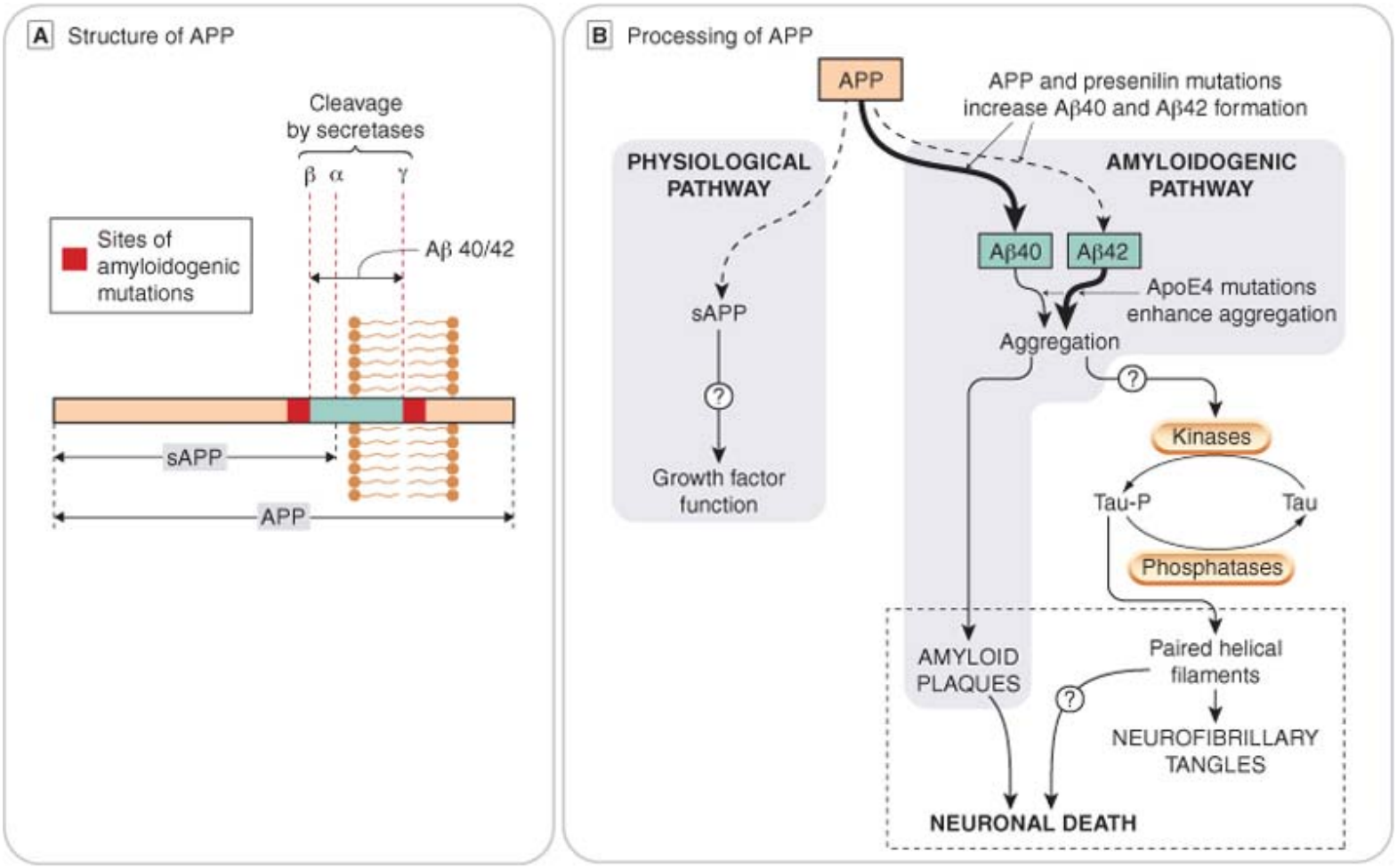
