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ALZHEIMER'S DISEASE PROGRESSION & TREATMENT

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1. ABSTRACT

Alzheimer's disease is one of the most devastating brain disorders of elderly humans. It is an undertreated and under-recognized disease that is becoming a major public health problem. The last decade has witnessed a steadily increasing effort directed at discovering the etiology of the disease and developing pharmacological treatment. Recent developments include improved clinical diagnostic guidelines and improved treatment of both cognitive disturbance and behavioral problems. Symptomatic treatment mainly focusing on cholinergic therapy has been clinically evaluated by randomized, double-blind, placebo- controlled, parallel-group studies measuring performance-based tests of cognitive function, activities of daily living, and behavior. Cholinesterase inhibitors, including donepezil, tacrine, rivastigmine, and galantamine are the recommended treatment of cognitive disturbance in patients with Alzheimer's disease. The role of estrogen replacement, anti-inflammatory agents, and antioxidants is controversial and needs further study. Antidepressants, antipsychotics, mood stabilizers, anxiolytics, and hypnotics are used for the treatment of behavioral disturbance. Future directions in the research and treatment of patients with Alzheimer's disease include: applying functional brain imaging techniques in early diagnosis and evaluation of treatment efficacy; development of new classes of medications working on different neurotransmitter systems (cholinergic, glutamatergic, etc), both for the treatment of the cognitive deficit and the treatment of the behavioral disturbances; and developing preventive methods (amyloid p-peptide immunizations and inhibitors of β-secretase and γ-secretase).

KEYWORDS: Alzheimer's disease, etiology, epidemiology, apolipoprotein E4,

cholinesterase inhibitor, antioxidant, anti-inflammatory agent, estrogen replacement therapy, behavioral disturbance.

Alzheimer's disease (AD) is a significant public health problem secondary to the increased life expectancy of the general population and a better appreciation of the socioeconomic consequences of the disease. It was defined by Alois Alzheimer in 1906 using criteria of progressive memory loss, disorientation, and pathological markers (senile plaques and neurofibrillary tangles).

2. INTRODUCTION

Alzheimer’s disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tas CVks. In most people with the disease—those with the late-onset type—symptoms first appear in their mid-60s. Early-onset Alzheimer’s occurs between a person’s 30s and mid-60s and is very rare. Alzheimer’s disease is the most common cause of dementia among older adults.Older woman with Alzheimer's looking out of a window

The disease is named after Dr. Alois Alzheimer. In 1906, Dr. Alzheimer noticed changes in the brain tissue of a woman who had died of an unusual mental illness. Her symptoms included memory loss, language problems, and unpredictable behavior. After she died, he examined her brain and found many abnormal clumps (now called amyloid plaques) and tangled bundles of fibers (now called neurofibrillary, or tau, tangles).

These plaques and tangles in the brain are still considered some of the main features of Alzheimer’s disease. Another feature is the loss of connections between nerve cells (neurons) in the brain. Neurons transmit messages between different parts of the brain, and from the brain to muscles and organs in the body. Many other complex brain changes are thought to play a role in Alzheimer’s, too.

This damage initially appears to take place in the hippocampus, the part of the brain essential in forming memories. As neurons die, additional parts of the brain are affected. By the final stage of Alzheimer’s, damage is widespread, and brain tissue has shrunk significantly. Is Alzheimer's Disease?

Alzheimer’s disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks. In most

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3. History

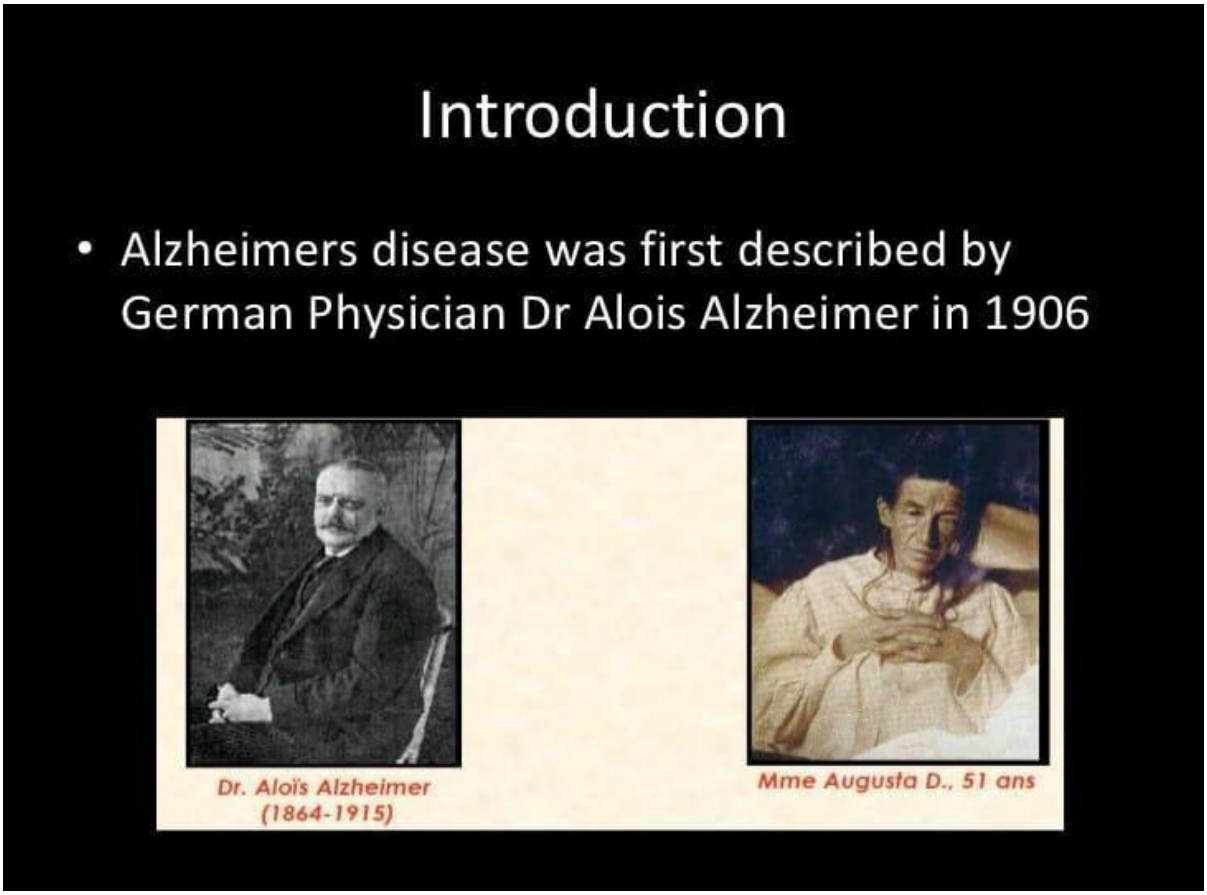


Fig No 1: Alois Alzheimer's patient Auguste Deter in 1902. Hers was the first described case of what became known as Alzheimer's disease.

