

Antidepressants and Lithium, pharmacology of Alzheimer's disease

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History and epidemiology

- ▶ Depression is the most common of the *affective disorders* (disorder of mood rather than disturbances of thought or cognition)
- ▶ Worldwide, depression is a major cause of disability and premature death.
- ▶ Genetic factors are also important (identical twins: bipolar disorders 33-90%)
- ▶ Hippocrates: thought that **melancholia** was caused by too much black bile in the spleen...
- ▶ In ancient Rome and Greece, gymnastics, massage, special diets, music, and baths, as well as a concoction of poppy extract and donkey's milk were used to alleviate depressive symptoms

Nowadays antidepressants are „commonly used drugs”

Major indications:

- MDD (major depressive disorder)
- BD (bipolar disorder / maniac-depressive disorder)

Other indications of antidepressants

- GAD (generalised anxiety disorder)
- PTSD (post-traumatic stress disorder)
- OCD (obscessive-compulsive disorder)
- PMDD (premenstrual dysphoric disorder)
- Enuresis/Incontinence

Symptoms of depression

- ▶ Emotional symptoms include:
 - ▶ low mood, excessive rumination of negative thoughts, misery, apathy and pessimism
 - ▶ low self-esteem: feelings of guilt, inadequacy and ugliness
 - ▶ indecisiveness, loss of motivation
 - ▶ lack of joy (anhedonia), loss of reward.
- ▶ Biological symptoms include:
 - ▶ retardation of thought and action
 - ▶ loss of libido
 - ▶ sleep disturbance
 - ▶ loss of appetite

Other characteristics

- ▶ often seasonal, more severe in winter
- ▶ sleep EEG changes characteristically
 - ▶ earlier and more frequent REM phases
 - ▶ decrease in REM latency is typical
- ▶ infections are common (high steroid hormone-levels?)
- ▶ Disturbance in derivation of aggressive impulses?
- ▶ Loss-experience? mother-child relationship
- ▶ emotional retardation- "Depressio sine (without) depressio" - inability to experience even the low mood