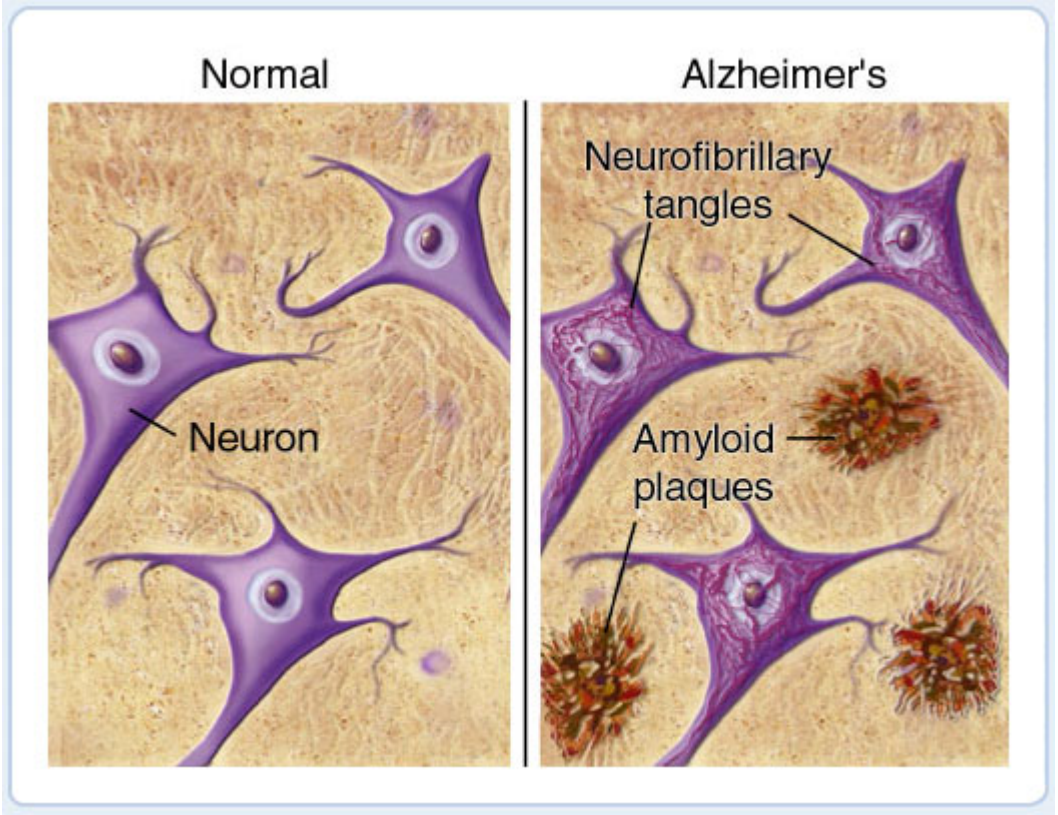
Alzheimer's disease

