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## Alzheimer's disease: A Review

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### Abstract

Alzheimer's dementia (AD) is increasingly being recognized as one of the most important medical and social problems in older people in industrialized and nonindustrialized nations. To date, only symptomatic treatments exist for this disease, all trying to counterbalance the neurotransmitter disturbance. Three cholinesterase inhibitors (CIs) are currently available and have been approved for the treatment of mild to moderate AD. A further therapeutic option available for moderate to severe AD is memantine, an N-methylD-aspartate receptor noncompetitive antagonist. Treatments capable of stopping or at least effectively modifying the course of AD, referred to as 'disease-modifying' drugs, are still under extensive research.

**Keywords:** Alzheimers, disorders

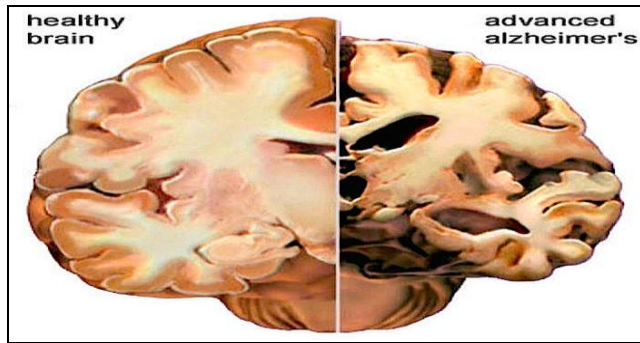
### Introduction

Alzheimer disease (AD) is characterized by a progressive decline in cognitive function. Alzheimer disease is substantially increased among people aged 65 years or more, with a progressive decline in memory, thinking, language and learning capacity. Alzheimer disease should be differentiated from normal age-related decline in cognitive function, which is more gradual and associated with less disability [1]. Disease often starts with mild symptoms and ends with severe brain damage. People with dementia lose their abilities at different rates. The pathophysiology of Alzheimer disease is related to the injury and death of neurons, initiating in the hippocampus brain region that is involved with memory and learning, then atrophy affects the entire brain. Amyloid beta, also written  $A\beta$ , is a short peptide that is an abnormal proteolytic byproduct of the transmembrane protein amyloid precursor protein (APP), whose function is unclear but thought to be involved in neuronal development. Amyloid beta monomers are soluble and contain short regions of beta sheet at sufficiently high concentration, they undergo a dramatic conformational change to form a beta sheet-rich tertiary structure that aggregates to form amyloid fibrils [2].

These fibrils deposit outside neurons in dense formations known as senile plaques or neuritic plaques, in less dense aggregates as diffuse plaques, and sometimes in the walls of small blood vessels in the brain in a process called amyloid angiopathy or congophilic angiopathie. In Alzheimer disease abnormal aggregation of the tau protein, a microtubule-associated protein expressed in neurons is also observed. Tau protein acts to stabilize microtubules in the cell cytoskeleton. Like most microtubule associated proteins, tau is normally regulated by phosphorylation [3]. In Alzheimer disease patients, hyper phosphorylated tau P-tau accumulates as paired helical filaments that in turn aggregate into masses inside nerve cell bodies known as neurofibrillary tangles and as dystrophic neurites associated with amyloid plaques., tau, and P-tau, which are not static. Current evidence indicates changes in CSF levels of A over the course of the disease. The mechanism that drives the formation of senile plaques and neurofibrillary tangles is still unknown at present. Senile plaques and neurofibrillary tangles prompt the injury and death of neurons, and as a consequence memory loss and behavioural symptomatic changes. As well, current hypotheses include circulating  $\alpha$  oligomers as potentially neurotoxic (not just the plaques). Abnormal release of neurotransmitters such as glutamate contributes to neuronal death and inflammation. Neuroinflammation is also involved in the complex cascade leading to Alzheimer disease pathology and symptoms. Considerable pathological and clinical evidence documents immunological changes associated with Alzheimer disease, including increased pro inflammatory cytokine concentrations in the blood and cerebrospinal fluid [4]. Whether these changes may be a cause or consequence of Alzheimer disease remains to be fully understood, but inflammation within the brain, including increased reactivity of the resident microglia towards amyloid deposits, has been implicated in the pathogenesis and progression of Alzheimer disease [5].

