

**A REVIEW ON CAUSES, STAGES AND TREATMENTS USED IN
ALZHEIMER'S DISEASE****Diptesh T. Patil*¹, Aditya Singh¹ and Dr. Vanita Kanase²**

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ABSTRACT

Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder which reduced the person's ability to think clearly, perform everyday tasks and ultimately, remember who they even are. As it worsens over the time, patient must get early detection and proper treatment. Cholinesterase inhibitors are used as a first line of defence to treat the cognitive symptoms (memory loss, confusion, and problems with thinking and reasoning) of AD. As new targets are hypothesized and new drugs are in phase 2-3 clinical trials soon the better therapeutic effect may be achieved. The proper harmony must involve between pharmacological treatments with non-pharmacological treatments.

KEYWORDS: Donepezil, Huperazine A, Memantine, Rivastigmine, GTS-21, Statins, Coenzyme Q.

INTRODUCTION

Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder characterised by three primary groups of symptoms. The first group (cognitive dysfunction) includes memory loss, language difficulties, and executive dysfunction (that is, loss of higher level planning and intellectual coordination skills). The second group comprises psychiatric symptoms and behavioural disturbances for example, depression, hallucinations, delusions, agitation collectively termed non-cognitive symptoms. The third group comprises difficulties

with performing activities of daily living (deemed “instrumental” for more complex activities such as driving and shopping and “basic” for dressing and eating unaided).^[1] The symptoms of Alzheimer’s disease progress from mild symptoms of memory loss to very severe dementia. Increasingly, the coexistence of vascular disease and Alzheimer’s disease is being recognised clinically, pathologically, and epidemiologically.^[2]

In November 1906, at a German psychiatrists meeting, Alois Alzheimer presented the pathological findings on a brain of a 56-yr. woman who died after a progressive dementia. She was under the care of Dr. Alzheimer until her death in 1906. He did an autopsy, examined her brain & described the typical abnormalities of what would be called later Alzheimer’s disease.

Stages of AD

1. Pre-dementia^[3]: Problems with the executive functions of attentiveness, planning, flexibility, and abstract thinking, or impairments in semantic memory.
2. Early^[4]: Increasing impairment of learning and memory
3. Moderate^[4]: Speech difficulties, Behavioural and neuropsychiatric changes, outbursts of unpremeditated aggression, or resistance to care giving and other delusional symptoms.
4. Advanced^[4]: Loss of verbal language abilities, Muscle mass reduced and person becomes immobile.

Causes of AD

1. Genetic: This form of the disease is known as early onset “familial Alzheimer's disease” Around 0.1% of the cases are familial forms of autosomal (not sex-linked) dominant inheritance, which have an onset before age 65. Most of autosomal dominant familial AD can be attributed to mutations in one of three genes: those encoding amyloid precursor protein (APP) and presenilins 1 and 2.^[5]
2. Cholinergic hypothesis: The oldest hypothesis which proposes that AD is caused by reduced synthesis of the neurotransmitter acetylcholine and most currently available drug therapies are based.^[6]
3. Amyloid hypothesis: It postulated that extracellular amyloid beta ($A\beta$) deposits are the fundamental cause of the disease. Various proteins are involved in the formation of amyloid build-up in the brain.^[7]
4. Tau hypothesis: The tau hypothesis proposes that tau protein abnormalities initiate the disease cascade. In this model, hyperphosphorylated tau begins to pair with other threads

of tau. Eventually, they form neurofibrillary tangles inside nerve cell bodies. When this occurs, the microtubules disintegrate, destroying the structure of the cell's cytoskeleton which collapses the neuron's transport system.^[8]

5. Other hypotheses

- Poor functioning of the blood–brain barrier.^[9]
- Smoking and air pollution.^{[10][11]}
- Spirochetes bacteria infection.^[12]
- Retrogenesis.^[13]
- Plasmin Hypothesis.^[14]
- Calcium hypothesis.^[15]

Ten warning signs of Alzheimer's disease

- 1) Memory loss.
- 2) Difficulty to performing familiar tasks.
- 3) Problems with language.
- 4) Disorientation to time and place.
- 5) Poor or decreased judgment.
- 6) Problems with abstract thinking.
- 7) Misplacing things.
- 8) Changes in mood or behavior.
- 9) Changes in personality.
- 10) Loss of initiative.