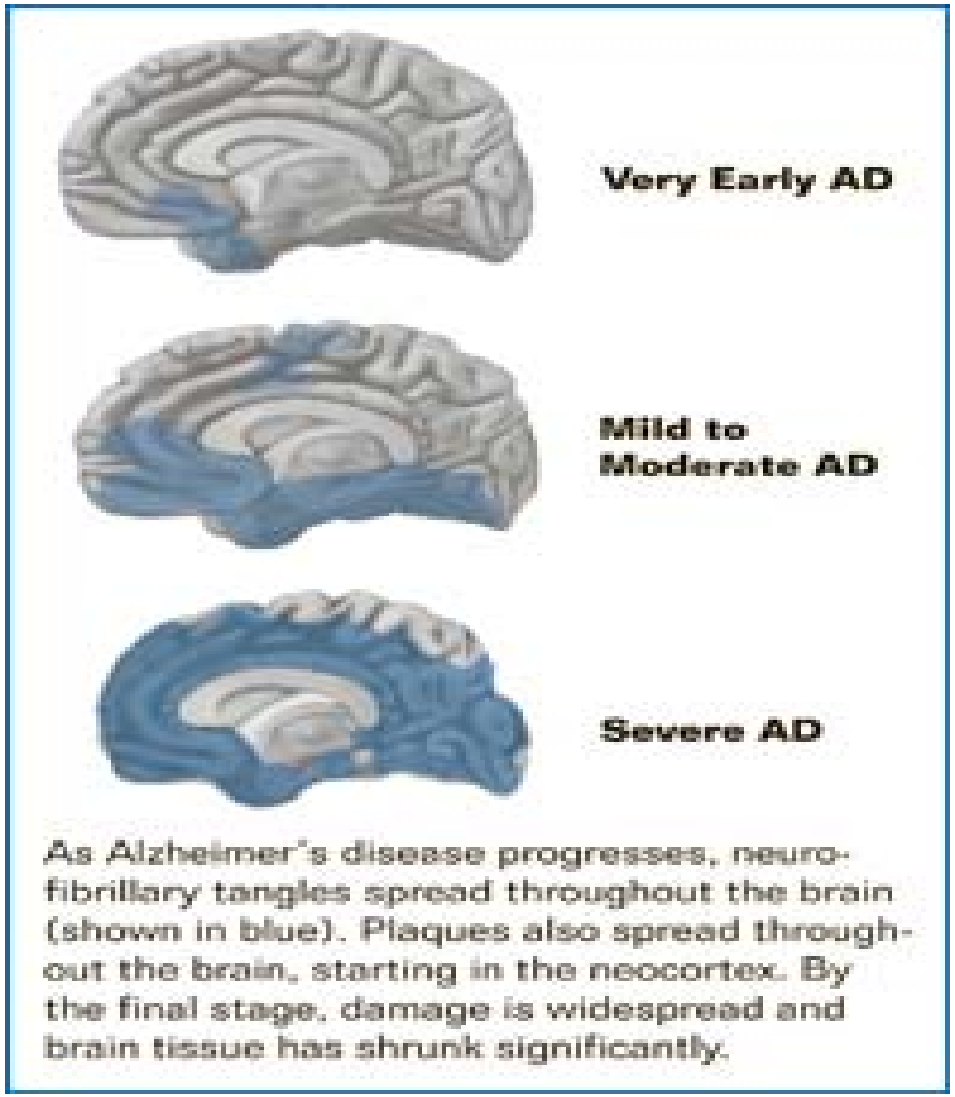
Alzheimer's disease

- Alzheimer's disease (AD) is a common age-related dementia distinct from vascular dementia associated with brain infarction.
- The main pathological features of AD comprise amyloid plaques, neurofibrillary tangles and a loss of neurons (particularly cholinergic neurons of the basal forebrain).
- Amyloid plaques consist of aggregates of the Aβ fragment of amyloid precursor protein (APP), a normal neuronal membrane protein, produced by the action of β- and γ-secretases. AD is associated with excessive Aβ formation, resulting in neurotoxicity.
- Familial AD (rare) results from mutations in the *APP* gene, or in *presenilin* genes (involved in γ-secretase function), both of which cause increased Aβ formation.
- Neurofibrillary tangles comprise intracellular aggregates of a highly phosphorylated form of a normal neuronal protein (Tau). The relationship of these structures to neurodegeneration is not known.
- Loss of cholinergic neurons (in Meynert nucleus (nucleus basilaris) is believed to account for much of the learning and memory deficit in AD, because they project to the frontal cortex and to hippocampus.

