



THE BASICS OF PATHOGENESIS, TREATMENT, AND RECENT ADVANCES OF ALZHEIMER'S DISEASE

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ABSTRACT:

Alzheimer's disease is characterized by loss of memory associated with other severe cognitive impairment. Alzheimer primarily affects the neurons known as neurofibrils and causes the amyloid protein aggregation to further causes plaque deposition, neurovascular abnormalities, and oxidative stress cause severe cognitive impairment. In Alzheimer's, the major cause is seen to be dementia and cognitive impairments, in which the person suffers from various CNS defects. Monoclonal antibodies can be utilized as a recent therapeutic approach, and if the problem persists, the patient should be shifted to other drug therapy. The drugs belong to natural sources that are easily available for everyone and affordable as well as meditation shows proper disease management.

As per the study, medications used for the management of Alzheimer's disease can precipitate severe adverse effects as well as toxicities. Recent advances discussed within our topics are used to treat such condition which harms the patient body instead of getting benefits. A study on herbal drugs and physiotherapy for the management of Alzheimer's disease shows improvement without any toxicities due to their targeted effect and proper administration. The study suggests the need to perform further clinical trials to use recent therapies for the management of Alzheimer's and to reduce the adverse effects associated with various drugs.

KEYWORDS:

Alzheimer's disease, Dementia, Cognitive impairment, Amyloid, oxidative stress, toxic effects.

INTRODUCTION:

- **Definition:**

A progressive disease characterized by loss of memory associated with other severe cognitive impairment. Brain cell connections and the cells themselves degenerate and die, eventually destroying memory and other important mental functions ^[5,20]

Alzheimer's is a disease that affects people's memory. At first, the patient has a hard time remembering just events that happened, In people easily seen that they recall things that happened years ago ^[1]

Generally, in people symptoms are seen as follow:

1. Trouble focusing
2. A hard time doing ordinary activities
3. Feeling confused or frustrated, especially at night
4. Dramatic mood swings - anger, anxiety, and depression
5. Disorientation and getting lost easily
6. Physical problems, such as an odd walk or poor coordination
7. Trouble communicating^[20]

People with Alzheimer's disease forget their loved ones also and little things like how to dress, feed themselves, and use the toilet. The disease affects brain tissue break down over time. It generally is seen in people over age 65. A person can stay with Alzheimer's disease for just a few years. More often, however, people live with it for about 9 years for last. In Women disease occur more than man^[1]

- **Etiology:**

- Etiological factors for Alzheimer's disease production are as follow:

1. Genetic factor: Inherited by parents to offspring.
2. Age.: More than 65 commonly occur
3. Gender.: Most seen in women
4. History of head injury: Injury of the head can affect brain area and memory power also.
5. Exposure to the toxins: Toxins circulated through the body result in the cellular damage brain area.
6. Heavy metal poisoning.
7. Positive family history: As the disease is inherited from parents to offspring the history can say the status of precipitation of disease in the next generation.
8. Trisomy.
9. Protein deficiency.
10. Mitochondrial dysfunction.
11. Protein degradation^[2,10,11]

- **Clinical features:**

Patient who suffers from Alzheimer's undergoes dementia i.e. cognitive impairment.

- **Sign and symptom's :**

1. Forget recent events and conversation
2. Severe memory impairment^[5,18]
3. Mood swings
4. Lack of concentration.

5. Driving impairment
6. Hypothyroidism.
7. Weight loss.
8. Stress
9. Depression
10. Anxiety
11. Sleeplessness.
12. Restlessness ^[5,14]

Due to cognitive impairment, the patient undergoes anxiety as well as stress which results due to enzymatic abnormality and lack of electrical impulse discharge from brain cells ^[5,14]. Hypothyroidism occurs Due to a lack of supply of thyroid-stimulating hormone precipitation results in Alzheimer's disease ^[5,14]. Due to malnutrition and lack of electrolyte balance person suffers from dehydration and weight loss ^[5,14]. Afterward, the cognitive changes get worsen and the patient can also feel restlessness with lack of sleep. Generally, in people symptoms are seen as follow:

1. Trouble focusing
2. A hard time doing ordinary activities
3. Feeling confused or frustrated, especially at night
4. Dramatic mood swings -- outbursts of anger, anxiety, and depression
5. Feeling disoriented and getting lost easily
6. Physical problems, such as an odd walk or poor coordination
7. Trouble communication^[20]

People with Alzheimer's disease forget their loved ones also. They can forget little things like how to dress and feed themselves, and how to use the toilet. The disease causes brain tissue to break down over time. It is generally seen in people over age 65. A person can stay with Alzheimer's disease for just a few years. More often, however, people live with it for about 9 years for last. In women, the disease occurs more than in men ^[1].