Symptoms

- 1) Confusion.
- 2) Disturbances in short-term memory.
- 3) Problems with attention and spatial orientation.
- 4) Personality changes.
- 5) Language difficulties.
- 6) Unexplained mood swings.

Progression of AD

- 1) Stage 1: Normal

Not detectable and no memory problems or other symptoms of dementia are evident.

2) Stage 2: Normal aged forgetfulness

Minor memory problems or lose things around the house, although not to the point where the memory loss can easily be distinguished from normal age related memory loss. the disease is unlikely to be detected by physicians.

3) Stage 3: Mild cognitive impairment.

- Difficulty in finding the right word during conversations.
- Remembering names of new acquaintances.
- Planning and organizing.
- People with stage three Alzheimer's may also frequently lose personal possessions, including valuables.

4) Stage 4: Mild Alzheimer's.

- Have difficulty with simple arithmetic.
- May forget details about their life histories.
- Have poor short term memory (may not recall what they ate for breakfast, for example).

5) Stage 5: Moderate Alzheimer's disease

Patients begin to need help with many day to day activities. People in stage five of the disease may experience.

- Significant confusion.
- Inability to recall simple details about themselves such as their own phone number
- Difficulty dressing appropriately.

6) Stage 6: Moderately severe Alzheimer's disease.

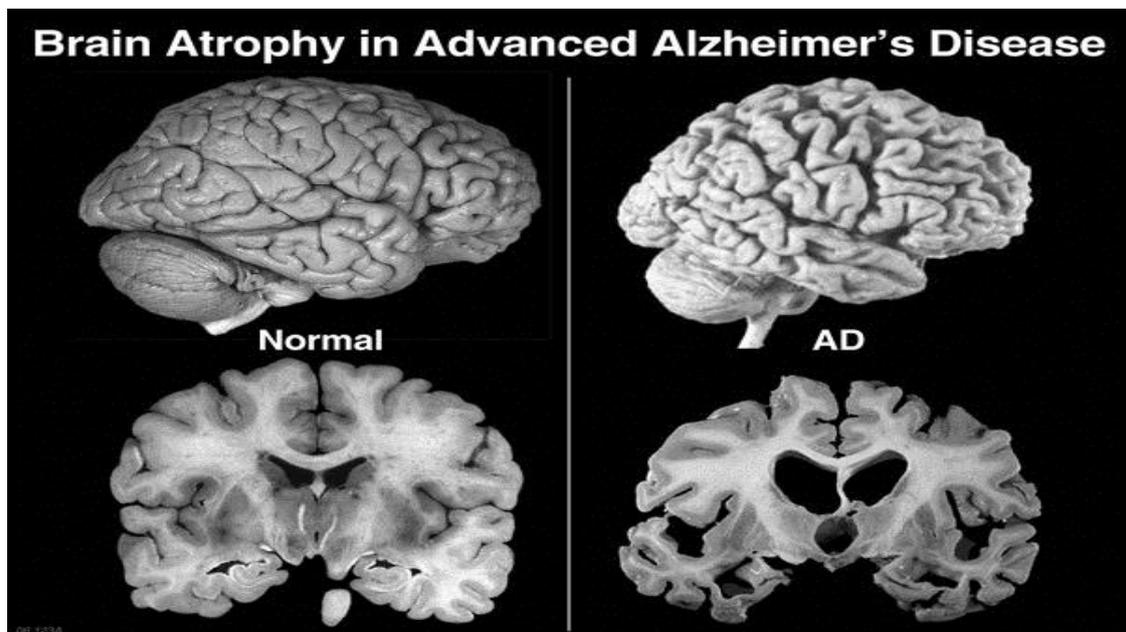
- Confusion or unawareness of environment and surroundings
- Major personality changes and potential behavior problems.
- The need for assistance with activities of daily living such as toileting and bathing.
- Inability to recognize faces except closest friends and relatives.
- Inability to remember most details of personal history.
- Loss of bowel and bladder control.
- Wandering.