The ancient Greek and Roman philosophers and physicians associated old age with increasing dementia. It was not until 1901 that German psychiatrist Alois Alzheimer identified the first case of what became known as Alzheimer's disease, named after him, in a fifty-year-old woman he called Auguste D. He followed her case until she died in 1906, when he first reported publicly on it. During the next five years, eleven similar cases were reported in the medical literature, some of them already using the term Alzheimer's disease. The disease was first described as a distinctive disease by Emil Kraepelin after suppressing some of the clinical (delusions and hallucinations) and pathological features (arteriosclerotic changes) contained in the original report of Auguste D. He included Alzheimer's disease, also

named presenile dementia by Kraepelin, as a subtype of senile dementia in the eighth edition of his Textbook of Psychiatry, published on 15 July, 1910.

For most of the 20th century, the diagnosis of Alzheimer's disease was reserved for individuals between the ages of 45 and 65 who developed symptoms of dementia. The terminology changed after 1977 when a conference on AD concluded that the clinical and pathological manifestations of presenile and senile dementia were almost identical, although the authors also added that this did not rule out the possibility that they had different causes. This eventually led to the diagnosis of Alzheimer's disease independent of age. The term senile dementia of the Alzheimer type (SDAT) was used for a time to describe the condition in those over 65, with classical Alzheimer's disease being used to describe those who were younger. Eventually, the term Alzheimer's disease was formally adopted in medical nomenclature to describe individuals of all ages with a characteristic common symptom pattern, disease course, and neuropathology

4. ALZHEIMER'S DISEASE

Alzheimer's (AHLZ-high-merz) is a disease of the brain that causes problems with memory, thinking and behavior. It is not a normal part of aging. Alzheimer's gets worse over time. Although symptoms can vary widely, the first problem many people notice is forgetfulness severe enough to affect their ability to function at home or at work, or to enjoy hobbies. The disease may cause a person to become confused, get lost in familiar places, misplace things or have trouble with language. It can be easy to explain away unusual behavior as part of normal aging, especially for someone who seems physically healthy. Any concerns about memory loss should be discussed with a doctor.

Alzheimer's disease More than 5 million Americans have Alzheimer's disease, the most common form of dementia. Alzheimer's accounts for 60 to 80 percent of all dementia cases. That includes 11 percent of those age 65 and older and one-third of those 85 and older. The disease also impacts more than 15 million family members, friends and caregivers. Dementia Dementia is a general term for the loss of memory and other cognitive abilities serious enough to interfere with daily life. Other types of dementia » Vascular dementia is a decline in thinking skills caused by conditions that block or reduce blood flow to the brain, depriving brain cells of vital oxygen and nutrients. These changes sometimes occur suddenly following strokes that block major brain blood vessels. It is widely considered the second most common cause of dementia after Alzheimer's disease.

» Mixed dementia is a condition in which abnormalities characteristic of more than one type of dementia occur simultaneously. Symptoms may vary, depending on the types of brain changes involved and the brain regions affected, and may be similar to or even indistinguishable from those of Alzheimer's or another dementia.

» Parkinson's disease dementia is an impairment in thinking and reasoning that many people with Parkinson's disease eventually develop. As brain changes gradually spread, they often begin to affect 3 mental functions, including memory and the ability to pay attention, make sound judgments and plan the steps needed to complete a task.

5. Classification

(1) FAD v SAD: Familial AD versus Sporadic AD

- No complete consensus
- Usually FAD = at least 1 first degree relative affected
- Sometimes 2 second degree relatives

(2) Early v Late Onset

- Early onset = usually before 65
- Early onset correlated with FAD
- LOAD = late onset AD

6. Causes

Alzheimer's disease is believed to occur when abnormal amounts of proteins, amyloids and possibly tau proteins, form in the brain and begin to encroach upon the organ's cells. The resultant plaque disrupts normal function and chemistry, and leads to a significant deficit of neurotransmitters, resulting in a progressive loss of brain function. As for why these protein 'malfunctions' occur in the first place, the ultimate cause is poorly understood, and subject to ongoing research and speculation.

The cause for most Alzheimer's cases is still mostly unknown except for 1% to 5% of cases where genetic differences have been identified. Several competing hypotheses exist trying to explain the cause of the disease.

Genetic

The genetic heritability of Alzheimer's disease (and memory components thereof), based on

reviews of twin and family studies, ranges from 49% to 79%. Around 0.1% of the cases are familial forms of autosomal (not sex-linked) dominant inheritance, which have an onset before age 65. This form of the disease is known as early onset familial Alzheimer's disease. Most of autosomal dominant familial AD can be attributed to mutations in one of three genes: those encoding amyloid precursor protein (APP) and presenilins PSEN1 and PSEN2. Most mutations in the APP and presenilin genes increase the production of a small protein called Aβ42, which is the main component of senile plaques. Some of the mutations merely alter the ratio between Aβ42 and the other major forms— particularly Aβ40—without increasing Aβ42 levels. Two other genes associated with autosomal dominant Alzheimer's disease are ABCA7 and SORL1.

Cholinergic hypothesis

Osaka mutation

A Japanese pedigree of familial Alzheimer's disease was found to be associated with a deletion mutation of codon 693 of APP. This mutation and its association with Alzheimer's disease was first reported in 2008. This mutation is known as the Osaka mutation. Only homozygotes with this mutation develop Alzheimer's disease.

Tau hypothesis

In Alzheimer's disease, changes in tau protein lead to the disintegration of microtubules in brain cells.

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. This may result first in malfunctions in biochemical communication between neurons and later in the death of the cells.

Other hypotheses

An inflammatory hypothesis is that AD is caused by a self-perpetuating progressive inflammation in the brain culminating in neurodegeneration. A possible role of chronic periodontal infection and the gut microbiota has been suggested.

A neurovascular hypothesis stating that poor functioning of the blood–brain barrier may be

involved has been proposed. Spirochete infections have also been linked to dementia.