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**Fig 1:** Brain changes in Normal and Alzheimer

The German psychiatrist and neuropathologist Dr. Alois Alzheimer is credited with describing for the first time a dementing condition which later became known as Alzheimer disease. In his landmark 1906 conference lecture and a subsequent 1907 article, Alzheimer described the case of Auguste D, a 51 year old woman with a ‘peculiar disease of the cerebral cortex,’ who had presented with progressive memory and language impairment, disorientation, behavioral symptoms (hallucinations, delusions, paranoia), and psychosocial impairment [6]. Remarkably, many of the clinical observations and pathological findings that Alzheimer described more than a century ago continue to remain central to our understanding of Alzheimer disease today [7].

### Epidemiology

The aging of populations has become a worldwide phenomenon. In 1990, nations had more than two million elderly citizens aged 65 years and older, and the projections indicate that an additional 34 countries will join the list by 2030. In 2000, the number of old people (65+ years) in the world was estimated to be 420 million and it was projected to be nearly one billion by 2030, with the proportion of old people increasing from 7 to 12%. The largest increase in absolute numbers of old people will occur in developing countries; it will almost triple from 249 million in 2000 to an estimated 690 million in 2030. The developing regions' sharing the worldwide aging population will increase from 59 to 71%. Developed countries, which have already shown a dramatic increase in people over 65 years of age will experience a progressive aging of the elderly population. Underlying global population aging is a process known as the “demographic transition” in which mortality and then fertility decline. Decreasing fertility and lengthening life expectancy have together reshaped the age structure of the population in most regions of the planet by shifting relative weight from younger to older groups [8].

Alzheimer's disease was first identified more than 100 years ago, but research into its symptoms, causes, risk factors and treatment has gained momentum only in the last 30 years. Although research has revealed a great deal about Alzheimer's, the precise physiologic changes that trigger the development of Alzheimer's disease largely remain unknown. The only exceptions are certain rare, inherited forms of the disease caused by known genetic mutations. Alzheimer's disease affects people in different ways, but the most common symptom pattern begins with gradually worsening ability to remember new information. This occurs because disruption of brain cell function usually begins in brain regions involved in forming new memories

[9]. As damage spreads, individuals experience other difficulties. The following are warning signs of Alzheimer's disease: memory loss that disrupts daily life; challenges in planning or solving problems; difficulty completing familiar tasks at home, at work or at leisure; confusion with time or place; trouble understanding visual images and spatial relationships; new problems with words in speaking or writing; misplacing things and losing the ability to retrace steps; decreased or poor judgment; withdrawal from work or social activities; and changes in mood and personality [10].

As the disease progresses, the individual's cognitive and functional abilities decline. In advanced Alzheimer's disease, people need help with basic activities of daily living, such as bathing, dressing, eating and using the bathroom. Those in the final stages of the disease lose their ability to communicate, fail to recognize loved ones and become bed bound and reliant on around the clock care. When an individual has difficulty moving because of Alzheimer's disease, they are more vulnerable to infections, including pneumonia

### Cognitive Enhancement

Several studies have specifically examined the potential effects of cognitive engagement on the risk of Alzheimer disease. The studies used self-report of the frequency of involvement in specific activities that potentially have a cognitive component. In the Three City cohort study, analyses were carried out on 5698 dementia free participants aged 65 and over. Stimulating leisure activities were significantly associated with a reduced risk of Alzheimer disease (hazard ratio (HR) ¼ 0.39). This finding was independent of other proxies of cognitive reserve and remained significant after adjusting for vascular risk factors, depressive symptoms and physical functioning [11].

### Pathology of Alzheimer disease

Neuropathology of Alzheimer's disease is a progressive neurodegenerative brain disorder that causes a significant disruption of normal brain structure and function. At the cellular level, Alzheimer disease is characterized by a progressive loss of cortical neurons, especially pyramidal cells that mediate higher cognitive functions. Substantial evidence also suggests that Alzheimer disease causes synaptic dysfunction early in the disease process, disrupting communication within neural circuits important for memory and other cognitive functions. Alzheimer disease related degeneration begins in the medial temporal lobe, specifically in the entorhinal cortex and hippocampus. Damage to these brain structures results in memory and learning deficits that are classically observed with early clinical manifestations of Alzheimer disease. The degeneration then spreads throughout the temporal association cortex and to parietal areas. As the disease progresses, degeneration can be seen in the frontal cortex and eventually throughout most of the remaining neocortex. Of note is the fact that Alzheimer disease causes pronounced damage to multiple components of the limbic system, including the hippocampal formation and the major fiber tracts that connect it to the cerebral cortex (fornix and cingulum), amygdala, cingulate gyrus, and thalamus. This widespread pattern of neurodegeneration, affecting both limbic and neocortical regions, correlates closely with the array of cognitive deficits and behavioral changes that Alzheimer disease patients exhibit. In addition to cognitive