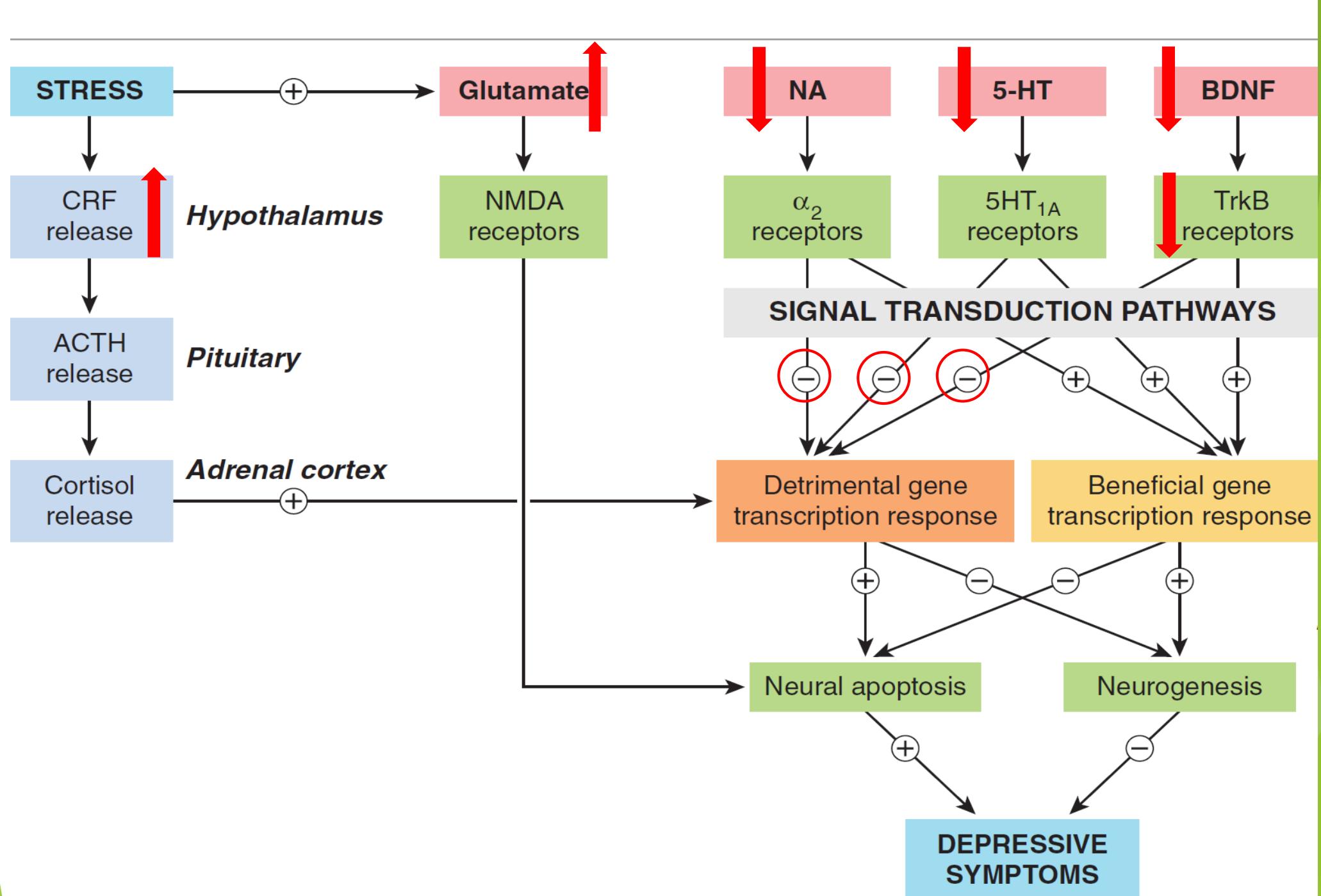
Types of depression

- ▶ **Unipolar (75%):**
- ▶ **1. Major**
 - ▶ 2 weeks depressed mood accompanied by 4 additional symptoms
- ▶ **2. Minor (dysthymic disorder)**
 - ▶ 2 yrs depressed mood (for more days than not)
- ▶ **Bipolar:** depression alternates with mania.
 - ▶ Mania is in most respects exactly the opposite, with excessive speech, enthusiasm and self-confidence, accompanied by impulsive actions

Hypothesis of MDD

- Monoamine hypothesis
 - Decreased NE, 5HT, D levels (cortically, and in limbic system)
- Neurotrophic hypothesis:
 - Level of Brain-derived neurotrophic factor (BDNF) is lower in depression
 - or the BDNF-receptor (trkB) is dysfunctional
 - Neurodegeneration in depression (decreased neural plasticity) and reduced neurogenesis e.g.: in the hippocampus, prefrontal cortex, anterior cingulate (glutamate may also be involved?)
 - antidepressant treatment elevates BDNF levels
- Neuroendocrine hypothesis:
 - corticotropinreleasing hormone/factor (CRH/CRF) mimics some effects of depression, such as:
 - diminished activity,
 - loss of appetite and
 - increased signs of anxiety.
 - CRH concentrations of depressed patients are increased

Possible Mechanisms



Antidepressant drug classifications

- ▶ Monoamin reuptake inhibitors
 - ▶ Classical Tricyclic antidepressants (TCA)
 - ▶ Newer Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)
 - ▶ Selective Serotonin Reuptake Inhibitors (SSRI)
 - ▶ Norepinephrine Reuptake Inhibitors (NRI)
- ▶ MAO-inhibitors
 - ▶ Non-selective
 - ▶ Selective MAO-A inhibitors
- ▶ Monoamine receptor antagonists

TCAs (Tricyclic antidepressants)

► Mechanism of action:

- ▶ competitive inhibition of SERT & NET reuptake transporters
- ▶ α_1 -blocking effect
- ▶ H_1R blocking effect
- ▶ Antagonism on 5HT Rs
- ▶ Antagonism on Musc. R