Smoking is a significant AD risk factor. Systemic markers of the innate immune system are risk factors for late-onset AD.

7. Signs and symptoms

Effects of ageing on memory but not AD

Forgetting things occasionally

Misplacing items sometimes

Minor short-term memory loss

Not remembering exact details

Early stage Alzheimer's

Not remembering episodes of forgetfulness

Forgets names of family or friends

Changes may only be noticed by close friends or relatives

Some confusion in situations outside the familiar

Middle stage Alzheimer's

Greater difficulty remembering recently learned information

Deepening confusion in many circumstances

Problems with sleep

Trouble determining their location

Late stage Alzheimer's

Poor ability to think

Problems speaking

Repeats same conversations

8. Stages of Alzheimer’s Disease

Every person with Alzheimer’s experiences the disease differently, but people tend to experience a similar trajectory from the beginning of the illness to its end. The precise number of stages of Alzheimer’s is somewhat arbitrary. Some experts use a simple three-phase model (early, moderate and end), while others have found a granular breakdown to be a more useful aid to understanding the progression of the illness. What Are the 7 Stages of Alzheimer’s Disease?

The most common system, developed by Dr. Barry Reisberg of New York University, breaks

the progression of Alzheimer's disease into seven stages. This framework for understanding the progression of the disease has been adopted and used by a number of healthcare providers as well as the Alzheimer's Association.

Here is a summary of the seven stages of Alzheimer's based on Dr. Resiberg's system:

Stage 1: No Impairment

During this stage, Alzheimer's is not detectable and no memory problems or other symptoms of dementia are evident.

Stage 2: Very Mild Decline

The senior may notice 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 person will still do well on memory tests and the disease is unlikely to be detected by loved ones or physicians.

Stage 3: Mild Decline

At this stage, the family members and friends of the senior may begin to notice cognitive problems. Performance on memory tests are affected and physicians will be able to detect impaired cognitive function.

People in stage 3 will have difficulty in many areas including

Finding the right word during conversations

Organizing and planning

Remembering names of new acquaintances

People with stage three Alzheimer's may also frequently lose personal possessions, including valuables.

Stage 4: Moderate Decline

In stage four of Alzheimer's, clear-cut symptoms of the disease are apparent. People with stage four of Alzheimer's:

Have difficulty with simple arithmetic

Have poor short-term memory (may not recall what they ate for breakfast, for example)

Inability to manage finance and pay bills May forget details about their life histories.

Stage 5: Moderately Severe Decline

During the fifth stage of Alzheimer's, people begin to need help with many day-to-

day activities. People in stage five of the disease may experience.

Difficulty dressing appropriately

Inability to recall simple details about themselves such as their ownphone number

Significant confusion

On the other hand, people in stage five maintain functionality. They typically can still bathe and toilet independently. They also usually still know their family members and some detail about their personal histories, especially their childhood and youth.

Stage 6: Severe Decline

People with the sixth stage of Alzheimer's need constant supervision and frequently require professional care. Symptoms include.

Confusion or unawareness of environment and surroundings

Inability to recognize faces except for the closest friends and relatives

Inability to remember most details of personal history

Loss of bladder and bowel control

Major personality changes and potential behavior problems

The need for assistance with activities of daily living such as toileting and bathing Wandering.

Stages 7: Very Severe Decline

Stage seven is the final stage of Alzheimer's. Because the disease is a terminal illness, people in stage seven are nearing death. In stage seven of the disease, people lose the ability to communicate or respond to their environment. 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 Alzheimer's, people may lose their ability to swallow.

9. Pathophysiology

Histopathologic images of Alzheimer's disease, in the CA3 area of the hippocampus, showing an amyloid plaque (top right), neurofibrillary tangles (bottom left), and granulovacuolar degeneration (bottom center).

Neuropathology

Alzheimer's disease is characterised by loss of neurons and synapses in the cerebral cortex and certain subcortical regions. This loss results in gross atrophy of the affected regions,

including degeneration in the temporal lobe and parietal lobe, and parts of the frontal cortex and cingulate gyrus. Degeneration is also present in brainstem nuclei like the locus coeruleus. Studies using MRI and PET have documented reductions in the size of specific brain regions in people with AD as they progressed from mild cognitive impairment to Alzheimer's disease, and in comparison with similar images from healthy older adults.

Both Aβ plaques and neurofibrillary tangles are clearly visible by microscopy in brains of those afflicted by AD, especially in the hippocampus. Plaques are dense, mostly insoluble deposits of beta-amyloid peptide and cellular material outside and around neurons. Tangles (neurofibrillary tangles) are aggregates of the microtubule-associated protein tau which has become hyperphosphorylated and accumulate inside the cells themselves. Although many older individuals develop some plaques and tangles as a consequence of ageing, the brains of people with AD have a greater number of them in specific brain regions such as the temporal lobe. Lewy bodies are not rare in the brains of people with AD.

Disease mechanism

Exactly how disturbances of production and aggregation of the beta-amyloid peptide give rise to the pathology of AD is not known. The amyloid hypothesis traditionally points to the accumulation of beta-amyloid peptides as the central event triggering neuron degeneration. Accumulation of aggregated amyloid fibrils, which are believed to be the toxic form of the protein responsible for disrupting the cell's calcium ion homeostasis, induces programmed cell death (apoptosis). It is also known that Aβ selectively builds up in the mitochondria in the cells of Alzheimer's-affected brains, and it also inhibits certain enzyme functions and the utilisation of glucose by neurons.

Various inflammatory processes and cytokines may also have a role in the pathology of Alzheimer's disease. Inflammation is a general marker of tissue damage in any disease, and may be either secondary to tissue damage in AD or a marker of an immunological response. There is increasing evidence of a strong interaction between the neurons and the immunological mechanisms in the brain. Obesity and systemic inflammation may interfere with immunological processes which promote disease progression.

Alterations in the distribution of different neurotrophic factors and in the expression of their receptors such as the brain-derived neurotrophic factor (BDNF) have been described inAD.