7) Stage 7: Severe Alzheimer's disease

It is the final stage of Alzheimer's disease. Because Alzheimer's disease is a terminal illness, patients in stage seven are nearing death. In stage seven of the disease, patients lose ability to respond to their environment or communicate. While they may still be able to utter words and phrases, they have no insight into their condition and need assistance with all activities of daily living. In the final stages of the illness, patients may lose their ability to swallow.

Diagnostic Tests

- Psychiatric assessments.
- Mental status examination and neuro-psychological assessment.
- Laboratory tests.
- Brain imaging.
 - * CT scan
 - * MRI
 - * PET
 - * SPECT
- CSF Examination.
- Electro-encephalogram (EEG).
- Electromyogram.



PHARMACOLOGICAL TREATMENT

The 3 targets for Pharmacotherapy.

- Cognitive decline: memory, language, orientation, concentration, etc
- Behavioural abnormalities: delusions, aggressiveness, anxiety, depression, psychosis etc.
- Activities of Daily Living: dressing, bathing, feeding, use of household appliances, etc.

Mechanisms involved in Pharmacotherapy:

- Increasing global/ regional cerebral blood flow (CBF)
- Direct support of neuronal metabolism
- Enhancement of neurotransmission
- Improvement of discrete cerebral functions, e.g. memory

ALREADY IN USE DRUGS THERAPIES:

1. Cholinergic Activators
2. Glutamate (NMDA) Antagonists
3. Miscellaneous cerebroactive drugs

1. Cholinergic Activators:

These are *Cholinesterase inhibitors (ChEIs)*, they act by preventing the enzymatic degradation of the neurotransmitter acetylcholine (ACh) resulting in increased ACh concentrations in the synaptic cleft & enhanced cholinergic transmission.

Noncovalent inhibitors are used in AD for this purpose.

Noncovalent or “reversible” inhibitors

1st AChEI approved by FDA for treatment of AD was Tacrine which is a reversible inhibitor & no longer used now in many countries due to hepatotoxicity. 4 drugs of this class are currently in market, which are Donepezil, Rivastigmine, galantamine and Huperzine A.

I. Tacrine: Tacrine is a centrally acting anticholinesterase and indirect cholinergic agonist (parasympathomimetic). It was the first centrally acting cholinesterase inhibitor approved for the treatment of Alzheimer's disease, and was marketed under the trade name Cognex.^[16]

Tacrine is an anticholinesterase agent which reversibly binds with and inactivates cholinesterases. This inhibits the hydrolysis of acetylcholine released from functioning

cholinergic neurons, thus leading to an accumulation of acetylcholine at cholinergic synapses. The result is a prolonged effect of acetylcholine.^[17]

Major side effects: GI symptoms (Nausea, Diarrhea, Cramps), altered sleep, bradycardia & muscle cramps.

II. Donepezil: Donepezil is a piperidine derivative that is a centrally active, reversible inhibitor of acetylcholinesterase. This drug is structurally unrelated to other anticholinesterase agents. Donepezil's proposed mechanism of action involves the reversible inhibition of cholinesterases (eg. acetylcholinesterase), which prevents the hydrolysis of acetylcholine, and leads to an increased concentration of acetylcholine at cholinergic synapses. Evidence suggests that the anticholinesterase activity of donepezil is relatively specific for acetylcholinesterase in the brain.^[18]

It is more hydrophobic & has longer duration of action, readily cross blood–brain barrier to inhibit AChE in the CNS.

III. Rivastigmine: Rivastigmine is a carbamate derivative that is structurally related to physostigmine, but not to donepezil and tacrine. The precise mechanism of rivastigmine has not been fully determined, but it is suggested that rivastigmine binds reversibly with and inactivates cholinesterase (eg. acetylcholinesterase, butyrylcholinesterase), preventing the hydrolysis of acetylcholine, and thus leading to an increased concentration of acetylcholine at cholinergic synapses. The anticholinesterase activity of rivastigmine is relatively specific for brain acetylcholinesterase and butyrylcholinesterase compared with those in peripheral tissues.^[19]