RISK FACTORS:

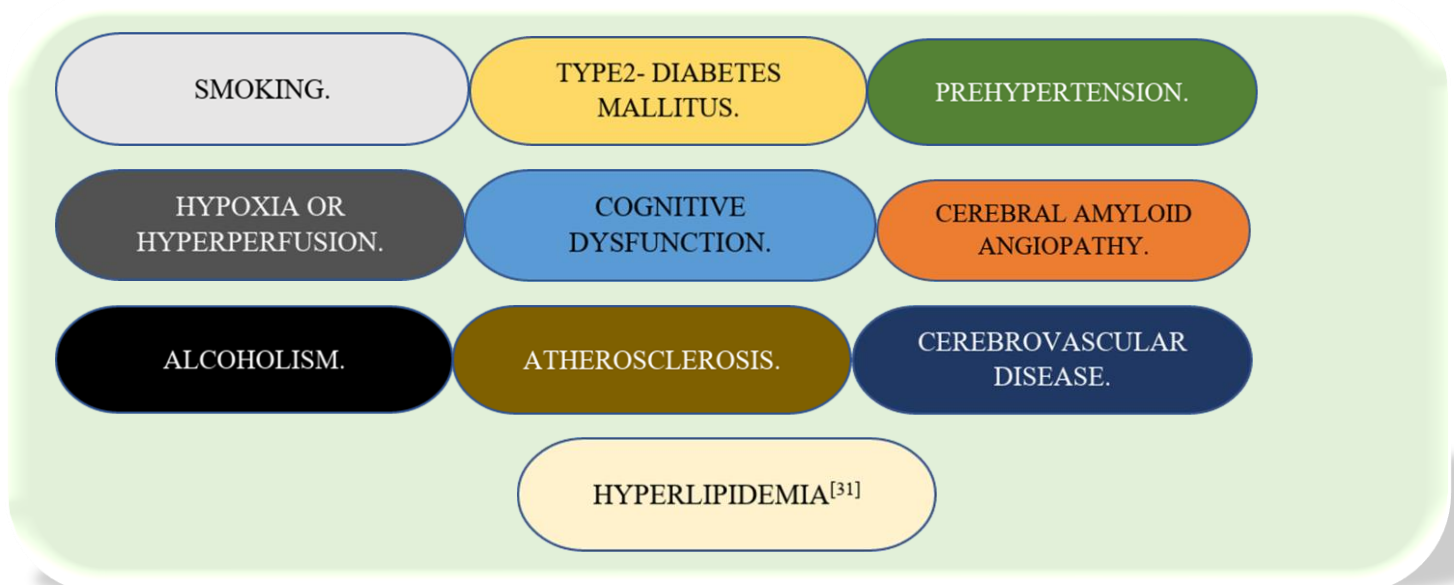


Fig No.:1 Risk Factors.

PATHOGENESIS:

Pathogenesis of Alzheimer's disease mainly depends on four factors:

1. Intracellular neurofibrillary tangles (NFTs)
2. Extracellular neurotic plaques
3. Degeneration of neurons
4. Cortical atrophy.

