AN OVERVIEW OF TREATMENT FOR ALZHEIMER’S DISEASE

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ABSTRACT
Alzheimer's is a type of dementia that causes problems with memory, thinking and behavior. Symptoms usually develop slowly and get worse over time, becoming severe enough to interfere with daily tasks. Alzheimer's is the most common form of dementia, a general term for memory loss and other cognitive abilities serious enough to interfere with daily life. Alzheimer's disease accounts for 60 to 80 percent of dementia cases.

KEYWORDS: Rivastigmine, Donepezil, Glantamine, Memantine, Alternative treatments, herbal drugs.

INTRODUCTION
Alzheimer's disease (AD), also referred to simply as Alzheimer's, is a chronic neurodegenerative disease that usually starts slowly and worsens over time. It is the cause of 60% to 70% of cases of dementia. The most common early symptom is difficulty in remembering recent events (short-term memory loss). As the disease advances, symptoms can include problems with language, disorientation (including easily getting lost), mood swings, loss of motivation, not managing self care, and behavioural issues. As a person's condition declines, they often withdraw from family and society. Gradually, bodily functions are lost, ultimately leading to death. Although the speed of progression can vary, the average life anticipation following diagnosis is three to nine years.

The cause of Alzheimer's disease is poorly understood. About 70% of the risk is believed to be genetic with many genes usually involved. Other risk factors include a history of head injuries, depression, or hypertension. The disease process is associated with plaques and tangles in the brain. A probable diagnosis is based on the history of the illness and cognitive testing with medical imaging and blood tests to rule out other possible causes. Initial symptoms are often mistaken for normal ageing. Examination of brain tissue is needed for a definite diagnosis. Mental and physical exercise, and avoiding obesity may decrease the risk of AD; however, evidence to support these recommendations is not strong. There are no medications or supplements that decrease risk.

No treatments stop or reverse its progression, though some may temporarily improve symptoms. Affected people increasingly rely on others for assistance, often placing a burden on the caregiver; the pressures can include social, psychological, physical, and economic elements. Exercise programmes may be beneficial with respect to activities of daily living and can potentially improve outcomes. Treatment of behavioural problems or psychosis due to dementia with antipsychotics is common, but not usually recommended, as there is little benefit with an increased risk of early death.

In 2015, there were approximately 29.8 million people worldwide with AD. It most often begins in people over 65 years of age, although 4% to 5% of cases are early-onset Alzheimer's which begin before this. It affects about 6% of people 65 years and older. In 2015, dementia resulted in about 1.9 million deaths. It was first described by, and later named after, German psychiatrist and pathologist Alois Alzheimer in 1906. In developed countries, AD is one of the most financially costly diseases.

SIGN AND SYMPTOMS
Early
- Memory problems, particularly remembering recent events.
- Increasing confusion.
- Reduced concentration.
- Personality or behaviour changes.
- Apathy and withdrawal or depression.
- Loss of ability to do everyday tasks.

**Moderate**
- Unable to perform most common activities of daily life.[20]
- Speech difficulties.
- Reading and writing skills are also progressively lost.[20][21]
- Behavioural and neuropsychiatric changes[20]

**Advanced**
- The patient is completely dependent upon caregivers
- complete loss of speech.
- apathy and exhaustion.[30]

**MECHANISM**

**Tau hypothesis**
The hypothesis that tau is the primary causative factor has long been grounded in the observation that deposition of amyloid plaques.[24] A mechanism for neurotoxicity has been proposed based on the loss of microtubule-stabilizing tau protein that leads to the degradation of the cytoskeleton.[25] However, consensus has not been reached on whether tau hyperphosphorylation precedes or is caused by the formation of the abnormal helical filament aggregates.[27] Support for the tau hypothesis also derives from the existence of other diseases known as tauopathies in which the same protein is identifiably misfolded.[26] However, a majority of researchers support the alternative hypothesis that amyloid is the primary causative agent.