impairment across multiple domains (memory, language, reasoning, executive, and visuospatial function), patients with Alzheimer disease show an impaired ability to perform activities of daily living and often experience psychiatric, emotional, and personality disturbances. It has been theorized that the neuronal damage seen in Alzheimer disease is related to the deposition of abnormal proteins both within and outside of neurons. These are the hallmark pathological lesions of Alzheimer disease known as 'plaques and tangles.' The abnormal proteins are deposited in the cerebral cortex following a stereotypical pattern of spread along neural pathways that mediate memory and other cognitive functions. 'Senile plaques' are extracellular accumulations of amyloid protein and consist of insoluble amyloid beta protein (Ab). Normally, cells throughout life release soluble Ab after cleavage of the APP a cell surface receptor.



**Fig 2:** Alzheimer disease patient expressions

Alzheimer disease involves abnormal cleavage of APP that results in the precipitation of Ab into dense beta sheets and formation of senile plaques. It is believed that microglia and astrocytes then mount an inflammatory response to clear the amyloid aggregates, and this inflammation likely causes destruction of adjacent neurons and their neuritis. 'Neurofibrillary tangles' (NFT) are intracellular aggregates of abnormally hyper phosphorylated protein tau, which in normal form serves as a microtubule stabilizing protein and plays a role in intracellular (axonal and vesicular) transport. It is possible that NFT interfere with normal axonal transport of components necessary for proper neuronal function and survival (e.g., synaptic vesicles with neurotransmitters, neurotrophic factors, and mitochondria), eventually causing neurons to die. Substantial evidence supports the idea that amyloid formation and deposition in the cerebral cortex is one of the earliest pathological processes in Alzheimer disease, preceding the clinical onset of the disease by 1020 years. Despite this, the temporal sequence of events in the deposition of amyloid plaques and formation of NFT during development of Alzheimer disease remains open to debate. In fact, a recent study suggests that the initial formation of NFT may occur in the brainstem rather than the medial temporal lobe and may precede the appearance of the first amyloid plaques in the neocortex.

### Diagnosis

The standard for the diagnosis of medical council of India, as well as for dementia, is a structured history focused on cognitive and functional changes and corroboration from a reliable informant. A detailed medical, psychiatric, and substance use history should be done to assess for other etiologies such as medication side effects, depression, alcohol or substance dependence, and delirium. A physical examination, including a full neurological examination, should also be performed, looking for acute and chronic

illness and focalities. Geriatric depression can also present with memory complaints; therefore, history taking should also include an evaluation for anhedonia, sleep and/or appetite disturbance, feelings of worthlessness and/or hopelessness, and suicidal ideation. Normalization of these symptoms as "part of getting older," masking them as "being anxious about seeing the doctor," or even denying them despite directly querying patients, may result in clinicians not detecting the presence of depression.

The Geriatric Depression Scale (GDS), an office screening tool, should also be administered and may be helpful to elicit depressive symptoms. A score >10 on the 30 item version suggests a mild depression and should trigger further history taking. The diagnosis of depression should not exclude the possibility of medical council of India, as depression may be the presenting symptom of a primary memory disorder.

There are no laboratory tests that definitely diagnose MCI; the purpose is to exclude other etiologies for memory loss, particularly reversible or treatable causes. Standard laboratory tests include vitamin B12, folic acid, rapid plasma reagin (syphilis), and thyroid stimulating hormone. Screening for risk factors and with as needed testing should also be done for substance use, human immunodeficiency virus (HIV), Lyme disease, and heavy metal exposure. Lumbar puncture is not generally necessary unless there is a suspicion of other treatable conditions, such as HIV, syphilis, or normal pressure hydrocephalus. Neuroimaging such as head computed tomography or, preferably, magnetic resonance imaging, can also be obtained. The main purpose is to exclude conditions such as hydrocephalus, stroke, severe white matter disease, and tumor. Unless a patient presents with atypical features such as pronounced language or behavioral disturbances, focal neurologic symptoms or signs, or a history of cancer with a known predilection for the central nervous system, these scans are usually unremarkable, showing at most age related atrophy or nonspecific white matter changes. Electroencephalography should be considered in atypical cases, such as fluctuating cognitive status or automatisms that may be consistent with partial complex seizures; or rapid onset and progression of memory loss over the course of weeks to months, which may suggest a rapidly neurodegenerative disorder such as Creutzfeldt Jakob disease.