► Adverse effects:

- ▶ anti-cholinergic effect (atropin-like)
- ▶ orthostatic hypotension - α -blocking effect
- ▶ weight gain, sedation - H_1R blocking effect
- ▶ cardiac toxicity, conduction disturbances, QT prolongation
- ▶ Anti-arrhythmic at therapeutic doses, Arrhythmogenic at toxic doses



Tricyclic antidepressants:

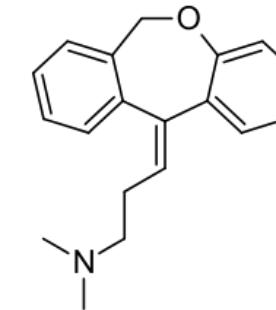
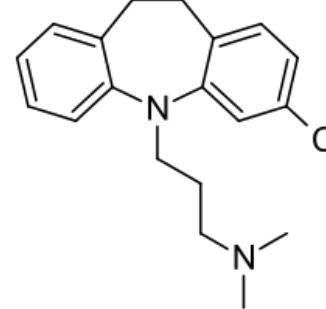
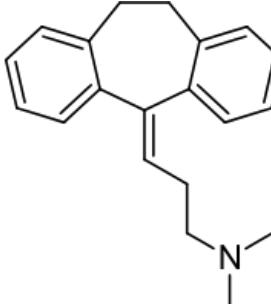
- desipramin** (Norpramin)
- imipramin** (Tofranil, Melipramin)
- clomipramin** (Anafranil)
- dibenzepin** (Noveril)
- amitriptylin** (Teperinep)
- doxepin** (Deptran, Sinequan)
- maprotilin** (Ludiomil)
- nortriptyllin** (Allegron)
- trimipramin** (Surmontil)

TCAs (Tricyclic antidepressants)

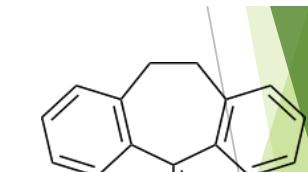
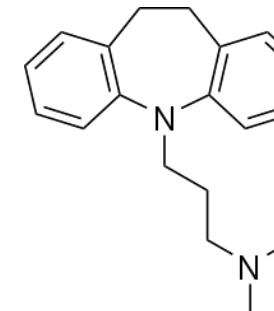
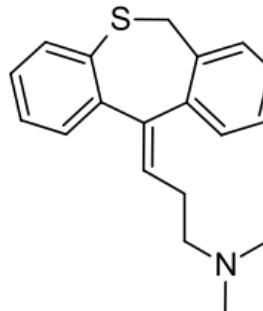
TCA-structures:
amitriptyline
clomipramine
doxepin

Pharmacokinetics

- ▶ Absorption is rapid
- ▶ Peak: 2-3 h
- ▶ Metabolism: extensive 1st pass
- ▶ Oxidation, hydroxylation, demethylation
- ▶ 5% = “slow acetylators”
- ▶ Protein bound: 90 – 95%
- ▶ Renally cleared

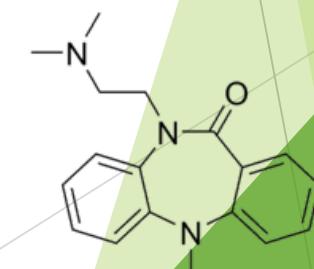
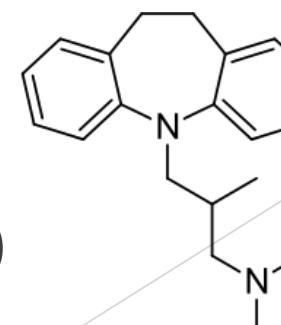