Pathogenesis of Alzheimer's disease

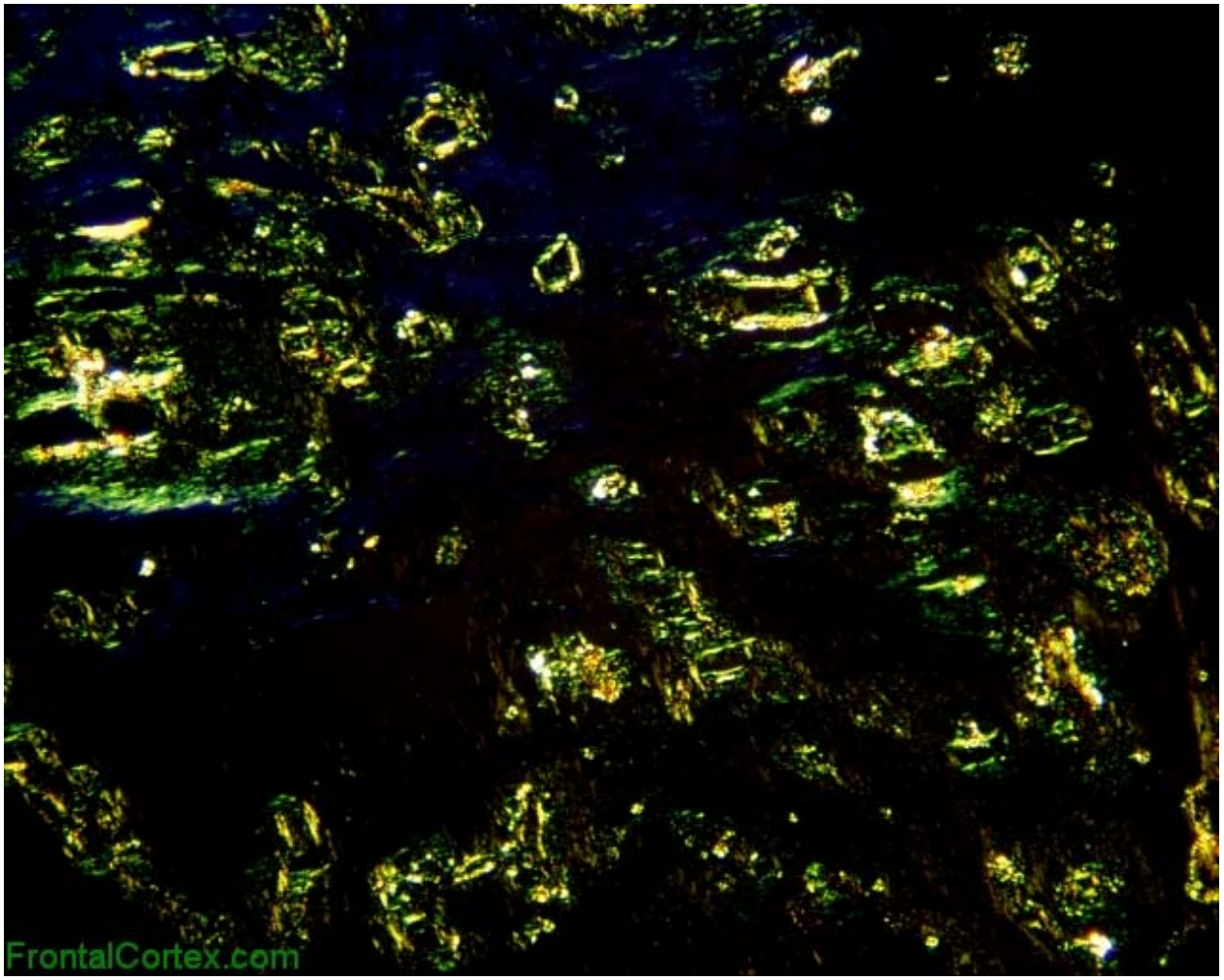



Normal
Alzheimer's
Neuron
Neurofibrillary tangles
Amyloid plaques

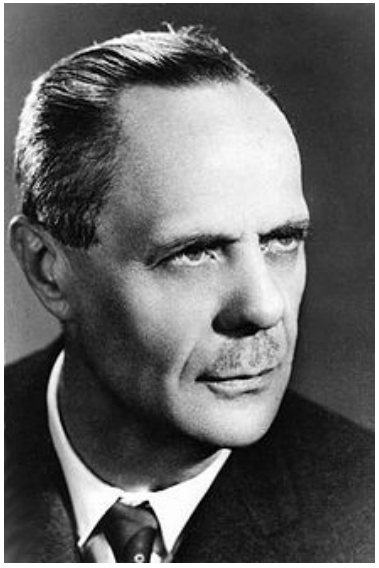


As Alzheimer's disease progresses, neurofibrillary tangles spread throughout the brain (shown in blue). Plaques also spread throughout the brain, starting in the neocortex. By the final stage, damage is widespread and brain tissue has shrunk significantly.