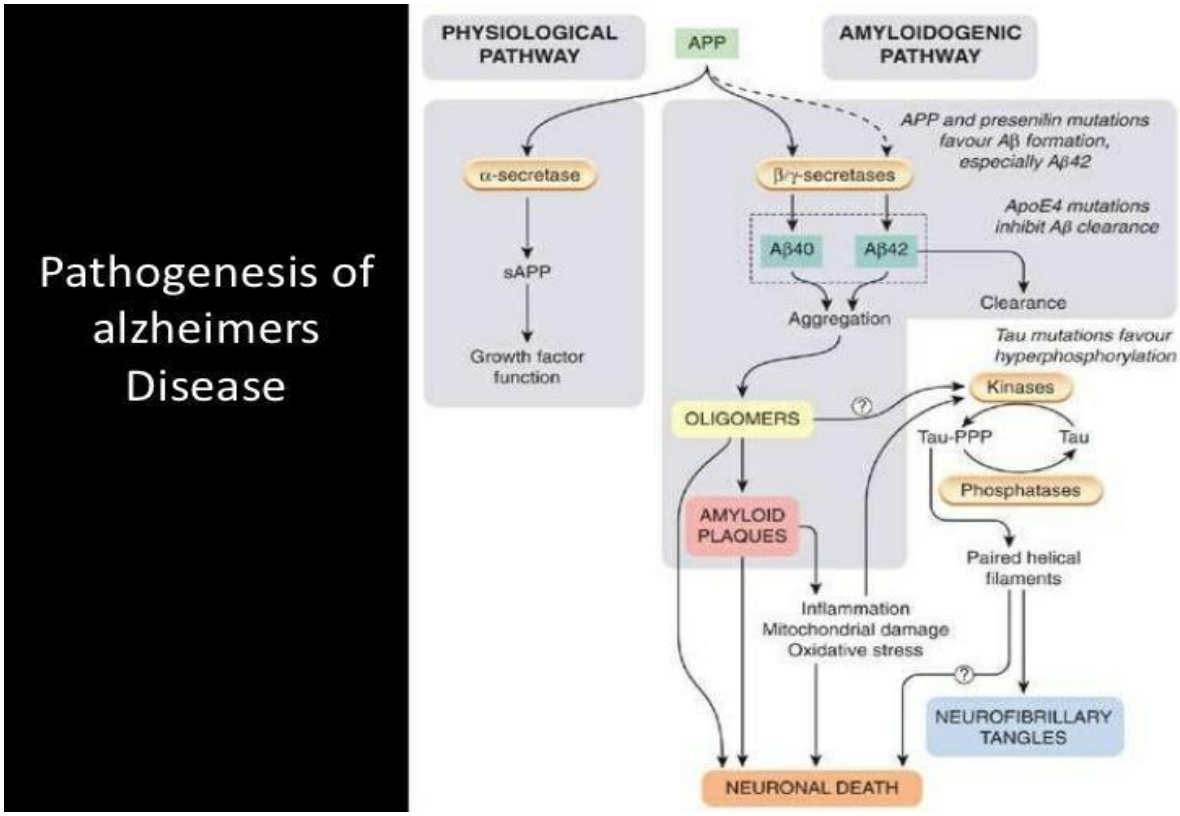


Fig No: 02: Pathogenesis of Alzheimers.

10. HOW ALZHEIMER'S AFFECTS THE BRAIN

The changes that take place in the brain begin at the microscopic level long before the first signs of memory loss. What goes wrong in the brain The brain has 100 billion nerve cells (neurons). Each nerve cell connects to many others to form communication networks. In addition to nerve cells, the brain includes cells specialized to support and nourish other cells. Groups of nerve cells have special jobs. Some are involved in thinking, learning and memory. Others help us see, hear, smell and tell our muscles when to move. Brain cells operate like tiny factories. They receive supplies, generate energy, construct equipment and get rid of waste. Cells also process and store information and communicate with other cells. Keeping everything running requires coordination as well as large amounts of fuel and oxygen. Scientists believe Alzheimer's disease prevents parts of a cell's factory from running well. They are not sure where the trouble starts. But just like a real factory, backups and breakdowns in 5 one system cause problems in other areas. As damage spreads, cells lose their ability to do their jobs and, eventually, die.

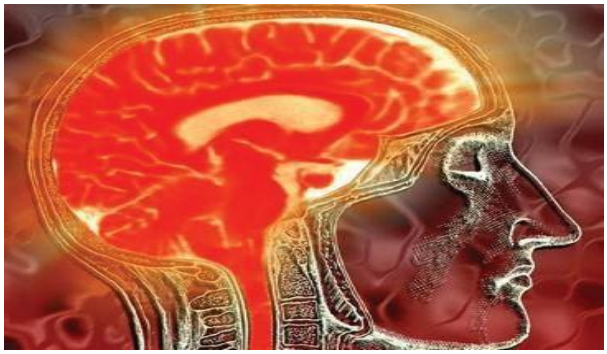


Fig. No 03: Most TAKE A CLOSER LOOK Take our Inside the Brain.

The role of plaques and tangles The brains of individuals with Alzheimer's have an abundance of plaques and tangles. Plaques are deposits of a protein fragment called beta-amyloid that build up in the spaces between nerve cells. Tangles are twisted fibers of another protein called tau that build up inside cells. Though autopsy studies show that most people develop some plaques and tangles as they age, those with Alzheimer's tend to develop far more and in a predictable pattern, beginning in the areas important for memory before spreading to other regions. Scientists do not know exactly what role plaques and tangles play in Alzheimer's disease.

How Alzheimer's spreads in the brain

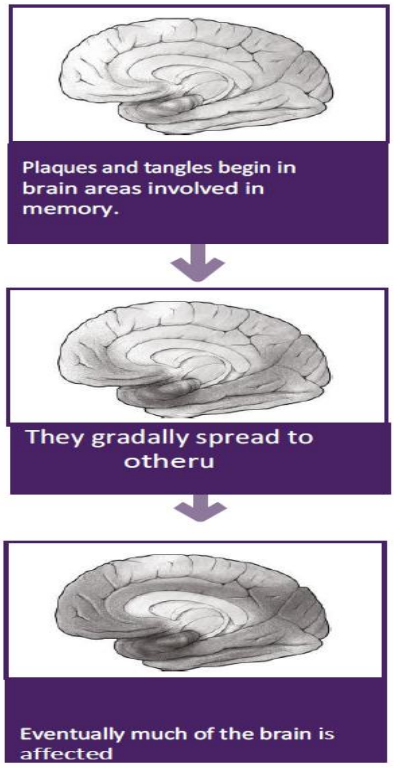


Fig. No. 04.