**Amyloid hypothesis**
In 1991, the amyloid hypothesis postulated that extracellular amyloid beta (Aβ) deposits are the fundamental cause of the disease.[28][29] Support for this postulate comes from the location of the gene for the amyloid precursor protein (APP) on chromosome 21, together with the fact that people with trisomy 21 (Down Syndrome) who have an extra gene copy almost universally exhibit at least the earliest symptoms of AD by 40 years of age.[30][31] Also, a specific isoform of apolipoprotein, APOE4, is a major genetic risk factor for AD. While apolipoproteins enhance the breakdown of beta amyloid, some isoforms are not very effective at this task (such as APOE4), leading to excess amyloid buildup in the brain.[32] These toxic oligomers, also referred to as amyloid-derived diffusible ligands (ADDLs), bind to a surface receptor on neurons and change the structure of the synapse, thereby disrupting neuronal communication.[33] One receptor for Aβ oligomers may be the prion protein, the same protein that has been linked to mad cow disease and the related human condition, Creutzfeldt-Jakob disease, thus potentially linking the underlying mechanism of these
neurodegenerative disorders with that of Alzheimer’s disease.\(^{84}\)

In 2009, this theory was updated, suggesting that a close relative of the beta-amyloid protein, and not necessarily the beta-amyloid itself, may be a major culprit in the disease. The theory holds that an amyloid-related mechanism that prunes neuronal connections in the brain in the fast-growth phase of early life may be triggered by ageing-related processes in later life to cause the neuronal withering of Alzheimer’s disease.\(^{35}\) N-APP, a fragment of APP from the peptide’s N-terminus, is adjacent to beta-amyloid and is cleaved from APP by one of the same enzymes. N-APP triggers the self-destruct pathway by binding to a neuronal receptor called death receptor 6 (DR6, also known as TNFRSF21).\(^{35}\) DR6 is highly expressed in the human brain regions most affected by Alzheimer’s, so it is possible that the N-APP/DR6 pathway might be hijacked in the ageing brain to cause damage.

**ALREADY USED DRUGS**

1. **Acetylcholine esterase Inhibitors**
   This drugs are inhibit the AchE enzyme & increase the concentration of Ach in brain.

   There is evidence for the efficacy of these medications in mild to moderate Alzheimer's disease\(^{17,30}\) and some evidence for their use in the advanced stage.\(^{36}\) The use of these drugs in mild cognitive impairment has not shown any effect in a delay of the onset of AD.\(^{10}\) The most common side effects are nausea and vomiting, both of which are linked to cholinergic excess. These side effects arise in approximately 10–20% of users, are mild to moderate in severity, and can be managed by slowly adjusting medication doses.\(^{10}\) Less common secondary effects include muscle cramps, decreased heart rate (bradycardia), decreased appetite and weight, and increased gastric acid production.\(^{10}\)

   **AchE are commonly prescribe**
   - Donepezil (Aricept) is approved to treat all stages of Alzheimer's.
   - Rivastigmine (Exelon) is approved to treat mild to moderate Alzheimer's.
   - Galantamine (Razadyne) is approved to treat mild to moderate Alzheimer's.

2. **NMDA antagonist**
   Memantine, the fifth Alzheimer’s drug, is an NMDA (N-methyl-D-aspartate) receptor antagonist, which works by regulating the activity of glutamate, an important neurotransmitter in the brain involved in learning and memory. Attachment of glutamate to cell surface “docking sites” called NMDA receptors permits calcium to enter the cell. This process is important for cell signaling, as well as learning and memory. In Alzheimer’s disease, however, excess glutamate can be released from damaged cells, leading to chronic overexposure to calcium, which can speed up cell damage. Memantine helps prevent this destructive chain of events by partially blocking the NMDA receptors.

**ALTERNATIVE TREATMENTS**

- **Caprylic acid (clinically tested as Ketasyn [AC-1202], marketed as a “medical food” called Axona®) and coconut oil.**
  Caprylic acid is the active ingredient of Axona, which is marketed as a “medical food.” Caprylic acid is a medium-chain triglyceride (fat) produced by processing coconut oil or palm kernel oil. The body breaks down caprylic acid into substances called “ketone bodies.” The theory behind Axona is that the ketone bodies derived from caprylic acid may provide an alternative energy source for brain cells that have lost their ability to use glucose (sugar) as a result of Alzheimer’s.