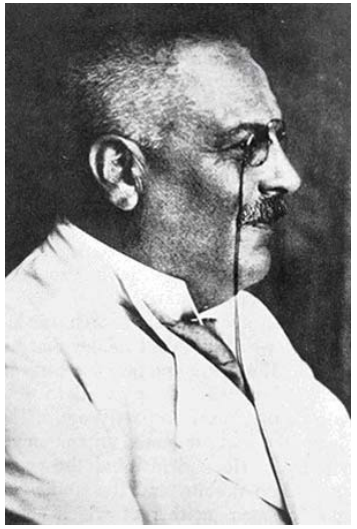
Amyloid is characterized by apple-green birefringence upon polarization of Congo red stained sections



Discoveries



Romhányi György (1905-1991)



Alois Alzheimer (1864-1915)

Stages of Alzheimer's Disease

1) Early Stage

- This is considered as a mild/early stage and the duration period is 2-4 years.
- Frequent recent memory loss, particularly of recent conversations and events.
- Repeated questions, some problems expressing and understanding language.
- Writing and using objects become difficult and depression and apathy can occur.
- Drastic personality changes may accompany functional decline.
- Need reminders for daily activities and difficulties with sequencing impact driving early in this stage.

Stages of Alzheimer's Disease

2) Second stage

- This is considered as a middle/moderate stage and the duration is 2-10 years.
- Can no longer cover up problems.
- Pervasive and persistent memory loss impacts life across settings.
- Rambling speech, unusual reasoning, confusion about current events, time, and place.
- Potential to become lost in familiar settings, sleep disturbances, and mood or behavioral symptoms accelerate.
- Nearly 80% of patients exhibit emotional and behavioral problems which are aggravated by stress and change.
- Slowness, rigidity, tremors, and gait problems impact mobility and coordination.
- Need structure, reminders, and assistance with activities of daily living.

Stages of Alzheimer's Disease

3) Moderate stage

- Increased memory loss and confusion.
- Problems recognizing family and friends.
- Inability to learn new things.
- Difficulty carrying out tasks that involve multiple steps (such as getting dressed).
- Problems coping with new situations.
- Delusions and paranoia.
- Impulsive behavior.
- In moderate AD, damage occurs in areas of the brain that control language, reasoning, sensory processing, and conscious thought

Stages of Alzheimer's Disease

4) Last stage

- This is considered as the severe stage and the duration is 1-3 years.
- Confused about past and present. Loss of recognition of familiar people and places
- Generally incapacitated with severe to total loss of verbal skills.
- Unable to care for self. Falls possible and immobility likely.
- Problems with swallowing, incontinence, and illness.
- Extreme problems with mood, behavioral problems, hallucinations, and delirium.
- Patients need total support and care, and often die from infections or pneumonia

Diagnosis

- Alzheimer's disease is usually diagnosed clinically from the patient history, collateral history from relatives, and clinical observations, based on the presence of characteristic neurological and neuropsychological features and the absence of alternative conditions.
- Advanced medical imaging with computed tomography (CT) or magnetic resonance imaging (MRI), and with single photon emission computer tomography (SPECT) or positron emission tomography (PET) can be used to help exclude other cerebral pathology or subtypes of dementia.
- The diagnosis can be confirmed with very high accuracy post-mortem when brain material is available and can be examined histologically.

Diagnosis

- 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.
- Psychological tests for depression are employed, since depression can either be concurrent with AD, an early sign of cognitive impairment, or even the cause.
- When available as a diagnostic tool, SPECT and PET neuroimaging are used to confirm a diagnosis of Alzheimer's in conjunction with evaluations involving mental status examination. In a person already having dementia, SPECT appears to be superior in differentiating Alzheimer's disease from other possible causes, compared with the usual attempts employing mental testing and medical history analysis.