IV. Galantamine: Galantamine is a phenanthrene alkaloid and a reversible, competitive acetylcholinesterase inhibitor. It is not structurally related to other acetylcholinesterase inhibitors. Galantamine's proposed mechanism of action involves the reversible inhibition of acetylcholinesterase, which prevents the hydrolysis of acetylcholine, leading to an increased concentration of acetylcholine at cholinergic synapses. Galantamine also binds allosterically with nicotinic acetylcholine receptors and may possibly potentiate the action of agonists (such as acetylcholine) at these receptors.^[20]

V. Huperzine A: As a quasi-irreversible inhibitor of acetylcholinesterase, Huperzine A is a chemical that inhibits the cholinesterase enzyme from breaking down acetylcholine, so increasing both the level and duration of action of the neurotransmitter acetylcholine.^[37]

2. Glutamate (NMDA) Antagonists

Acts by blocking overexcited NMDA receptors which blocks entry of Ca^{++} thereby decreasing glutamate release & inhibiting processes which led to neurotoxicity.

Memantine is the only one drug of this class which is used in the treatment.

Memantine

Memantine exerts its action through uncompetitive NMDA receptor antagonism, binding preferentially to the NMDA receptor-operated cation channels. Prolonged increased levels of glutamate in the brain of demented patients are sufficient to counter the voltage-dependent block of NMDA receptors by Mg^{2+} ions and allow continuous influx of Ca^{2+} ions into cells, ultimately resulting in neuronal degeneration. Studies suggest that memantine binds more effectively than Mg^{2+} ions at the NMDA receptor, and thereby effectively blocks this prolonged influx of Ca^{2+} ions through the NMDA channel whilst preserving the transient physiological activation of the channels by higher concentrations of synaptically released glutamate. Thus memantine protects against chronically elevated concentrations of glutamate. Memantine also has antagonistic activity at the type 3 serotonergic (5-HT₃) receptor with a potency that is similar to that at the NMDA receptor, and lower antagonistic activity at the nicotinic acetylcholine receptor. This drug has no affinity for γ -aminobutyric acid (GABA), benzodiazepine, dopamine, adrenergic, histamine, or glycine receptors or for voltage-dependent calcium, sodium, or potassium channels.^[21]

3. Miscellaneous cerebroactive drugs

I. Piracetam

Piracetam improves the function of the neurotransmitter acetylcholine via muscarinic cholinergic (ACh) receptors, which are implicated in memory processes. Furthermore, piracetam may have an effect on NMDA glutamate receptors, which are involved with learning and memory processes.^[22]

II. Pyritinol (Pyrithioxine)

It is a semi-synthetic water-soluble analog of vitamin B6 (Pyridoxine HCl). Pyritinol has been shown to increase choline uptake and therefore increase acetylcholine levels, leading to increased brain functions regarding reasoning, learning, and memory.^[23]

III. Dihydroergotoxine (Codergocrine)

Ergoloid mesylates act centrally, decreasing vascular tone and slowing the heart rate, and acts peripherally to block alpha-receptors. One other possible mechanism is the effect of ergoloid mesylates on neuronal cell metabolism, resulting in improved oxygen uptake and cerebral metabolism, thereby normalizing depressed neurotransmitter levels.^[24]

IV. Piribedil

It is an antiparkinsonian agent, yet used in treatment of AD to, maintain levels of Dopamine and ACh in balance.^[25]

V. Ginkgo biloba

Ginkgo biloba is thought to have both antioxidant and anti-inflammatory properties, to protect cell membranes and to regulate neurotransmitter function.

DRUGS UNDER EVALUATION

1. Nicotinic Receptor Agonist: 4 OH-GTS-21

GTS-21 is an orally active alpha-7 nicotinic acetylcholine (nACh) receptor agonist. It displays nootropic and neuroprotective effects.^[26]

2. Antioxidants: Vitamine E, Melatonin

Antioxidants reduce the oxidative stress in CNS which helps in protection of neuron from degradation by stress.

Melatonin acts at different levels relevant to the development and manifestation of AD. The antioxidant, mitochondrial and antiamyloidogenic effects may be seen as a possibility of interfering with the onset of the disease.^[27]

3. PPAR Gamma Agonists: Pioglitazone

Peroxisome proliferator-activated receptor- γ (PPAR- γ) is a ligand-activated nuclear transcription factor that is mainly expressed in endothelial cell, the immune system, and also neuronal cultures. It is a target of the class of drugs known as thiazolidinediones (TZDs) and

commonly used to treat type II diabetes, due to inhibitory action on microglial activation and neuronal damage.