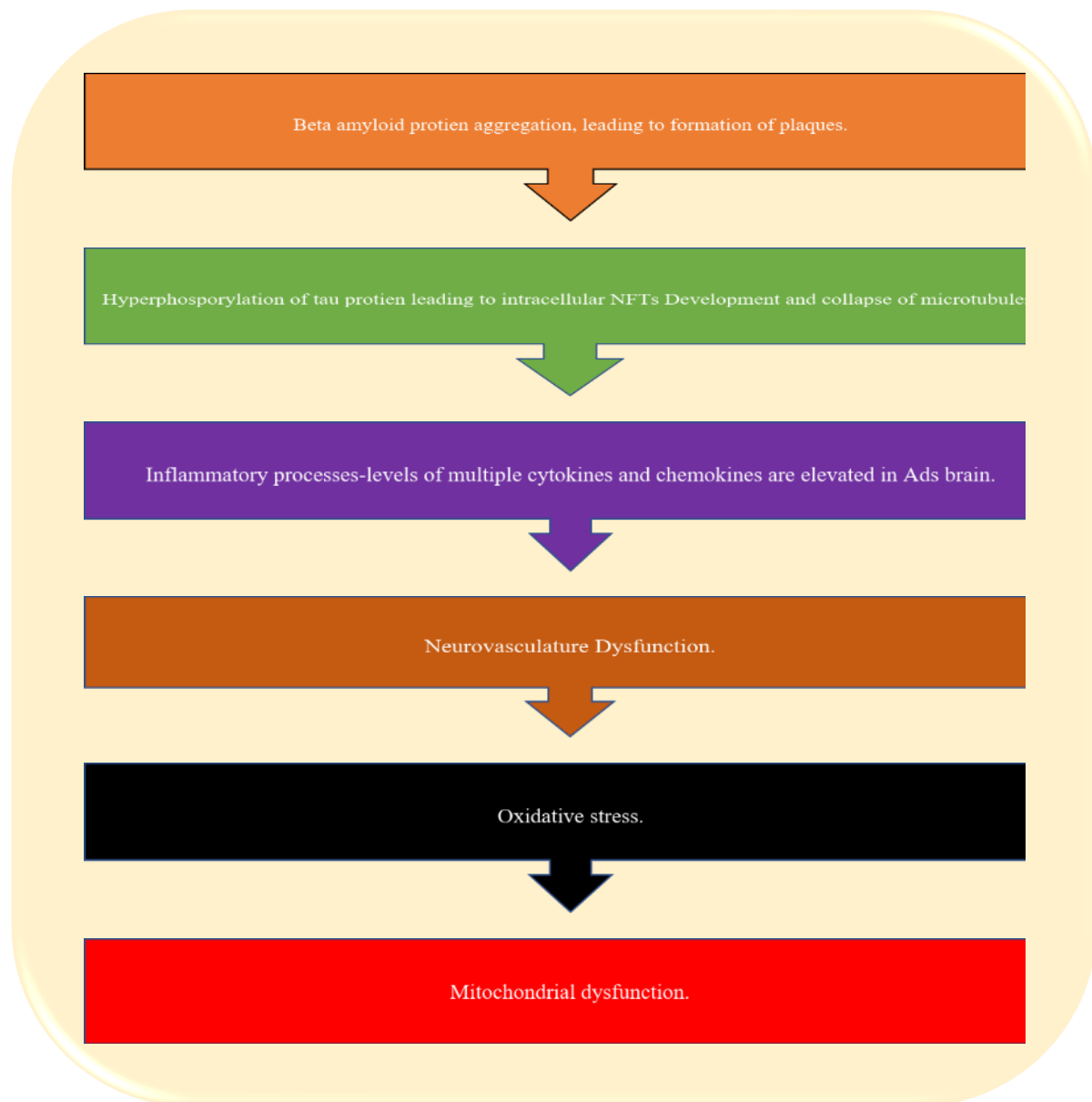


Fig. No: 2 Pathogenesis of Alzheimer's disease.

DIAGNOSIS:

Dementia is the cognitive impairment related to persons having Alzheimer's disease and Parkinson's disease ^[10,11]

To diagnose Alzheimer's disease, the most common criteria used are mentioned below:

1. History and physical examinations:

Alzheimer's disease is caused due to various risk factors as already discussed above various social factors like smoking, alcoholism certain types of chemical exposure should cause AD's. There is the significance of transmitting AD's Genetically in offspring from parents so it is important to take a family history. Disease conditions like Down syndrome and parkinsonism are a major risk for Alzheimer's disease. Utilization of certain anticholinergic agents used for selectively GIT and muscle relaxation purpose induces Alzheimer's risk in the elderly patient for determination of such factors clinical pharmacist do proper diagnosis within-person.

2. Cognitive impairment and Brain function

The person suffering from Alzheimer's disease undergoes severe cognition defects and loss of memory associated with abnormal brain function. The Clinical pharmacist determines the facts by asking questions to that person about the recent fact which are happened, the relation family members with him, something which has performed before some time, information about his professional status, family problem and friendship factor are within his life. If the person don't have any idea or link between these facts there is a major chance of severe cognitive defect and abnormal brain function^[10]

➤ **Laboratory investigation:**

1. **CBC**

Complete blood count is utilized to detect the cognitive function balance as well as blood efficiency and infectious state of body.

2. **Liver function test.:**

Enzymatic imbalance can be seen abnormal liver function and lack of enzyme action which regards to proper brain function

3. **Thyroid function test.**

Thyroid stimulating hormone is secreted by pituitary gland which regulates the function of thyroid gland and cognitive impairment can result in the low activity of brain area affect the followed to thyroid gland impairment.

4. **Serological test of neurosyphilis.**

Neurosyphilis can occur in some condition of Alzheimer's disease which can be result severe infection of brain cells

5. **Level of vitamin B12 & folate depletion.**

6. **Serum mineral and electrolyte balance.**^[5,10]

TREATMENT:

➤ **NON-PHARMACOLOGICAL TREATMENT:**

- The patient should have to manage the sleep disturbances, wandering, urinary incontinence, agitation, behavioral interventions
- Patient has to be educated with the diagnosis and the course of illness, decision, and treatment priority.
- Physician have to maintain the patients mental, physical, and emotional factors to minimize the intervention^[5]

- **About diet:**

Patient has to improve his diet utilization of following products to minimize the other complication as well as disease progression.

1. Low fat food.
2. Maintain cholesterol.
3. green vegetables
4. Ripe fruits having Antioxidant^[5]

- **About lifestyle:**

1. Patient has to maintain his weight and avoid smoking and alcohol consumption.
2. Do regular exercise for proper physical maintenance to manage his health.
3. Do aerobic exercise to minimize O₂ deficiency complication which may causes ischemia further condition can be progressive for AD.