dosulepin
imipramine
nortriptyline
trimipramine
dibenzepin



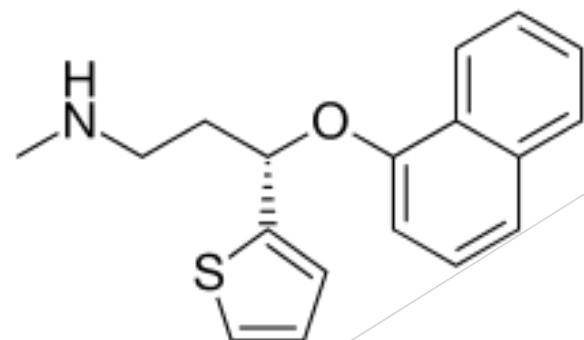
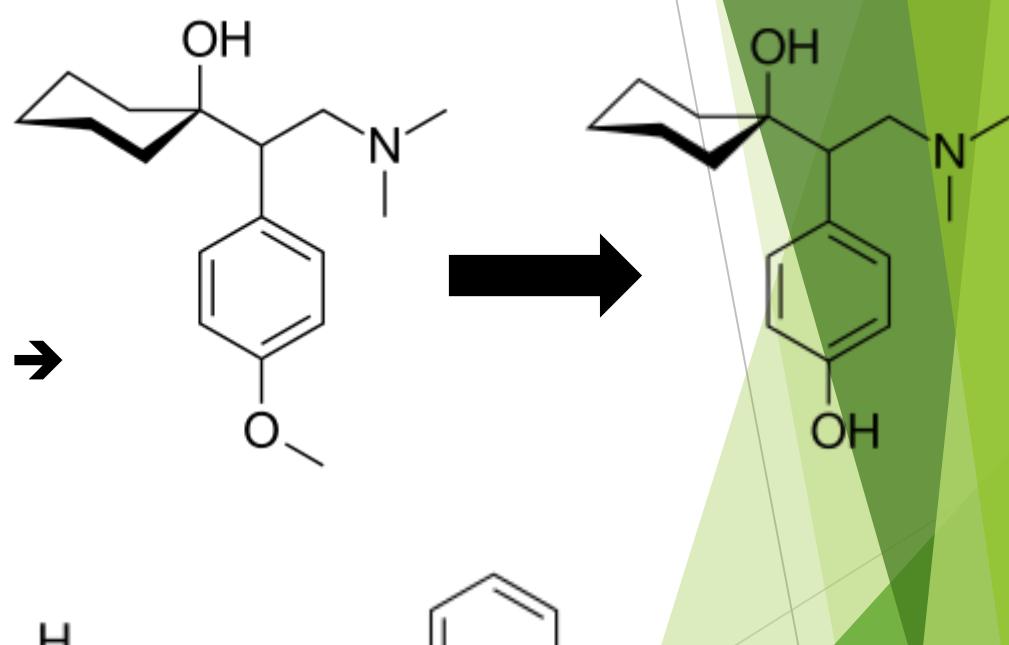
Clinical indication:

- ▶ Major depression
- ▶ OCD (obsessive-compulsive disorder)
(clomipramine)



Newer SNRI = Serotonin-Norepinephrine Reuptake Inhibitors

- Mechanism of action.:
 - selective inhibition of SERT & NET
 - **venlafaxine**
 - weak inhibitor of NET as well
 - **duloxetine** (Cymbalta®, Dulsevia®)
 - balanced inhibitor of SERT & NET
- Adverse effects:
 - narrow adverse effect profile (<TCAs)
 - BP↑, HR↑ (venlafaxine)
- Pharmacokinetics:
 - Venlafaxine (pro-drug) → metabolised → desvenlafaxine (active metabolite; antidepressant effect)
- Clinical indication:
 - Major depression
 - anxiety disorders (venlafaxine)
 - pain syndromes (diabetic neuropathy, fibromyalgic pain) (duloxetine)
 - incontinence (duloxetine)
- Similar agents: Milnacipran, Tofenacin



SSRIs

most commonly prescribed antidepressants

- Mechanism of action:

- selective inhibition of SERT
- CNS stimulation

- Adverse effects:

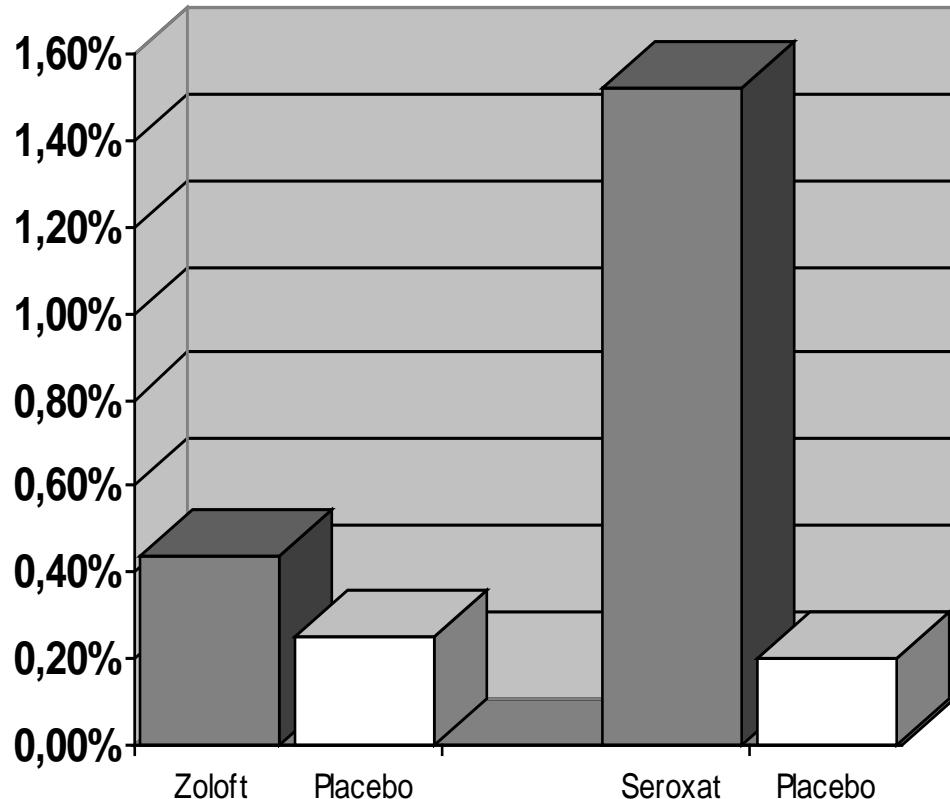
- Serotonin syndrome
- seizures, convulsions
- sexual dysfunctions, loss of libido
(effect on spinal neurons)
- QT prolongation (citalopram)
- increase in suicidal thoughts on starting treatment (in children and adolescents)



