes
Cerebrovascular disease	Hemiparesis Sudden onset or stepwise progression Urinary incontinence Apathy or depression Vascular risk factors	Gait disturbance Asymmetry of sensation, movement, or reflexes	Diffuse white matter disease Large/strategic lacunar or cortical infarction
Lewy body disease	REM sleep behavior disorder Visual hallucinations Falls Unexplained loss of consciousness Marked fluctuations in attention and/or cognition	Extrapyramidal signs "rigidity, tremor, slowness Gait disturbance	Marked visuospatial dysfunction on neuropsychological testing Occipital hypometabolism on FDG-PET
Frontotemporal lobar degeneration	Changes in personality Disinhibition or euphoria Early inability to communicate meaningfully Ritualized behaviors Age 55-65 years	Expressive aphasia	Disproportionate atrophy of frontal lobes or one temporal lobe
Delirium	Sudden or subacute onset	Fluctuating level of alertness Overt confusion	Laboratory abnormalities

Table 2: FDA-Approved Medications for Symptoms of Alzheimer Disease

Drug name	Mechanism of Action Daily Dose Range and Formulations	Dose	Adverse effects
Donepezil	Acetyl cholinesterase Inhibitor	Dose: 2.5 mg-23 mg 5/10/23 mg daily tab 5/10 mg oral dissolvable daily tab 23 mg extended-release daily tab	Nausea, Loose stool Anorexia, Drowsiness Insomnia, Vivid dreams
Galantamine	Dose: 4 mg-24 mg 4/8/12 mg BID tab	Adverse effects Nausea, Loose stool, Anorexia, Drowsiness Insomnia, Vivid dreams	

Rivastigmine	5mg		
Drug	Mechanism	Dose	Adverse effects
Memantine	NMDA glutamate receptor antagonist	Dose: 5 mg-28 mg. Titration pack of 5 and 10 mg 5/10 mg BID tab 10 mg/5 mL oral	Nausea, Loose stool Anorexia, Drowsiness Insomnia, Vivid dreams

- These include donepezil, galantamine, rivastigmine and memantine.
- Whether these medications are used will depend on the severity of the condition.
- Donepezil, galantamine and rivastigmine (known as AChE inhibitors) can be prescribed for people with early to mid-stage Alzheimer's disease.
- Memantine may be prescribed for people with mid-stage disease who cannot take AChE inhibitors, or for those with late-stage disease.
- Glutamate is a useful excitatory neuro transmitter of the nervous system, although excessive amounts in the brain can lead to cell death through a process called excitotoxicity which consists of the overstimulation of glutamate receptors.
- Excitotoxicity occurs not only in Alzheimer's disease, but also in other neurological diseases such as Parkinson's disease and multiple sclerosis.
- Memantine is a noncompetitive NMDA receptor antagonist first used as an anti-influenza agent. It acts on the glutamatergic system by blocking NMDA receptors and inhibiting their overstimulation by glutamate.
- Memantine has been shown to have a small benefit in the treatment of Alzheimer's disease. Reported adverse events with memantine are infrequent and including hallucinations, confusion, dizziness.
- Psychosocial interventions are used as an adjunct to pharmaceutical treatment and can be classified within behaviour-, emotion-, cognition- or stimulation-oriented approaches. Research on efficacy is unavailable and rarely specific to AD, focusing instead on dementia in general [12]

Side effects

- Donepezil, galantamine and rivastigmine can cause side effects such as:
- feeling and being sick
- diarrhoea
- headache
- fatigue (extreme tiredness)
- Insomnia (difficulty getting to sleep or staying asleep)
- Muscle cramps [13]

Common side effects of meantime

Include dizziness, headaches, tiredness, constipation, problems with balance, and shortness of breath.

Supportive measures and treatments

- In addition to medication, treatment for Alzheimer's disease involves a wide range of other measures and treatments to help people with dementia live as independently as possible.