➤ **NON PHAMACOLOGICAL RECENT ADVANCES:**

1) **Herbal Remedies For Management:** These agents don't have any specific role in treatment but are beneficial in the management of the disease. Herbal agents show their activity on the primary lead agent which are precipitating disease in the body as these are controlled then disease exacerbation also can be managed.

- ***Curcumin (Turmeric):***

- **INTRODUCTION AND MOA:** Curcumin is a natural product that occur very easily and act by showing inflammation and minimizing oxidative stress in person which results caring of Alzheimer's disease in patient.

- **BIOLOGICAL SOURCE:** Plant- Curcuma longa.

- **FAMILY:** Zingiberaceae.

- **CHEMICAL CONSTITUENTS: VOLATILE OIL:** Turmerone, Germacrone, Atlantes, Zingiberene^[22].

- ***Cinnamon (Cinnamon Zeylanicum):***

Cinnamon verum is plant from which bark is removed for therapeutic benefits within it. It is small evergreen tree from family laureaceae which have properties for correction of central nervous defects.

- **CHEMICAL CONSTITUENTS:** Cinnamaldehyde, Acetaldehyde, Eugenol, mucilage, tannins.

- **MECHANISM OF ACTION:** Chemical constituents within cinnamon bark are extracted for therapeutic purpose. It acts by management of AB40,42 APP Production resulting the plaque formation of amyloid and also have quality of reducing oxidative stress^[36,37]

- ***Pomegranate (Punica Granatum)***

Pomegranate is most occurred in northern India which is fruit bearing flowering plant belongs to family lytharaceae. These fruits are help in prevention of neurodegenerative disorder which causes cognition defects.

- **CHEMICAL CONSTITUENTS:** Eliagic acid, ellagitannin, punicalagin, punicic acid, punicallin, gallagic acid, pedunculagin,

- **MECHANISM OF ACTION:** Active chemical products within these fruits are acts by direct interference into the production of AB 40 On clinical trials. It was found to be reduces peroxide which are lead to genesis of oxidative stress and increase the cognitive function within patient^[36,37]

○ **Ginger (Zingiber Officinale):**

Ginger is rhizome which is used as traditional spices in India on daily basis. But shows Antioxidant properties as well as minimizes the aggregation of the amyloids on neurons and depression also and belongs to the family zingerberaceae.

- **CHEMICAL CONSTITUENTS:** Gingerol, shagol, zingiberene, zingerone, citral, bisabolone, paradol.
- **MECHANISM OF ACTION:** Herbal agent having properties like inhibition of AB40 Aggregation lows the amounts of oxidant production and reduces the AchCl can generate the Alzheimer's disease^[36,37]

2) **Physiotherapy And Meditation Management Therapy:**

○ **Communication Aids :**

As per knowledge ADs shows the depression state and relativeness with social mates can be minimize the disease progressiveness in person.^[12]

○ **Home Care Robots:**

Robots are helps to patient for proper medication and frequency of drugs during their cognitive impairment.^[12]

○ **Memesto-Music Device Therapy Of Alzheimer's:**

Music device plays role in calming of patient which enhance proper cognitive function and correct the Alzheimer's disease condition.^[19]

○ **Jelly Drops- Prevents Dementia:**

Jelly drops method developed by Lewis Hornby. The solution of disease Alzheimer's disease or dementia by hydration therapy as per patients are suffers from dehydration during ADs.^[19]

○ **Motions Of Sensors Light:**

Motions of centers are helpful in the conserve energy in case of dementia helps to tracking in the light switches.^[13]

○ **Maintaining Clock Consciousness:**

Clock is the clear way for making the powerful memory power and cure the cognitive impairment in person due to concentration and clear vision on clock and particular time factors determination^[13].

○ **Reiki: Physiotherapy:**

Reiki is an old Indian therapy that is fluently utilized nowadays other than India. The therapy is given by a qualified practitioner who has completed the course within it there are 12 steps in procedure hand position are changed by the practitioner for transferring the positive energy in the patient body. 7 chakra activation shows hormonal balance. Reiki is mainly utilized for patients having the neurodegenerative disorder, oxidative stress, depression which are associated with Alzheimer's disease. Reiki utilization is beneficial than the use of placebo therapy^[38,39]