11. Diagnosis

PET scan of the brain of a person with AD showing a loss of function in the temporal lobe Alzheimer's disease is usually diagnosed based on the person's medical history, history from relatives, and behavioural observations. The presence of characteristic neurological and neuropsychological features and the absence of alternative conditions is supportive. Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single-photon emission computed tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia. Moreover, it may predict conversion from prodromal stages (mild cognitive impairment) to Alzheimer's disease.

Criteria

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA, now known as the Alzheimer's Association) established the most commonly used NINCDS-ADRDA Alzheimer's Criteria for diagnosis in 1984, extensively updated in 2007. These criteria require that the presence of cognitive impairment, and a suspected dementia syndrome.

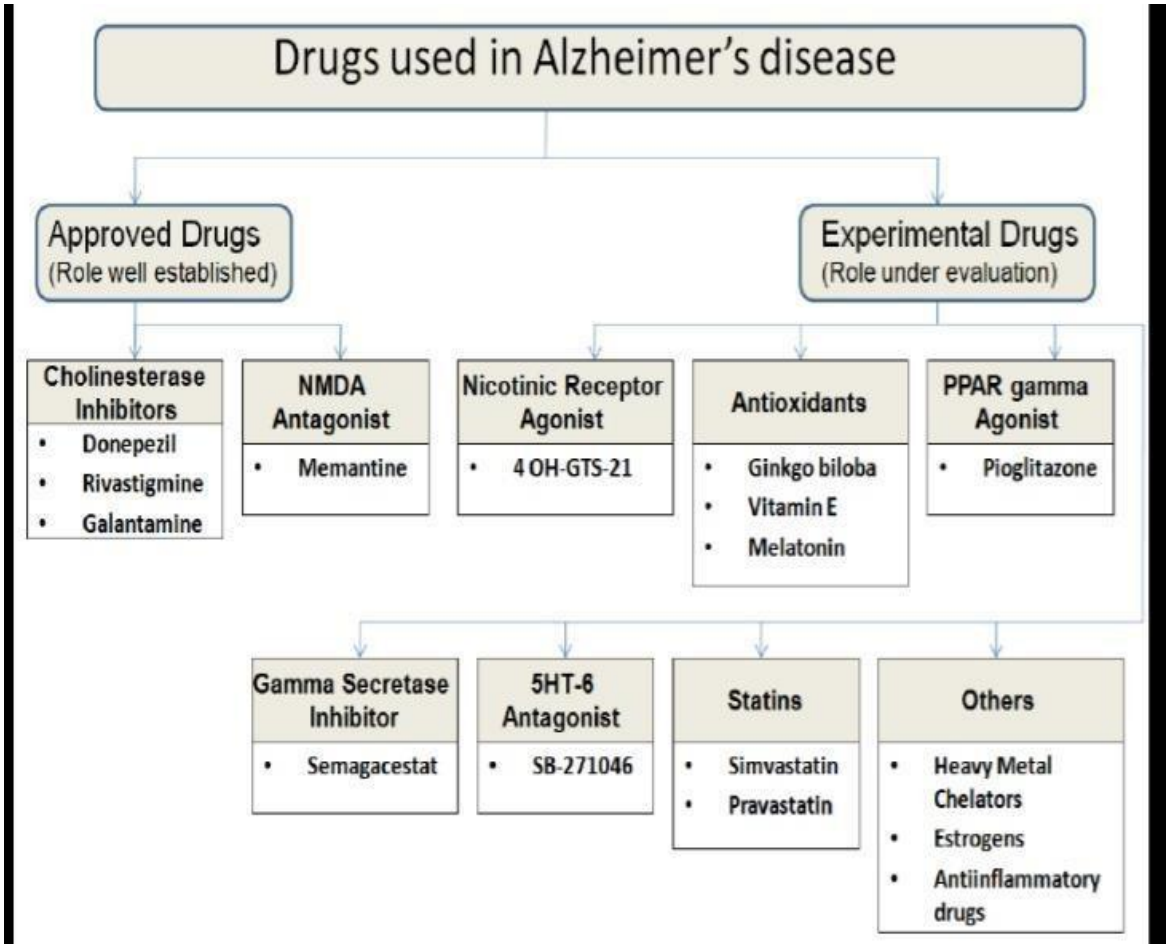
Techniques

Neuropsychological screening tests can 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. Neurological examination in early AD will usually provide normal results, except for obvious cognitive impairment, which may not differ from that resulting from other diseases processes, including other causes of dementia.

12. ANTI-ALZHEIMER'S DRUG

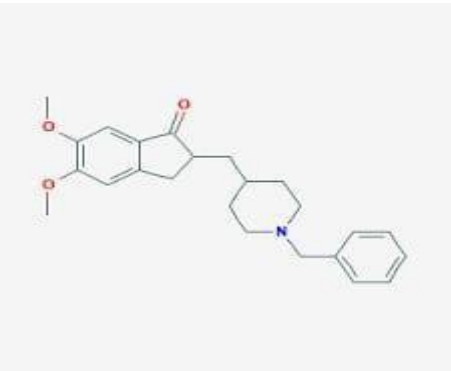
Classifications



Classification of Anti-alzheimer's drugs 1.Approved Drugs

A. Cholinesterase inhibitors

a) Donepezil



Structure of Donepezil

Mechanism of action

Donepezil hydrochloride is a piperidine derivative and a centrally acting, rapid, reversible inhibitor of acetylcholinesterase. Acetylcholinesterase is an enzyme that degrades acetylcholine after release from the presynapse. Donepezil binds reversibly to acetylcholinesterase and inhibits the hydrolysis of acetylcholine, thus increasing the availability of acetylcholine at the synapses, enhancing cholinergic transmission. Some in vitro data has suggested that anticholinesterase activity of donepezil is relatively specific for acetylcholinesterase in the brain. It is structurally unrelated to other anticholinesterase agents like tacrine and physostigmine.

Some noncholinergic mechanisms have also been proposed. Donepezil upregulates the nicotinic receptors in the cortical neurons, adding to neuroprotective property. It inhibits voltage-activated sodium currents reversibly and delays rectifier potassium currents and fast transient potassium currents, although this action is unlikely to contribute to clinical effects.