Ach level elevation

- **Tacrine**, Trials showed modest improvements in tests of memory and cognition in about 40% of AD patients, but no improvement in other functional measures that affect quality of life. Tacrine has to be given four times daily and produces cholinergic side effects such as nausea and abdominal cramps, as well as **hepatotoxicity** in some patients, so it is far from an ideal drug. Later compounds, which also have limited efficacy but are more effective than tacrine in improving quality of life, include **donepezil, rivastigmine** and **galantamine** (extracts from the bulb of daffodil (Narcissus pseudonarcissus).

Used drugs in the treatment

- **Aricept**
  Donepezil

  Used to delay or slow the symptoms of AD
  - Loses its effect over time
  - Used for mild, moderate and severe AD
  - Does not prevent or cure AD

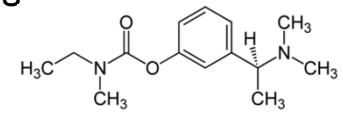
- **Celexa**
  Citalopram

  Used to reduce depression and anxiety
  - May take 4 to 6 weeks to work
  - Sometimes used to help people get to sleep

- **Depakote**
  Sodium Valproate

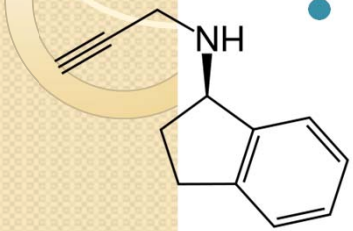
  Used to treat severe aggression
  - Also used to treat epilepsy

- **Exelon**
  Rivastigmine

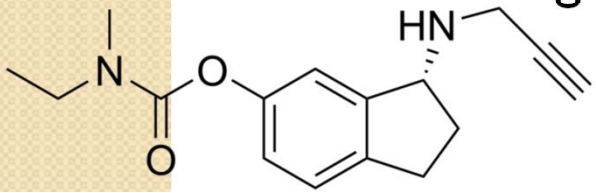
  

  Used to delay or slow the symptoms of AD
  - Loses its effect over time
  - Used for mild to moderate AD
  - Can get in pill form or as a skin patch
  - Does not prevent or cure AD

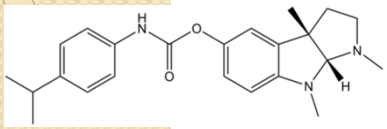
Drugs under development



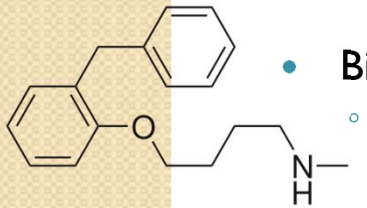
- Rasagiline
  - (Azilect, AGN 1135) is an irreversible inhibitor of monoamine oxidase used as a monotherapy in early Parkinson's disease or as an adjunct therapy in more advanced cases. It is selective for MAO type B over type A by a factor of fourteen.
- Ladostigil
  - Ladostigil (TV-3,326) is a novel neuroprotective agent being investigated for the treatment of neurodegenerative disorders like Alzheimer's disease, Lewy body disease, and Parkinson's disease.[1] It acts as a reversible acetylcholinesterase and butyrylcholinesterase inhibitor, and an irreversible monoamine oxidase B inhibitor, and combines the mechanisms of action of older drugs like rivastigmine and rasagiline into a single molecule.



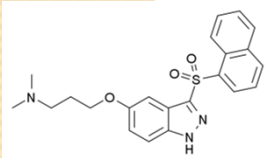
Drugs under development



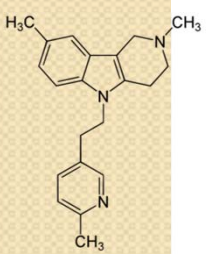
- Cymserine
  - Cymserine is a drug related to physostigmine, which acts as a reversible cholinesterase inhibitor, with moderate selectivity (15x) for the plasma cholinesterase enzyme butyrylcholinesterase, and relatively weaker inhibition of the more well known acetylcholinesterase enzyme. This gives it a much more specific profile of effects that may be useful for treating Alzheimer's disease without producing side effects like tremor, lacrimation and salivation that are seen with the older non-selective cholinesterase inhibitors currently used for this application, such as donepezil.