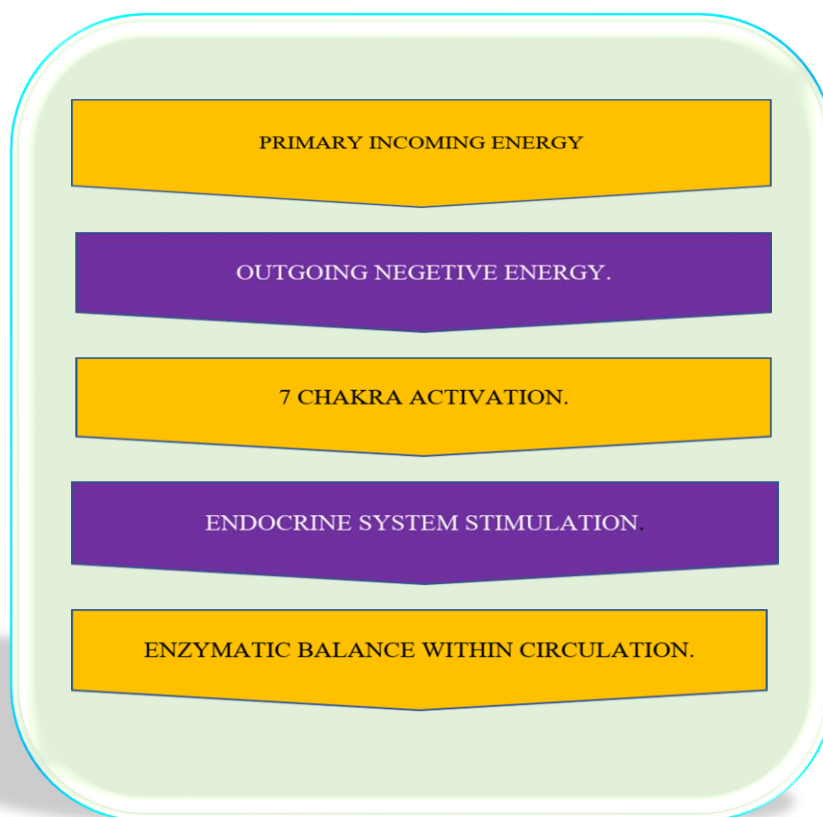


Fig. No.: 3 Action Of Reiki Therapy Within Body.

➤ **PHARMACOLOGICAL TREATMENT:**

These therapeutics agents are utilized for management of Alzheimer's disease. All the categories of agent are relates to the its treatment by interference into deposition of amyloid protein aggregation and chemical massage systems.

• **Cholinesterase inhibitor:**

Cholinesterase inhibitors are following 4 agents which are utilized for especially for Alzheimer's disease. Act by interference into degradations of cholinesterase into choline and acetate which are transmitter of massage within nerves cells, minimizes acetylcholine.

- 1) Donepezil.
- 2) Rivastigmine.
- 3) Tacrine (first cholinesterase used for AD)
- 4) Galantamine.

ADRS: GI symptoms, nausea, vomiting, diarrhea, headache syncope, dizziness, bradycardia^[5,6,16,18]

• **Miscellaneous therapies:**

- 1) Carbamazepine:

Carbamazepine is drug of anticonvulsant category. It blocks the nerve impulse at the time of Alzheimer's disease causes cognitive impairment. Improves the psychosis and behavioral disturbances in AD patients.

- 2) Oxazepam:

Special type of benzodiazepine utilized for management of Alzheimer's disease. Convulsions caused by improper nerves impulse caused within AD'S. It shows resting phase of cellular membrane causes improper nervous stimulations. Benzodiazepine also used to prevent Anxiety, agitation, depression, etc. Associated with Alzheimer's disease. ^[5,6,16,18]

- **Antipsychotic.**

The Class of drug are utilized for management of psychosis caused due to increased amount of dopamine which results the excitatory transmission of impulse within body cause convulsions as well as cognitive defects.

1. Haloperidol.
2. Olanzapine.
3. Quetiapine.^[5,6,16,18]

- **Antidepressants.**

These agents are inhibits the serotonin reuptake transmission within neurons causes certain excitations of neuronal area which shows chemicals massaging to others neurons for cognition precipitation.

1. Citalopram.
2. Escitalopram.
3. Fluoxetine.^[5,6,16,18]

- **Other drugs:**

1. Memantines : (Namenda)

Memantines is special class of drugs utilized in low proportion than cholinesterase inhibitors. Used for treatment of moderate to severe condition of Alzheimer's. It acts by blocking the glutamatergic neurotransmitters by antagonizing them as like NMDA receptor and given as monotherapy. Agent is having longer plasma half concentration i.e. 60-80 hrs so the dose and frequency should to monitor.

ADR's : Drowsiness, dizziness, headache.

2. Ginkgo biloba:

It is natural extracted derivative of plant products which shows benefits by minimizing higher risk cognitive impulses and improve loss of memory which associated with the Alzheimer's disease but should be avoided if the patient is on treatment of anticoagulant and antiplatelet therapy to minimize drug-drug interaction.