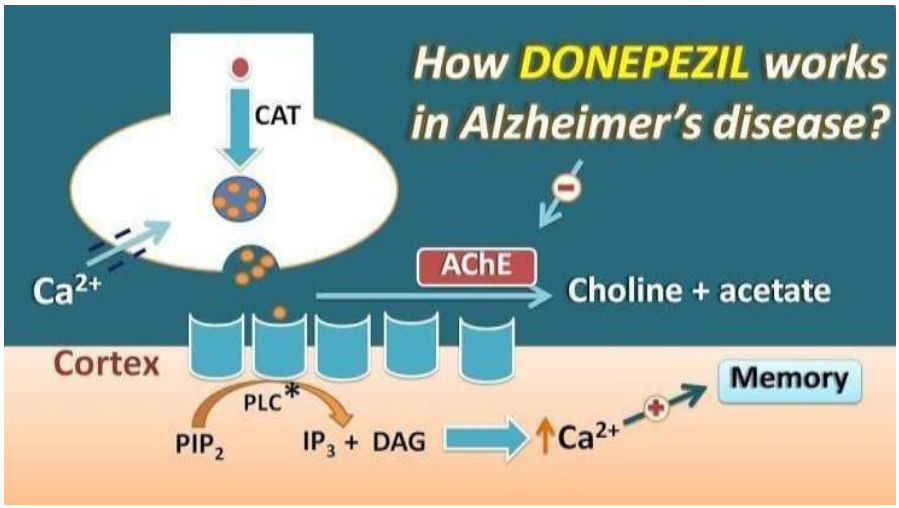


Fig No. 05: Mechanism of action of Donepezil Long plasma half life 70 hrs.

Dose-5-10 mg daily

Several controlled trials have shown modest benefits in cognition and behaviour

- Not hepatotoxic.
- Adverse effects: Nausea, diarrhoea, vomiting, fatigue, muscle cramps, bradycardia.

DONEPEZIL5MGB RANDSIN INDIA

Product	Company	Price Action
Donecept 5 Mg Tablet 10s	Cipla	105.04
Dopezil-5mg	Ranbaxy	106.26
Alzil 5mg Tablet 10s	Intas	106.55
Donep-5 Tab	Alkem Labs	171.35

Fig No: 06 USES OF DONEPEZIL 5MG

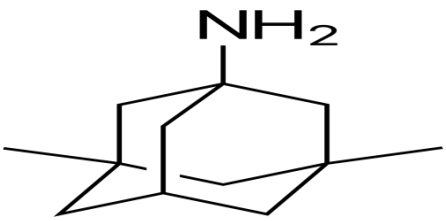
Donepezil is used in the treatment of Alzheimer's disease . SIDE EFFECTS OF DONEPEZIL 5MG.

Nausea, vomiting, anorexia, wt loss, diarrhoea, insomnia, fatigue, muscle cramps; headache and dizziness; syncope, bradyca Fig No: 06.

Fig No: 06.

B.NMDA ANTAGONIST

a) Memantine



structure Memantine

Mechanism of action

Memantine is a clinically useful drug in many neurological disorders, including Alzheimer's disease. The principal mechanism of action of memantine is believed to be the blockade of

current flow through channels of N-methyl-d- aspartate (NMDA) receptors--a glutamate receptor subfamily broadly involved in brain function.

Molecular Formula C12H21N

MECHANISM OF ACTION

NMDA receptor antagonist approved for treatment of moderate to severe AD

- Uncompetitive
- low affinity
- voltage dependent
- Interacts with Mg2+ binding site of channel to prevent excessive excitation while sparing normal functions

BRAND NAME Namenda XR, and Namenda

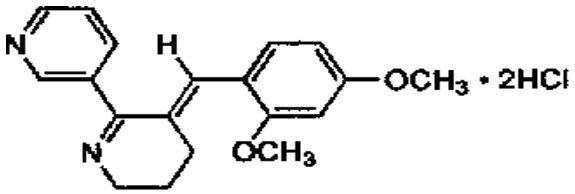
Fig no. 7.

2. EXPERIMENTAL DRUGS A.Nicotinic Receptor Agonist

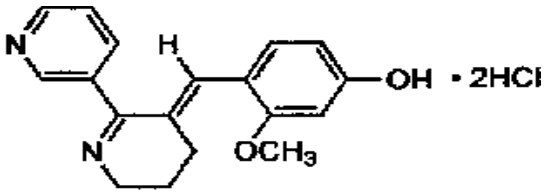
- a4B2 & a7 nicotinic receptor types localized in areas of brain associated with dementia and memory loss a7 nicotinic receptor agonist.

a) 4 OH-GTS21

- Protective action on cholinergic neurons.
- Antiamnestic effect in Alzheimers disease type amnesia
- EVP-6124: Currently in phase2 4OH-GST-21



GTS-21



4-OH-GTS-21

Structure

Mechanism of action

Auditory sensory gating, a biological measurement of the ability to suppress the evoked response to the second of two auditory stimuli, is diminished in people with schizophrenia. Deficits in sensory gating are associated with attentional impairment, and may contribute to cognitive symptoms and perceptual disturbances. This inhibitory process, which involves the alpha(7) nicotinic receptor mediated release of gamma-aminobutyric acid (GABA) by hippocampal interneurons, represents a potential new target for therapeutic intervention in schizophrenia. GTS-21 is an orally active alpha-7 nicotinic acetylcholine (nACh) receptor agonist.

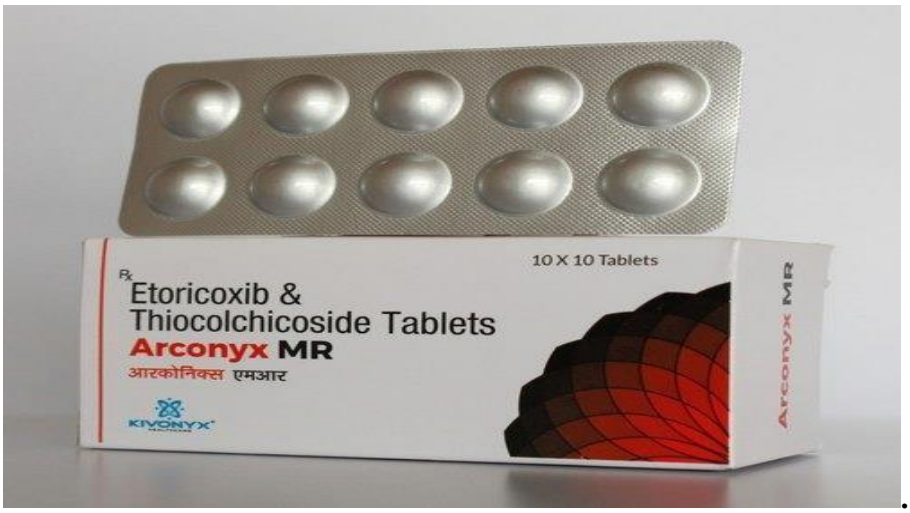


Fig No: 08

B. Antioxidants

a) Ginkgo biloba

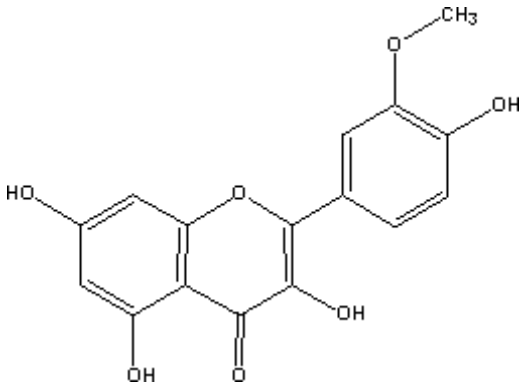
Ancient use in China and Japan as a tonic. Poor Circulation