- an occupational therapist he can identify the problem areas in patients everyday life, such as dressing yourself, and help you work out practical solutions
- psychological treatments, such as cognitive stimulation, may be offered to help improve the patient memory, problem-solving skills and language ability
- Medication, other psychological therapies, such as cognitive behavioural therapy, and relaxation therapies may also be offered to help reduce any depression, anxiety, agitation, hallucinations, delusions and challenging behaviour that often feature with Alzheimer's disease [14].

Practical Tips for Management of People with Alzheimer's

- keep a diary and write down things that you want to remember
- pin a weekly timetable to the wall
- put your keys in an obvious place, such as in a large bowl in your living room
- have a daily newspaper delivered to remind you of the day and date
- put labels on cupboards and drawers
- keep useful telephone numbers by the phone
- Write yourself reminders – for example, put a note on the front door to remind you to take your keys with you if you go out. programme people's names and numbers into your telephone
- set the alarm on your watch to act as a reminder
- install safety devices such as gas detectors and smoke alarms throughout your home

Palliative care: People with dementia often live for many years after their diagnosis. However, as it is a progressive condition, it's wise to make plans well in advance of the end-of-life phase.

End-of-life care, or palliative care, provides support for people with an incurable illness so they are able to live as well as possible until their death. It also involves support for family members. Care can be provided at home, a hospice, a care home or hospital [15].

Preventing Alzheimer's disease

However, there are some steps you can take that may help to delay the onset of dementia.

Reducing your risk of cardiovascular disease

- Cardiovascular disease (disease of the heart or blood vessels) has been linked with an increased risk of Alzheimer's disease and vascular dementia.
- stopping smoking if you smoke
- avoiding drinking large amounts of alcohol
- eating a healthy balanced diet, including at least five portions of fruit and vegetables every day

- exercising for at least 150 minutes (2 hours and 30 minutes) every week by doing moderate-intensity aerobic activity (such as cycling or fast walking) – this will improve both your physical and mental health

Preventing dementia

It may possible to reduce your risk of Alzheimer's disease and other types of dementia by:

- reading
- writing for pleasure
- learning foreign languages
- playing musical instruments
- taking part in adult education courses
- playing tennis
- playing golf
- swimming
- group sports, such as bowling
- walking

3. Techniques

Neuropsychological screening test scan help in the diagnosis of AD. In the tests, people are instructed to copy drawings similar to the one shown in the picture, remember words, read, and subtract serial numbers. Neuropsychological tests such as the mini-mental state examination (MMSE) are widely used to evaluate the cognitive impairments needed for diagnosis. More comprehensive test arrays are necessary for high reliability of results, particularly in the earliest stages of the disease.

Early diagnosis

- Emphasis in Alzheimer's research has been placed on diagnosing the condition before symptoms begin. A number of biochemical tests have been developed to allow for early detection.
- One such test involves the analysis of cerebrospinal fluid for beta-amyloid or tau proteins, both total tau protein and phosphorylated tau 181 P protein concentrations.

Lifestyle: People who engage in intellectual activities such as reading, playing board games, completing crossword puzzles, playing musical instruments or regular social interaction show a reduced risk for Alzheimer's disease.

Diet

Those who eat a diet high in saturated fats and simple carbohydrates (mono- and disaccharide) have a higher risk. The mediterranean diet's beneficial cardiovascular effect has been proposed as the mechanism of action.

4. Conclusion

AD causes of dementia and its prevalence is increasing in the worldwide. The early detection and approaching the Neuropsychological, imaging, and spinal fluid tests can establish the diagnosis with highly accuracy of the disease medication treatments that slow the disease process and providing the cognitive and behavioral therapy[15] to the Alzheimers disease patients we can reduce the dementia. It can significantly improve the lives of patients and their caregivers. Although advanced age and genetics are the International Journal of Medicine and Pharmaceutical Research

predominant risk factors, several preventable risk factors also contribute to the likelihood of developing AD dementia. The better health related compliance towards patients though family and social support is needed. Providing high flavonoids such as cocoa, red wine, and tea may decrease the risk of AD[15].

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