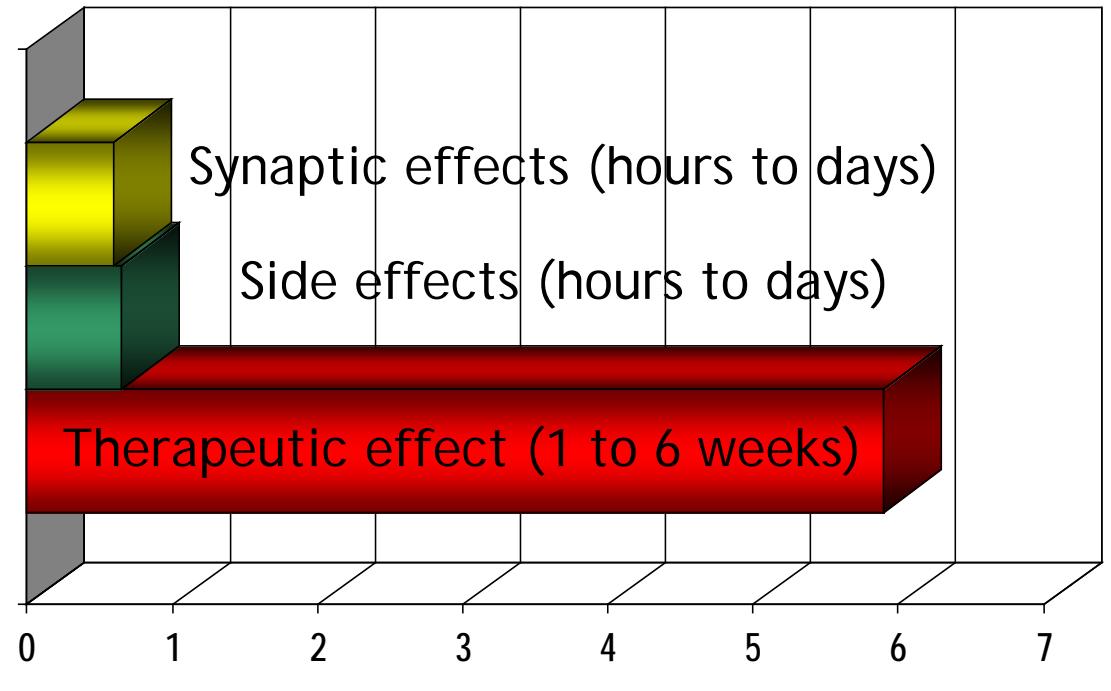
- ▶ citalopram (Cipramil, Seropram)
- ▶ escitalopram (Lexapro, Cipralex) (S-enantiomer of citalopram)
- ▶ fluoxetine (Prozac, Floxet)
- ▶ fluvoxamine (Favarin)
- ▶ paroxetine (Seroxat, Paroxat, Rexetin, Apodepi, Parogen)
- ▶ sertraline (Zoloft, Sertadepi, Asentra, Stimuloton)



SSRIs



Time needed for development of effect



Zoloft (sertraline) means a **twofold**, Seroxat (paroxetine) more than a **seven-fold risk for suicide** events according to studies (especially in children)