Apoptosis was observed when sera from AD was exposed to endothelial cells. Various studies confirm the beneficial effects of PPAR- γ agonist for neurodegenerative disorders.^[28]

4. Gamma Secretase Inhibitors: Semagacestat

The main constituent of amyloid plaques in the brains of Alzheimer's disease patients is β -Amyloid, which is formed by proteolysis of amyloid precursor protein (APP). Semagacestat blocks the enzyme γ -secretase, which (along with β -secretase) is responsible for APP proteolysis.^[29]

5. 5HT-6 Antagonist: SB-271046

5-HT6 receptor blockade induces acetylcholine release, reductions in 5-HT6 receptors may represent an effort to restore acetylcholine levels in a deteriorated cholinergic system. In addition, it has been reported that a dysregulation of 5-HT6 receptor activation by 5-HT in the temporal cortex may be related to behavioral symptoms in AD.^[30]

6. Statins: Simvastatin, Pravastatin

Statins inhibit β -secretase & activate α -secretase thereby decreasing A β load. Thus it reduces the risk of dementia & cognitive impairment by modifying the vascular risk factors that have been implicated in both vascular dementia & Alzheimer's disease.^[33]

7. Others: Heavy metal chelators, Estrogens, Anti-inflammatory drugs.

1. Heavy metal chelators.

Alzheimer's disease is an accumulation of metallic particles. There are six toxic metals which cause Alzheimer's disease: aluminum, mercury, lead, cadmium, iron and manganese. Chelation therapy consists of injections of a synthetic amino acid, a protein, whose name is ethylene diamine tetraacetic acid, also known as EDTA. It actually captures a metallic particle floating in the bloodstream or brain fluid, surrounds it and draws it into its center where it is trapped. The body has no use for EDTA and gets rid of it, so the EDTA molecule with the trapped metallic particle is urinated out of your system within 24 hours. This is an effective way of detoxifying your arteries and your brain cells.^[34]

2. Estrogens

Evidence from epidemiological studies supports enhanced cognitive function in women with AD taking estrogen replacement therapy (ERT) as well as a reduced risk for developing AD in healthy women receiving ERT. Additional clinical evidence suggests that estrogen may modulate specific cognitive functions such as working memory and verbal learning and memory. However, results from more recent controlled trials have not consistently shown a beneficial effect of estrogen on the cognitive function of women with AD.^[35]

3. Anti-inflammatory drugs

Past studies found patients who reported higher use of NSAIDs were less likely to develop AD compared to patients with less frequent NSAID use. These findings suggested that NSAIDs may have neuroprotective properties against development of AD. Recent double blind, placebo controlled trials have failed to demonstrate any therapeutic benefit in the development of AD.

POTENTIAL NEW DRUGS

1. Caprylic acid 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. Glucose is the brain’s chief energy source. Imaging studies show reduced glucose use in brain regions affected by Alzheimer’s.^[36]

2. 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.^[36]

3. 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. The chief omega-3 in the brain is DHA, which is found in the fatty membranes that surround nerve cells, especially at the microscopic junctions where cells connect to one another.

Theories about why omega-3s might influence dementia risk include their benefit for the heart and blood vessels; anti-inflammatory effects; and support and protection of nerve cell membranes.^[36]

4. Phosphatidylserine

Phosphatidylserine is a kind of lipid, or fat that is the primary component of the membranes that surround nerve cells. In Alzheimer's disease and similar disorders, nerve cells degenerate for reasons that are not yet understood. The theory behind treatment with phosphatidylserine is its use may shore up the cell membrane and possibly protect cells from degenerating.^[36]

5. Tramiprosate

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. Analysis of the Phase 3 trial data was initially inconclusive for a variety of reasons.^[36]