- Inner ear disorders Absent

mindedness, Dementia, Depressio n, and Hypertension in the elderly

- Impotence in men

Chinese used leaves and nuts



Structure of Ginko Biloba

Mechanisms of action

May include anti oxidant neurotransmitter receptar modulatory and anti platelet activating factor properties. While safe caution is advise when recommending ginko to patients anti coagulant.

Name	Composition	Company
cerestar cap	Dried extract of Ginkgo biloba 60mg equiv. To Ginkgoflavonglycosides 14.4mg	solus
geritisin tab	Ginkgo biloba 40mg	f.d.c.
ginkoba tab	Ginkgo biloba 40mg	micro nova
ginkonex tab	Ginkgo biloba 40mg	nexus (india)

Fig no. 9: Side effects

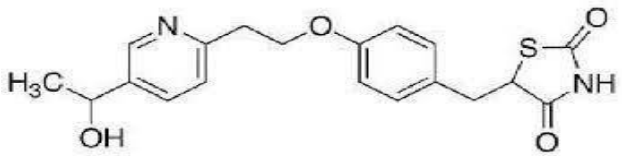
Hemorrhage, hematoma (rupture of blood vessels), and hyphema (bleeding in eye). In all trials <0.5% reported minor side effects including headaches, Gl distress and allergic skin reactions. Overall, ginkgo is relatively safe.

C. PPAR GAMA AGONIST

PPAR y agonists inhibit inflammatory gene expression, alter Amyloid B homeostasis & exhibit neuroprotective effects 15-30 mg pioglitazone daily in patients of AD

- Improved agitation & regional cerebral blood flow in parietal lobe
- cognitive and functional improvement

a) Pioglitazone



Structure of Pioglitazone

Mechanism of action

Pioglitazone selectively stimulates the nuclear receptor peroxisome proliferator- activated receptor gamma (PPAR-γ) and to a lesser extent PPAR-α. It modulates the transcription of the genes involved in the control of glucose and lipid metabolism in the muscle, adipose tissue.

Beand name	Company	Price (Rs.)
Piomed-15mg Tab	Ipca Labs	49.50
Pioglit 15mg Tab	Sun Pharma	51.00
Oglo-15 Tab	Panacea Biotec	61.49

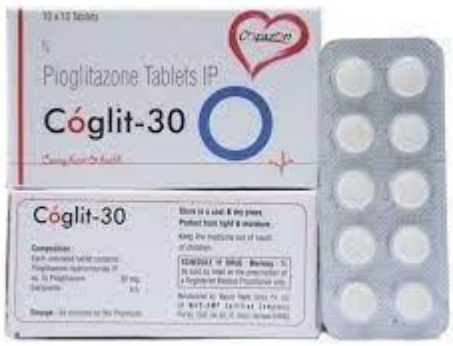


Fig no. 10.

D. GAMMA SECRETASE INHIBITOR•

Disease modifying agents in AD

a) Semagacestat

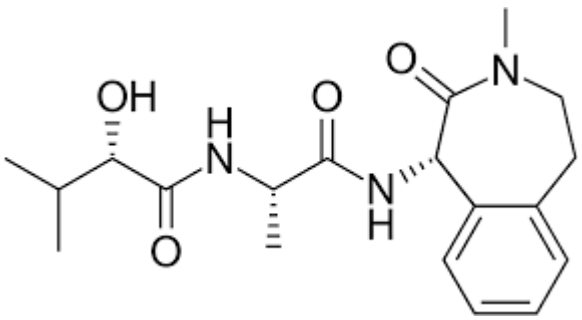
- 1 plasma and CSF A-B Concentratio

Phase 3 started in March 2008

- Interrupting Alzheimers Dementia by Evaluating Treatment of Amyloid Pathology (IDENTITY -1 Trial)

– IDENTITY -2 trial started in September 2008

- Did not slow disease progression & worsened cognition and the ability to perform activities of daily living
- frisk of skin cancer
- Eli Lily halted the development



Structure of semagacestat

Mechanism of action

Research on laboratory rats suggest that the soluble form of this peptide is a causative agent in the development of Alzheimer's. Semagacestat blocks the enzyme γ-secretase, which (along with β-secretase) is responsible for APP proteolysis.

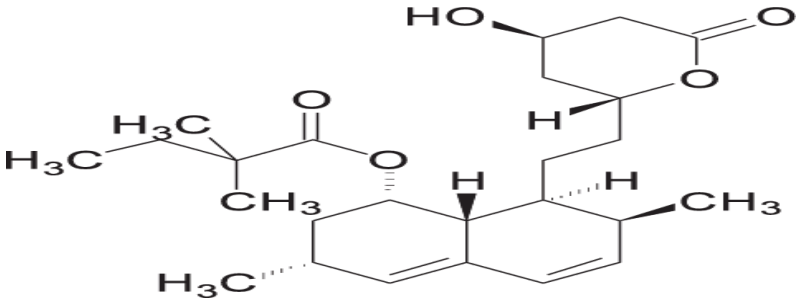
E. STATINS

Higher Cholesterol risk factor for AD

Lovastatin prevented death of nerve cells in animal experiments Results of various studies not promising

- No difference between drug and control in terms of dementia, cognitive function and neuropsychological tests

a) SIMVASTATIN



Structure of simvasratin

Mechanism of action

Simvastatin is in a class of medications called HMG-CoA reductase inhibitors (statins). It works by slowing the production of cholesterol in the body to decrease the amount of cholesterol that may build up on the walls of the arteries and block blood flow to the heart, brain, and other parts of the body.