Neuropsychological testing can be helpful in distinguishing depression from a primary memory disorder, providing a baseline, or obtaining objective evidence for cognitive decline. Of note, neuropsychological tests can help contextualize and normalize a patient's cognitive functioning as it relates to his or her age and education. Detailed testing may also be useful in patients who have extremes of education or comorbidities in which the overall pattern of cognitive performance can be examined to confirm a diagnosis of MCI or various subtypes of dementia, or confounding psychiatric symptoms such as depression. This comprehensive cognitive testing is performed by a trained neuropsychologist, and usually covers a number of areas including verbal memory [12].

### Homoeopathy treatment

With the help of homoeopathy medicines, can be prevent the progressive of disease. But homoeopathy medicines can be prescribed on base of totality of symptoms. Homoeopathy can be used as an adjunctive or stand-alone

therapy to treat or improve the symptoms of memory loss, poor concentration and leaning difficulties in both adults and children.

### **Ambra grisea**

People who need Ambra grisea are shy, timid, and easily embarrassed. They blush easily, dread the company of unfamiliar people, are anxious about what people think of them, and want to be left alone. While forgetful and dreamy, they may also jump from one subject to another when talking or ask questions without waiting for an answer. They find it difficult to understand what has just been read and have trouble with calculations - even simple mathematics. Sometimes they will sit for hours or days crying from sadness. Prematurely aging and senility often indicates the need for Ambra grisea.

### **Anacardium orientale**

Sudden loss of memory, especially under stress. Lack of confidence. Unkindness or cruelty. Those needing Anacardium orientale have sudden loss of memory as though something is blocking the thought. They become hesitant, suddenly forget the names of people and things, and can even feel as if they are going insane. It's a useful remedy for the sudden forgetfulness of anxious and under confident students before an exam but also treats forms of senile dementia. Anacardium types are often confused about their identity, feeling and behaving as if they have 'an angel on one shoulder and a devil on the other.' They can be cruel, irritable and hard hearted with a tendency to swear but also struggle with lack confidence or feeling helpless, hopeless and needy.

### **Helleborus Niger**

Apathy, dullness, slowness and blankness of mind. Poor concentration. Helleborus suits the symptoms of dullness, haziness and blankness of mind. It is often needed for poor memory following a stroke. The person finds it hard to concentrate and has a weakness of memory for what was just read, said or done. Often, things are not heard or seen properly. They are apathetic, concentration is difficult and they answer slowly <sup>[13]</sup>.

### **Lycopodium clavatum**

Gradual memory loss and confusion. Dyslexia. Words and syllables misused or misplaced. Lycopodium suits those who once may have enjoyed intellectual activities but, because of their gradually deteriorating memory, now feel confused. It also one of the remedies that suits children with dyslexia, learning difficulties and behavioural problems. Children and adults misspell words or misplace words or syllables while talking. They are bossy and rude at home, irritable in the morning on waking, but polite and friendly with strangers. Physical complaints start on the right side of the body and progress to the left side.

### **Nux moschata**

Spaced out feeling. Sudden loss of thoughts. Absent minded and dreamy. Nux moschata is indicated for those who feel vague or spaced-out - as if intoxicated. They are absent minded, forgetful of what they were about to do, and use the wrong words, especially during headaches. Their mind is dull and they feel confused or bewildered. Thoughts suddenly vanish while talking, reading or writing and there

may be complete loss of memory about the past. Sleepiness or clairvoyant states are often experienced <sup>[14]</sup>.

### **Conclusion**

Our understanding of Alzheimer disease pathogenesis has grown substantially over the past two decades. However, with the large numbers of individuals reaching the age of highest risk, some would say that we have a long way to go toward preventing or limiting the full impact of the disease. Current treatments are palliative at best and newer therapies remain unproven. Knowing who is a risk and why will make prevention and management easier in the future.

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