6. Astaxanthin

Astaxanthin is a powerful, naturally occurring carotenoid pigment that's found in certain marine plants and animals. Often called "the king of the carotenoids," astaxanthin is recognized as being one of the most powerful antioxidants found in nature. Astaxanthin is an antioxidant, so it naturally reduces free radicals in the body. But besides that, it also significantly reduces the oxidative load in the body by protecting the cells against oxidation. Because of astaxanthin's unique molecular structure, this red-colored pigment is an extremely powerful antioxidant that is very effective against singlet oxygen. It has a powerful scavenging ability for lipid and free radicals, and effectively breaks peroxide chain reactions.^[38]

HERBAL TREATMENT

| Sr. No. | Name of Plant | Chemical Constituent | Marketed Formulation |
|---------|--|--|--|
| 1 | Galanthus woronowii: (Amaryllidaceae) | Galantamine | Reminyl™ ER |
| 2 | Curcuma longa (Zingiberaceae) | Curcumin | Curcosome |
| 3 | Centella asiatica (Mackinlayaceae) | brahmoside, brahminoside, asiaticoside, indocentelloside etc.... | Gotu Kola - Vallarai – Tablets Impcops - Organic and Wild |

Other Herbal Plants

1. *Rosemarinus officinalis*
2. *Panax ginseng*
3. *Lycoris radiata*
4. *Melissa officinalis*
5. *Withania somnifera*
6. **Bacopa monnieri**
7. **Macleaya cordata**
8. **Vinca minor**
9. **Allium sativum**
10. **Coptis chinenses**

DO's and Dont's^[38]

The foods and liquids which should be added in eating and drinking include.

1. **Filtered water** – Helps to flush toxins from the body and hydrate the cells (including brain cells).
2. **Green tea or Matcha tea** – Both contain powerful antioxidants known as catechins which remove harmful toxins and chemicals from the body. A component in these teas has also been shown to decrease brain beta-amyloid plaque formation.
3. **Turmeric, Ginger, Cinnamon, Black pepper, Chilli's (Cayenne pepper), Rosemary, Coriander and Garlic** – All of these herbs and spices are potent anti-viral, anti-inflammatory and immune boosting foods (everything dementia sufferers need).
4. **Reishi and Cordyceps mushrooms** – Both are immune boosting and contain strong neuro-protective properties.
5. **Probiotics** – Needed for healthy gut function, which in turn produces healthy brain function and healthy immunity. You can learn how to make your own fermented foods such as kefir, sauerkraut, kombucha and yoghurt here... Cultures for Health.
6. **Whole foods** – Eating plenty of organic mixed berries, green leafy vegetables, liver (if you can stomach it), nuts and seeds such as chia and flaxseeds is vital. When it comes to buying these, fresh is definitely best.

For the foods, you should be avoiding or not eating at all, here's the top ones...

1. **Margarine** – This is a man-made death food that's guaranteed to fry your brain and make brain disorders such as dementia much worse. Don't touch it with a ten foot pole!

2. **Refined (processed) sugars** – Makes your blood sticky and restricts circulation to areas of the brain. Another man-altered death food.
3. **Gluten** – Has been repeatedly linked to brain disorders and learning disabilities so all gluten containing foods are best avoided.
4. **Trans fats** – Margarine, all baked goods, fast food and vegetable oils (especially the ones that you find sitting on the shelf in supermarkets in clear bottles) are full of brain damaging trans fats and free radicals. These must all be completely avoided if you want to prevent or reverse dementia.
5. **Processed dairy** – Pasteurized milk, cheese, cream and yoghurts are toxic gunk that stick to the lining of the gut and prevent the absorption of nutrients. Unless you have access to unpasteurized dairy products, use alternatives such as coconut milk or almond milk.

CONCLUSION

AD is not part of normal aging process, although it is now widely spreading on the adults of age more than 30-40 years. It is still incurable, yet the symptoms can be avoided with proper care and medication with certain important changes in lifestyle. Early diagnosis of disease can help patient and healthcare systems for proper care of patient. Pharmacotherapy proved to be effective, but at certain limit after which the treatment tends to be unresponsive or may lead to other attributes.

As multiple new novel targets are identified and few new hypotheses are generated about progression of disease, many new drug products may come to aid in treatment of AD in coming years showing promising effect in reversing the condition and enhancing the day to day life of patient.

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