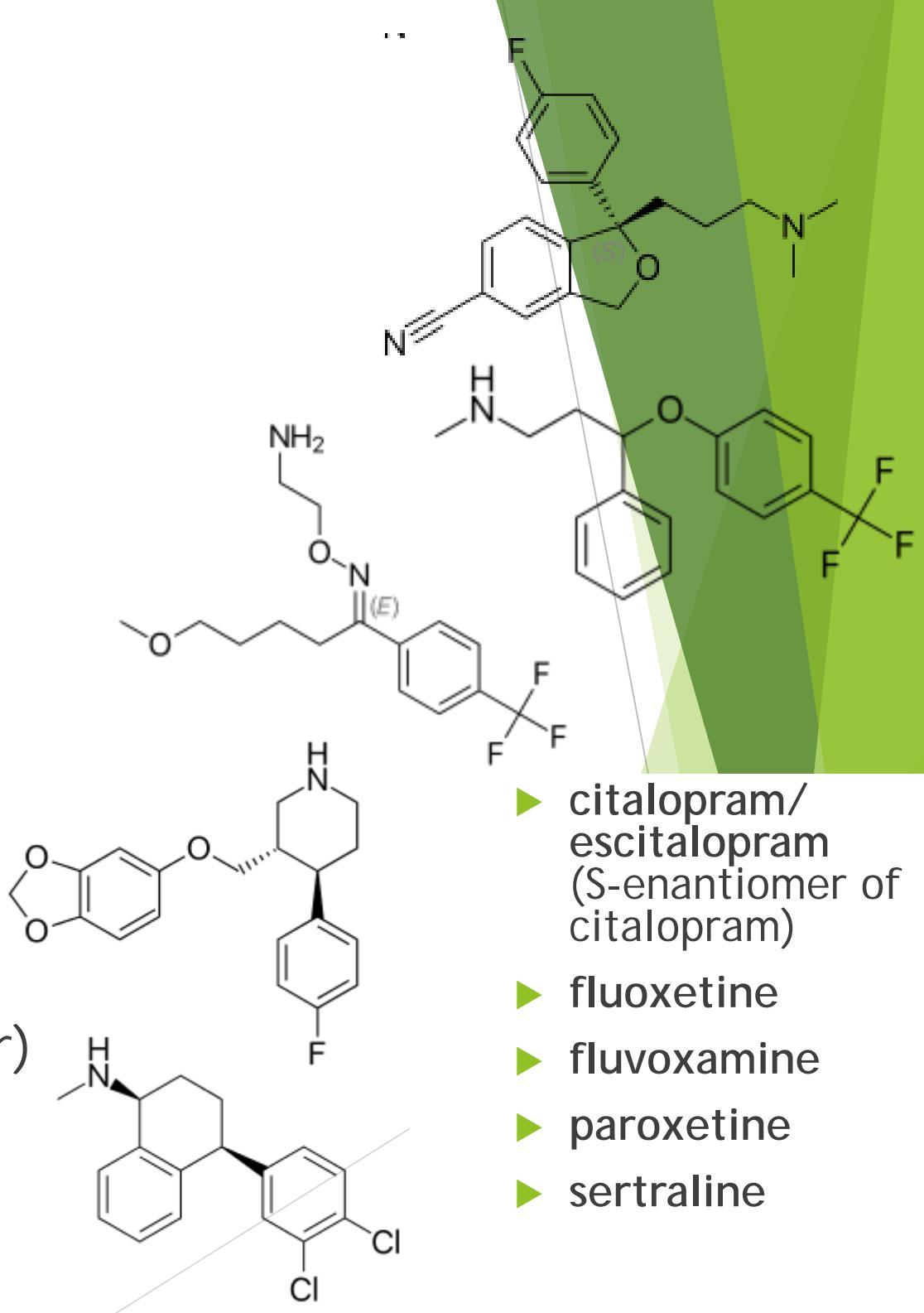
SSRIs

Pharmacokinetics:

- ▶ SSRIs are enzyme inhibitors of CYP 1A2, 2C19, 2D6, 3A4
→ increased side effect of co-administered drugs

Clinical indication:

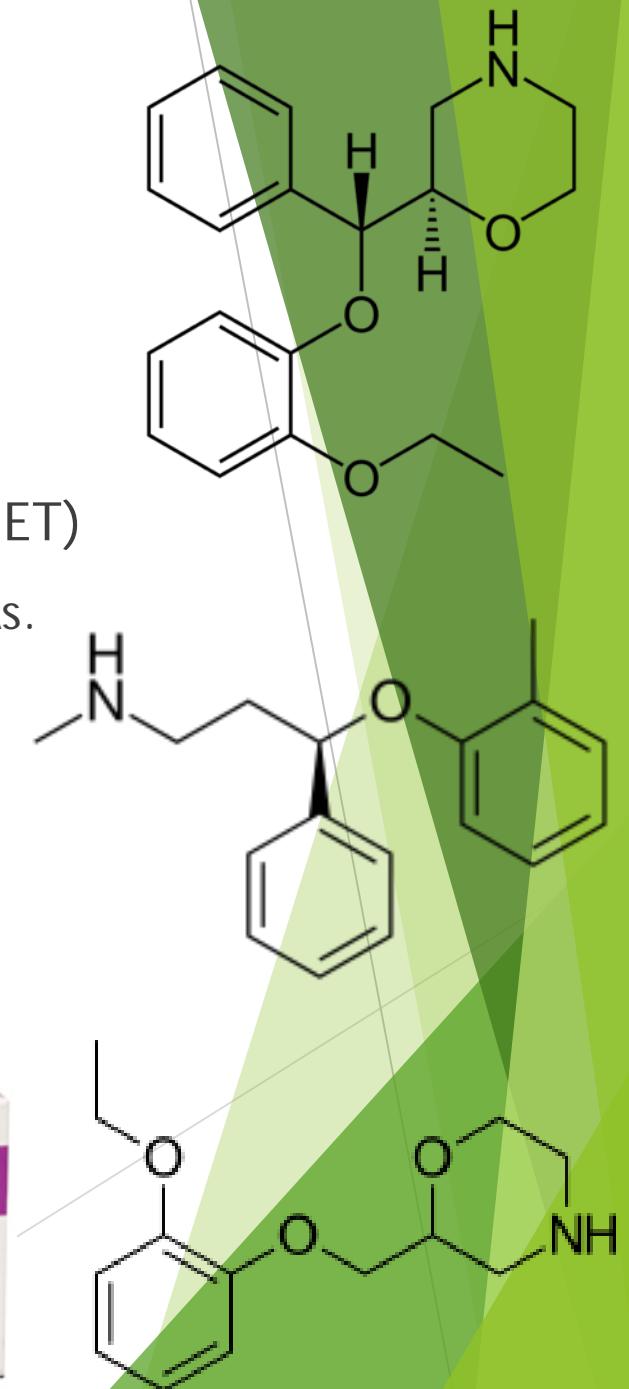
- ▶ Major depression,
- ▶ sleep disorders
- ▶ OCD (obscessive-compulsive disorder)
- ▶ bulimia
- ▶ GAD (generalised anxiety disorder)
- ▶ panic attacks
- ▶ social phobias