ADRS: nausea, vomiting, weakness, dizziness, hemorrhage^[5,6,16,18]

➤ **PHARMACOLOGICAL RECENT ADVANCES :**

1. **Monoclonal Antibodies:**

Monoclonal antibodies the immune cells which clone of there parenwta cells act by direct targeting on the antigens of substances which are showing the precipitation of disease. These are described for Alzheimer's disease as given below:

- ***Aducanumab:***

- **SOURCE:** Made up of monoclonal antibody.
- **TYPE:** Whole antibody.
- **ROUTE OF ADMINISTRATION:** Intravenous doses of aducanumab administered up to 4 weeks apart.^[9,21]
- **MOA/TARGET:** BETA AMYLOID.
- **BIOLOGICAL SOURCE:** HUMAN.^[9,21]

○ **Crenezumab:**

- **INTRODUCTION:** Crenezumab is fully humanized monoclonal antibody.
- It fight against 1-40 and 1-42 beta amyloid which beneficial in Alzheimer's disease.
- **MOA/TARGET:** Amyloid peptides.
- **SOURCE:** Humanized(from mouse).
- **PLASMA HALF LIFE:** 20 days.(long)
- **ROUTE OF ADMINISTRATION:** Intravenous.^[21,23]

○ **Gentenerumab:**

- **INTRODUCTION:** Monoclonal antibody for treatment of Alzheimer's disease developed by Hoffman-La Roche.
- **SOURCE:** Human.
- **MOA/TARGETS:** Beta amyloid number 40-42
- **STD.DOSE:** 105-225mg/day.
- **ROUTE OF ADMINISTRATION:** Intravenous.^[21,24]

○ **Action of Monoclonal Antibody:**

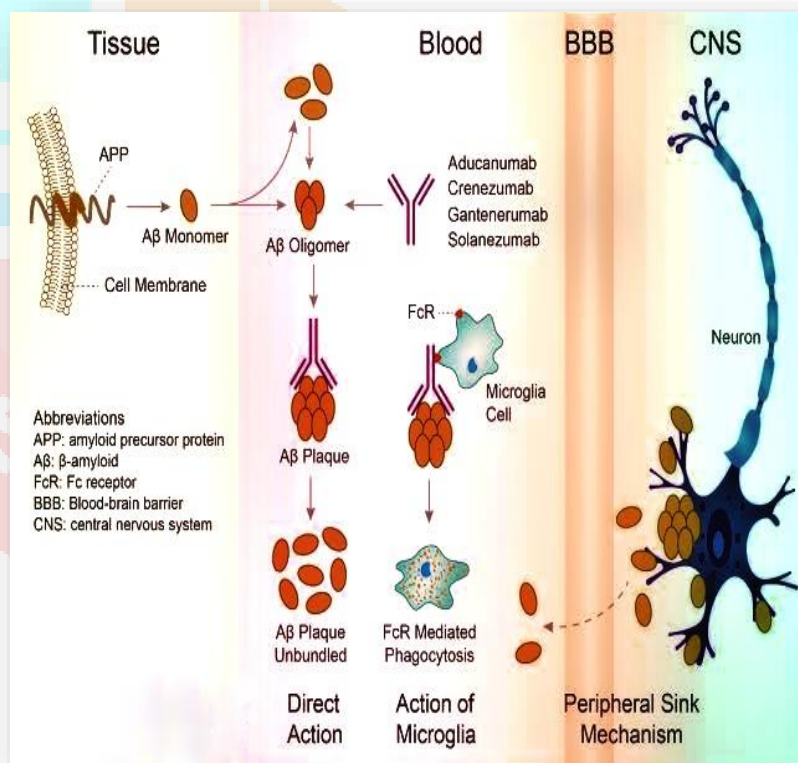


Fig.No.4: Mechanism of Monoclonal Antibodies.

2. Drug Advances On Alzheimer's Disease:.

○ *Statins (HMG Coa Reductase Inhibitors):*

● INTRODUCTION:

- Statins have been linked with reduce risk of all cause of dementia and even Alzheimer's disease.
- Statins are affects Alzheimer's disease pathology directly and reduces its risk by minimizing antibodies from plasma as well as CSF.

● MOA:

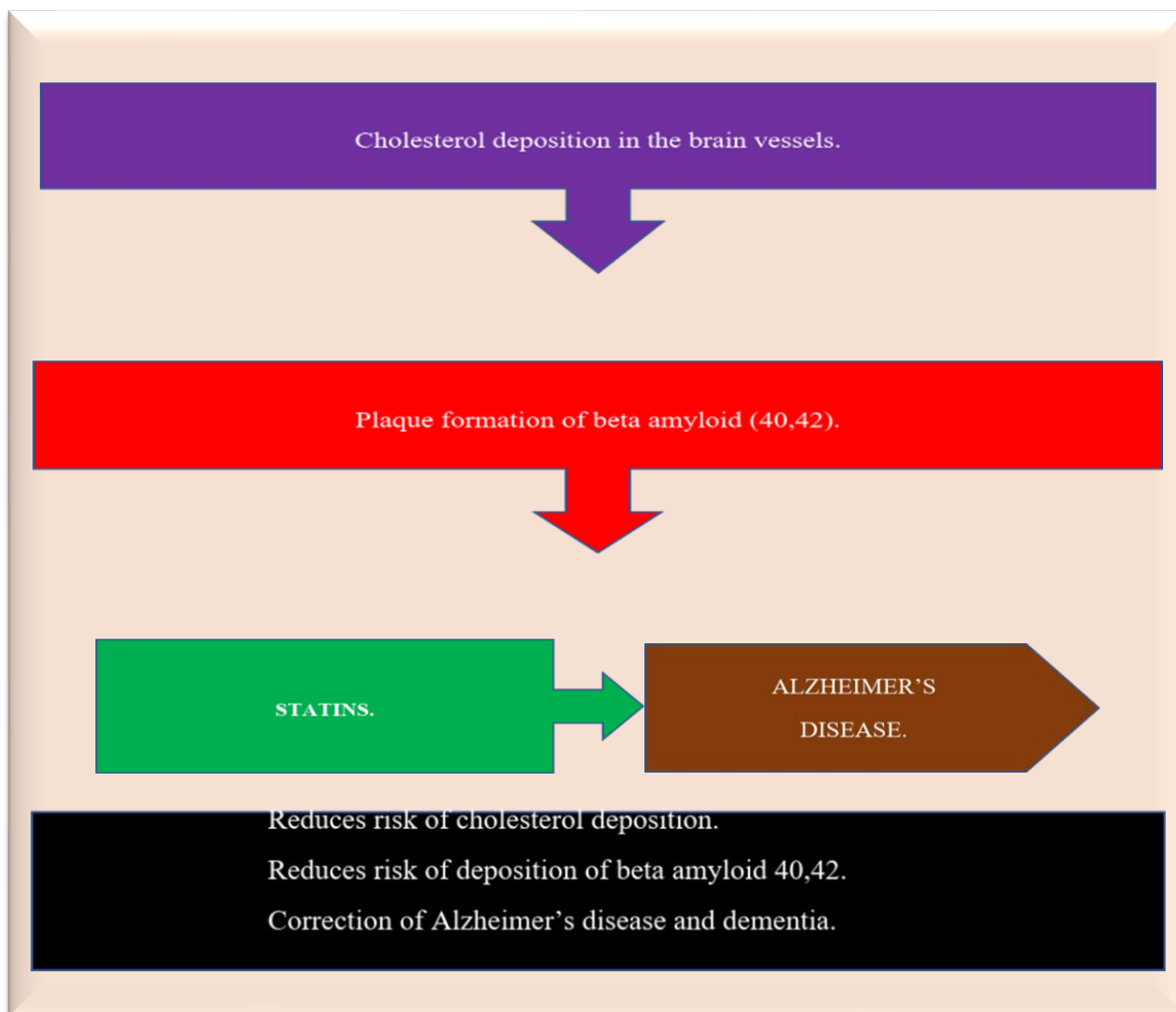


Fig.No.5: Mechanism of Statins.

- CATEGORY: HMG COA REDUCTASE INHIBITOR
- ADRs: Constipation, increased serum alanine transaminase, myopathy, increased creatinine kinase levels.
- E.g.: Atorvastatin, simuvastatin, lovastatin, rosuvastatin.
- CONTRAINDICATION: Active hepatic Disease, Hepatic enzyme Defects, Pregnancy, Breast feeding.^[5,26]

○ ***Gamma Secretase Inhibitors/ Modulators:***

When the selective drugs are treated on rats/mice then the activities are found as like inhibition of antibody production in plasma and CSF.

It mainly acts on AB-40 which are source to the deposition of amyloid in vascular area of brain. E.g. terenfubril, CHF-5054, NC 5-15.

- ADR'S: GIT irritation, thymus rodents.
- CONTRAINDICATIONS: Cellular dysfunction or inactivity^[25,34,35]

○ ***Alfa Secretase Activators:***

As given below within Alfa and beta secretase receptors Alfa secretase are ore active than that of beta secretases. Inhibition of beta secretase due to competition within both Alfa secretase is more active in nature it substrate to APP deposition which may results vascular culture damage and amyloid aggregation.

E.g.: ADAM 9, ADAM 10.

- ADR'S: GIT irritation.
- CONTRAINDICATION: Cellular damage or Dysfunction^[25,34,35]

○ ***M1 Muscarinic Receptors Agonist:***

M1 muscarinic receptors are mainly binding taken place for following acrivity:

- a. Hyperphosphorylation of tau.
- b. It blocked should results cognitive dysfunction also.

These agents are utilized for stimulation of such type of specific receptor shows proper binding of specific neurotransmitters to binding site.

E.g. AF 150 (S), AF 267B.