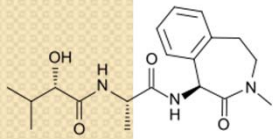
- Bifemelane
  - Bifemelane (Alnert, Celeport) is a pharmaceutical drug used in the treatment of senile dementia in Japan. It has nootropic, neuroprotective, and antidepressant effects, and acts through the cholinergic system in the brain.



- Cerlapirdine
  - Cerlapirdine (USAN; SAM-531, WAY-262,531, PF-05212365) is a drug which is under development by Wyeth/Pfizer for the treatment of cognitive disorders associated with Alzheimer's disease and schizophrenia.



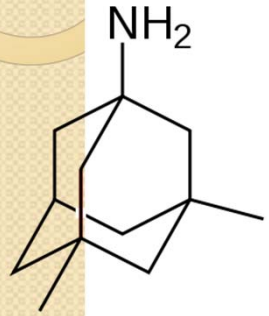
- Latrepirdine
  - Latrepirdine (INN, also known as dimebolin and sold as Dimebon), is an antihistamine drug which has been used clinically in Russia since 1983.



- Semagacestat
  - Semagacestat (LY450139) was a candidate drug for a causal therapy against Alzheimer's disease. It was originally developed by Eli Lilly and Élan, and clinical trials were conducted by Eli Lilly. Phase III trials included over 3000 patients,[2][3] but in August 2010, a disappointing interim analysis, in which semagacestat performed worse than the placebo, led to the trials being stopped.
  - Semagacestat blocks the enzyme γ-secretase, which (along with β-secretase) is responsible for APP proteolysis.

Drugs under development

- Mementine (NMDA receptor blocker)



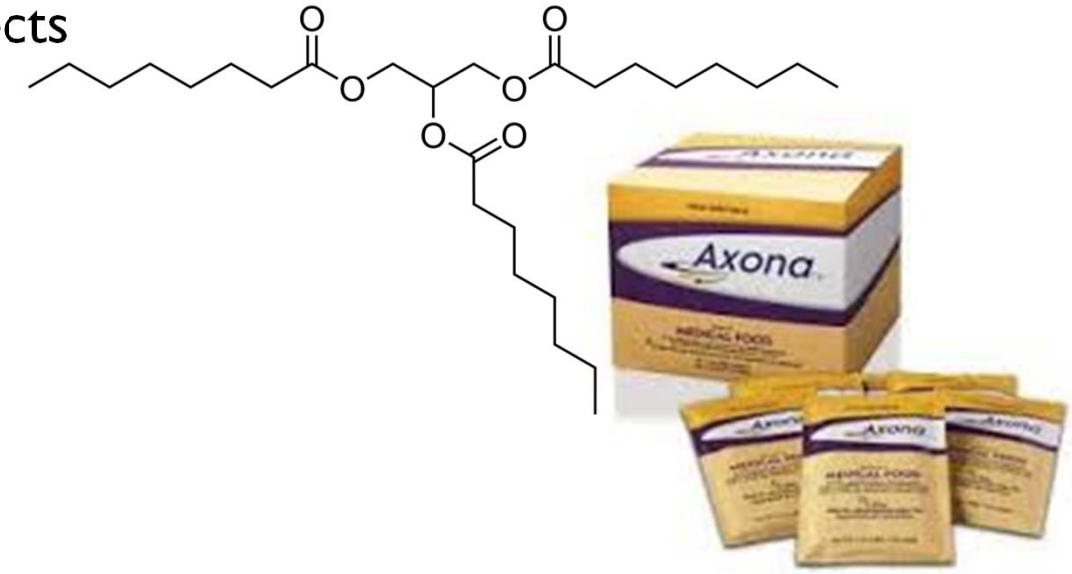
  - Memantine is the first in a novel class of Alzheimer's disease medications acting on the glutamatergic system by blocking NMDA-type glutamate receptors. It was first synthesized by Eli Lilly and Company in 1968. Memantine is marketed under the brands Axura and Akatinol by Merz, Namenda by Forest, Ebixa and Abixa by Lundbeck and Memox by Unipharm. Memantine has been shown to have a modest effect in moderate-to-severe Alzheimer's disease and in dementia with Lewy bodies. Despite years of research, there is little evidence of effect in mild Alzheimer's disease
- Beta-gamma secretase inhibitors (LY-450139, BMS-289948, BMS-299897)