Brand name

Simvastatin. Simvastatin(Zocor) generic is an HMG-CoA reductase inhibitor

Fig No 11.

13. Prevention

Intellectual activities such as playing chess or regular social interaction have been linked to a reduced risk of AD in epidemiological studies, although no causal relationship has been found.

There is no definitive evidence to support that any particular measure is effective in preventing AD. Global studies of measures to prevent or delay the onset of AD have often produced inconsistent results.

Medication

Cardiovascular risk factors, such as hypercholesterolaemia, hypertension, diabetes, and smoking, are associated with a higher risk of onset and worsened course of AD. Blood pressure medications may decrease the risk. Statins, which lower cholesterol however, have not been effective in preventing or improving the course of the disease.

Lifestyle

People who engage in intellectual activities such as reading books (but not newspapers), playing board games, completing crossword puzzles, playing musical instruments, or regular social interaction show a reduced risk for Alzheimer's disease. This is compatible with the cognitive reserve theory, which states that some life experiences result in more efficient neural functioning providing the individual a cognitive reserve that delays the onset of dementia manifestations. Physical exercise is also effective in reducing symptom severity in those with Alzheimer's disease.

Diet

People who maintain a healthy, Japanese, or Mediterranean diet have a reduced risk of AD. A Mediterranean diet may improve outcomes in those with the disease. 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.

14. RESULTS

The disease progression in mild to moderate AD patients across all available and relevant literature sources was estimated as 5.5 points per year. An Emax-type model best described the symptomatic drug effect of AChE inhibitors. The rate of disease progression (underlying disease progression) was no different between placebo and AChE-inhibitors groups. Baseline ADAS-cog is a significant covariate in disease progression. Baseline age was also tested as a covariate in the rate of disease progression, but the model was unable to describe any effects of age, likely because of the narrow distribution of mean age (literature-level analysis). There was no significant impact of publication year in the model.

15. CONCLUSIONS

Baseline ADAS-cog is a significant covariate affecting the rate of disease progression, and it describes or at least explains the different rates of deterioration evident in early or late stages

of the disease. There was no significant impact of publication year in the model, suggesting that disease progression has not slowed in more recent trials.

16. REFERENCES

1. K.D.Tripathi. Essentials of Medical Pharmacology, JAYPEE Brothers Medical Publishers (P) Ltd, New Delhi.
2. Rang H. P., Dale M. M., Ritter J. M., Flower R. J., Rang and Dale's Pharmacology, Churchil Livingstone Else.
3. Vinay Kumar, Abul K. Abas, Jon C. Aster; Robbins & Cotran Pathologic Basis of Disease; South Asia edition; India; Elsevier, 2014.
4. Harsh Mohan; Text book of Pathology; 6th edition; India; Jaypee Publications; 2010.
5. Laurence B, Bruce C, Bjorn K.; Goodman Gilman's The Pharmacological Basis of Therapeutics; 12th edition; New York; McGraw-Hill; 2011. Wilson and Giswold's Organic medicinal and Pharmaceutical Chemistry.vier.
6. https://www.slideshare.net/mobile/nasertadvi/drug-treatment-of-alzheimers- disease.
7. https://en.m.wikipedia.org/wiki/Alzheimer%27s_disease.
8. Burns A, Iliffe S (February 2009). "Alzheimer's disease". BMJ. 338: b158. doi:10.1136/bmj.b158. PMID 19196745. S2CID 8570146.
9. "Dementia Fact sheet". World Health Organization. September 2020.
10. Mendez MF (November 2012). "Early-onset Alzheimer's disease: nonamnestic subtypes and type 2 AD". Archives of Medical Research, 43(8): 677–85. doi:10.1016/j.arcmed.2012.11.009. PMC 3532551. PMID 23178565.
11. Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E (March 2011). "Alzheimer's disease". Lancet, 377(9770): 1019–31. doi:10.1016/S0140- 6736(10)61349-9. PMID 21371747. S2CID 20893019.
12. "Dementia diagnosis and assessment" (PDF). National Institute for Health and Care Excellence (NICE). Archived from the original (PDF) on 5 December 2014. Retrieved 30 November 2014.
13. Commission de la transparence (June 2012). "Drugs for Alzheimer's disease: best avoided. No therapeutic advantage" [Drugs for Alzheimer's disease: best avoided. No therapeutic advantage]. Prescrire International, 21(128): 150. PMID 22822592.
14. Querfurth HW, LaFerla FM (January 2010). "Alzheimer's disease". The New England Journal of Medicine, 362(4): 329–44. doi:10.1056/NEJMra0909142. PMID 20107219. S2CID 205115756.

15. GBD 2015 Disease Injury Incidence Prevalence Collaborators (October 2016). "Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015". Lancet, 388(10053): 1545–1602. doi:10.1016/S0140-6736(16)31678-6. PMC 5055577. PMID 27733282.
16. GBD 2015 Mortality Causes of Death Collaborators (October 2016). "Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015". Lancet, 388(10053): 1459–1544. doi:10.1016/S0140-6736(16)31012-1. PMC 5388903. PMID 27733281.
17. "Alzheimer's Disease Fact Sheet". National Institute on Aging. Retrieved 25 January 2021.
18. Todd S, Barr S, Roberts M, Passmore AP (November 2013). "Survival in dementia and predictors of mortality: a review". International Journal of Geriatric Psychiatry, 28(11): 1109–24. doi:10.1002/gps.3946. PMID 23526458. S2CID 25445595.
19. Hsu D, Marshall GA (2017). "Primary and Secondary Prevention Trials in Alzheimer Disease: Looking Back, Moving Forward". Current Alzheimer Research, 14(4): 426–40. doi:10.2174/1567205013666160930112125. PMC 5329133. PMID 27697063.
20. Thompson CA, Spilsbury K, Hall J, Birks Y, Barnes C, Adamson J (July 2007). "Systematic review of information and support interventions for caregivers of people with dementia". BMC Geriatrics. 7: 18. doi:10.1186/1471-2318-7-18. PMC 1951962. PMID 17662119.
21. Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S (April 2015). "Exercise programs for people with dementia". The Cochrane Database of Systematic Reviews (Submitted manuscript), 132(4): CD006489. doi:10.1002/14651858.CD006489.pub4. PMID 25874613.
22. National Institute for Health and Clinical Excellence. "Low-dose antipsychotics in people with dementia". National Institute for Health and Care Excellence (NICE). Archived from the original on 5 December 2014. Retrieved 29 November 2014.