- ADR'S: pyrexia, flushing, dizziness, nausea.
- CONTRAINDICATIONS: Asthma, COPD^[32,33]

○ ***Antineoplastic Agents (Retinoids):***

These class of agents are specially utilized to treat skin cancer type known as cutaneous T- cells lymphoma as addition to the previous medication which is already in therapy if non-beneficial.

Retinoid shows benefits in Alzheimer's disease but dose not have any specific role. These are acts by minimization in Apolipoprotein E4 which may cause deposition of the APP layer in neuronal brain area.

- MOA: These derivatives are act by binding to specific type of receptors RXR AND RAR. Which may shows activity on amyloid depositions by inactivity of the APP.
- ADR'S: dryness on skin, itching, sun sensitivity.
- CONTRAINDICATION: Hepatotoxicity, Hyperthyroidism.

○ ***Multivitamin Therapy:***

In Alzheimer's disease due to lack of neuro nutrition loss of memory can be occur so as per need of the neuronal area. The utilization of the multivitamins results in the neuronal nourishment which can lead to minimization of loss of memory associated with dementia as well as Alzheimer's disease. Supplementation shows balance of the biomolecules which are essential for development of humans. Multivitamins are shows purpose in other condition

than that of Alzheimer's also so its use will be beneficial. Vitamin D, folic acid as well B12 disturbances occur in such condition lead to neurodegenerative disorder^[40]

PREVENTIONS:

1. Do's:

- To do Regular exercise.
- To stay himself engaged with any entertainment.
- To take proper Healthy diet after time interval.
- To take meditation which helps in Mental stimulation.
- To take proper Quality sleep.
- Stress management with the utilization of such type of anxiolytic therapy.
- To maintain his Vascular network status in proper manner.^[7]

2. DONT'S:

- Avoid Alcohol than that of 13 units/ week
- Smoking cessation to minimize the ischemia which can lead to further progressive state.
- Low cholesterol consumption to avoid its deposition on plaque can be make it complicated.^[8]

DISCUSSION:

Alzheimer's disease is directly linked with the CNS with cognitive impairments. Alzheimer's disease being active nowadays which means need more proper management and the recovery period should also be less. In this article, we discussed the medication as well as meditation that is the physiological change that may show proper correction of disease. Recently as per research, monoclonal antibodies are found to treat Alzheimer's disease and are found to be a proper therapy without any systemic damage or adverse event. Some drugs utilized for disease state are showing systemic toxicity as well as a systemic adverse event which can be minimized by utilizing some specific recent drugs. Drugs that are specially utilized for another type of disease correction are showing some benefits in Alzheimer's disease, and hence can be utilized insufficient amount if the person needed larger drug amount of previous medication which may develop toxicity if used in the large amount.

The reason behind the selection of topics is to achieve Alzheimer's disease management/treatment targets. Alzheimer's is being active nowadays some patients having allergic reactions associated with the drug therapy utilized for treatment hence the recent advances which are discussed within our study are showing benefits in such type of condition. After studying some references on physiotherapy, like reiki, it is fluently utilized other than India which is having Indian origin are showing improvement as per non-pharmacological management as supportive therapy to drug therapy. After analysis of some references, we are found that the herbal character having plants are showing wonders effects in the correction of Alzheimer's disease. The chemical constituent within them directly acting on targets toxic molecules which precipitate such disease condition. The article also suggests the role of clinical pharmacists in managing adverse effects of drugs and for proper dose management. At the time of diagnosis, history taking should be done in a proper way, so that the risk behind disease condition can be determined and managed appropriately. The higher dose of some drugs has severe adverse events in the biological system so it should also be properly managed.

CONCLUSION:

In Alzheimer's disease, the proper management and treatment are most important than that of others so we utilize the medication for its management but as per our study, only drugs are not sufficient for it. The person should have to do meditation as well as communication aids and changes in physical activities. We have done a study on recent advances on Alzheimer's disease which are other than that of standard therapy. The study includes information about persons who became resistant to the therapy and drugs which cause the allergic condition due to the precipitation of adverse effects within the body. Recent advances on Alzheimer's disease are showing benefits in the management of its worse form which can lead to the harmful for the neuronal area and further progression leading to infarcts or stroke due to continuous aggregation of the Amyloid protein.

We concluded some drugs belongs to the herbal group don't have any adverse event on administration and their utilization is shown certain counter effects on molecules which can lead to the improvement of disease States. A recent study on monoclonal antibodies targets the protein aggregation within the nervous area without any adverse effects and toxicity. For minimizing toxicity dose management should be done.

Clinical pharmacists are having an important role in the management of Alzheimer's disease. Some drugs utilized for management of disease show longer plasma time, same adverse condition as well as drug-drug interactions, thus pharmacist has to manage the dose, frequency, and utilization of alternative drugs having same found within recent advances. The study of this topic was done for therapeutic approaches for the proper administration, toxicity monitoring, adverse event minimization.

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