NSAIDs

- **Ibuprofen** and **indometacin** have this effect, although other NSAIDs, such as **aspirin**, do not, nor do anti-inflammatory steroids such as **prednisolone**. Recent works suggest that NSAIDs may reduce Aβ42 formation by regulating γ-secretase, an effect unrelated to cyclo-oxygenase inhibition, by which NSAIDs reduce inflammation. It may therefore be possible to find compounds that target γ-secretase selectively without inhibiting cyclo-oxygenase, thus avoiding the side effects associated with current NSAIDs. Disappointingly, clinical trials with various NSAIDs have so far failed to show any effect on cognitive performance or disease progression in AD patients

Caprylidene (caprylic trigliceride, AXONA)

- Prescription medical food
- Metabolized to ketone bodies
- The brain can use these ketone bodies for energy when its ability to process glucose is impaired.
- Brain-imaging scans of older adults and those with Alzheimer disease reveal a dramatically decreased uptake of glucose.
- Adverse effects
  - >10%
    - Diarrhea
    - Flatulence
  - 1-10%
    - Dizziness
    - Headache
    - Dyspepsia



Multiple sclerosis

Etiology and pathogenesis

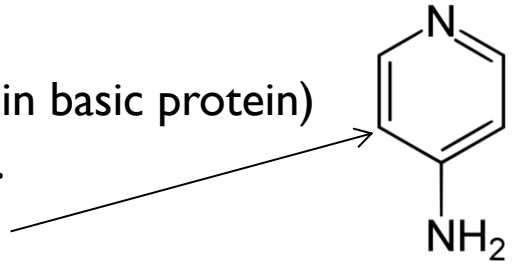
- Demyelinization of neurons
- Autoimmune or viral origin
- Inflammation and plaque formation in brain and spinal cord
- Pain, spasticity, weakness, ataxia, fatigue, problems with speach, vision, gait and bladder function
- Relapses and remissions

Treatment 1.

- Interferon beta-1b
  - MoA? (immunomodulating effect): NK cell activity↑, macrophage activity ↑, reduce interferon –γ (which can exacerbate MS)
  - Reduce the frequency of relapses
- Interferon beta-1a

Treatment 2.

- Natalizumab
  - Humanized monoclonal antibody against alpha-4 (α4) integrin → α4-integrin is required for white blood cells to move into organs
  - Reducing the ability of inflammatory immune cells to attach to and pass through the cell layers lining the intestines and blood–brain barrier.
  - Specific side effect: progressive multifocal leukoencephalopathy (PML) caused by JC virus.
- Mitoxantrone
  - Suppresses the activity of T, B cells and macrophages
- Glatiramer acetate
  - Synthetic protein (mimics the structure of myelin basic protein)
  - Myelin decoy → blocks myelin damaging T cells.
- Dalfampridine (4-AP, K^+ channel blocker)



- Fingolimod (sphingosine-1-phosphate receptor modulator): reduce lymphocytes migration

Amyotrophic lateral sclerosis (ALS)

- Lou Gehrig disease
- Defect of superoxide dismutase?
- Baclofen ($GABA_B$ agonist)
- Gabapentine
- Riluzole

Stephen Hawking, an English theoretical physicist and cosmologist, is one of the famous personalities that have been stricken with ALS disease.