Ketasyn was tested in a Phase II clinical study with mild to moderate Alzheimer’s.

- **Coenzyme Q10**
  Coenzyme Q10, or ubiquinone, is an antioxidant that occurs naturally in the body and is needed for normal cell reactions. This compound has not been studied for its effectiveness in treating Alzheimer’s. A synthetic version of this compound, called idebenone, was tested for Alzheimer’s disease but did not show any benefit. Little is known about what dosage of coenzyme Q10 is considered safe, and there could be harmful effects if too much is taken.

- **Ginkgo biloba**
  Ginkgo biloba is a plant extract containing several compounds that may have positive effects on cells within the brain and the body. Ginkgo biloba is thought to have both antioxidant and anti-inflammatory properties, to protect cell membranes and to regulate neurotransmitter function.

  The Ginkgo Evaluation and Memory (GEM) Study enrolled 3,000 individuals age 75 or older who had no signs of dementia or had mild cognitive impairment (MCI). Participants were randomly assigned to receive twice daily doses of either a placebo or 120 milligrams of ginkgo biloba extract. They were followed up every six months for six years.

- **Omega-3 fatty acids**
  Omega-3s are a type of polyunsaturated fatty acid (PUFA). Research has linked certain types of omega-3s to a reduced risk of heart disease and stroke. Research has also linked high intake of omega-3s to a possible reduction in risk of dementia or cognitive decline.

- **Tramiprosate (clinically tested as Alzhemed, marketed as a "medical food" called ViviMind™)**
  Tramiprosate is a modified form of taurine, an amino acid found naturally in seaweed. Amino acids are the chemical building blocks of proteins. Tramiprosate was
tested in a large Phase 3 clinical study as a possible Alzheimer's treatment.\cite{41}

HERBS
1. Ashwagandha (Withania somnifera)
500 mg/day was more effective.\cite{42} Withanamides A and C bind to the active beta-amyloid (Aβ 25-35) and prevent fibril formation.\cite{43,44} It is used to increase memory and learning.\cite{45} Aqueous extracts of this herb have been found to increase cholinergic activity, including increases in the acetylcholine content and cholineacetyl transferase activity in rats and this might partly explain the cognition-enhancing and memory-improving effects.\cite{46,47}

2. Turmeric (Curcuma longa)
Oral supplementation with up to 4 g/day of curcumin was safe.\cite{48,49,50} Curcumin reduced the amount of plaque deposition.\cite{47,48,50} It reduced oxidative damage and reversed the amyloid pathology in an AD.\cite{49,50} Direct injection of curcumin into the brains reduced the plaque levels.\cite{50}

3. Gotu kola (Centella asiatica)
Asiaticoside derivatives, including asiatic acid and asiaticoside, were shown to reduce hydrogen peroxide-induced cell death, decrease free radical concentrations, and inhibit beta-amyloid cell death in vitro.\cite{52}

4. Jyotishmati (Celastrus paniculatus)
Jyotishmati extracts also protected neuronal cells against glutamate-induced toxicity by modulating glutamate receptor function. In addition, the CP extracts protected neuronal cells by virtue of their free radical scavenging properties, reducing lipid peroxidation, and also by their ability to induce the antioxidant enzyme catalase.\cite{68,72-75}

In addition, aqueous extracts of CP seed have dose-dependent cholinergic activity, thereby improving memory performance.

5. Jatamansi (Nardostachys jatamansi)
This plant may prove to be useful in restoring memory in older individuals as well as in patients with age-associated dementia.

6. Guggulu
Guggulipid as a potential anti-dementia drug. It also inhibit the beta-amyloid-forming amyloidogenic pathway.\cite{53}

CONCLUSION
In the future, it is anticipated that advances in the fields of molecular biology and genetic engineering will assist in the management of Alzheimer's disease. These new treatments and therapies increases the quality of life of patients.

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