NRI (norepinephrin reuptake inhibitors)

reboxetine (Edronax), atomoxetine, viloxazine

- ▶ Newest antidepressives
- ▶ Mechanism of action:
 - ▶ Highly selective inhibitors of noradrenaline uptake (NET)
 - ▶ but their efficacy in depression is less than that of TCAs.
- ▶ Adverse effects:
 - ▶ many, not well-tolerated agent
- ▶ Indications:
 - ▶ most effective at improving social functioning in depression
 - ▶ attention-deficit hyperactivity disorder (ADHD) (Atomoxetine)

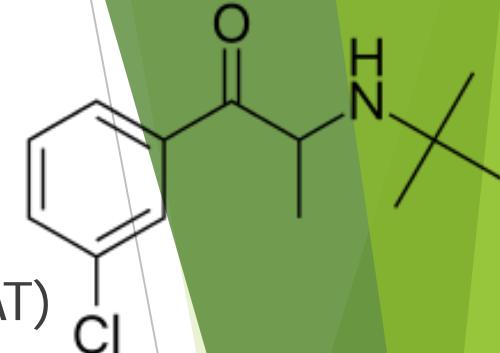


NDRI (norepinephrin dopamin reuptake inhibitors)

Bupropion (Wellbutrin)

► Mechanism of action:

- ▶ inhibits both noradrenaline and dopamine reuptake (NET, DAT) (but not 5-HT)
 - ▶ But does not induce euphoria and has no abuse potential (as e.g. cocaine and amphetamine)
- ▶ Antagonist on nicotinic receptors
- ▶ Activates POMC neurons in hypothalamus → reduces appetite



► Pharmacokinetics:

- ▶ It is metabolised to active metabolites.

► Indications:

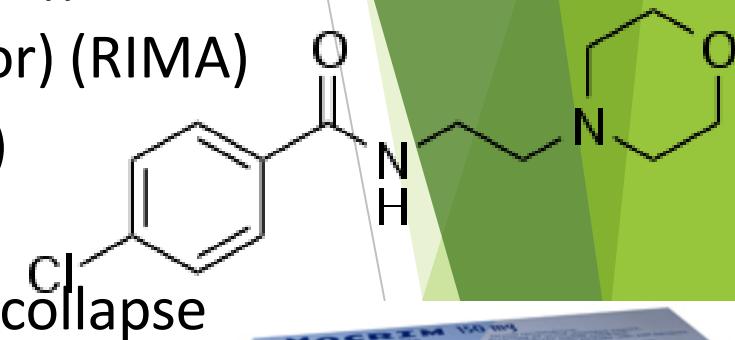
- ▶ It is also used to treat nicotine dependence
- ▶ Bupropion + naltrexon → anorexigenic
- ▶ does not cause sexual dysfunction (as most antidepressants)



MAO inhibitors

MAOIs less used due to adverse effects and serious interactions.

- Mechanism of action:
 - selective blockade of MAO-A/MAO-B
 - (phenelzine (irreversible nonselective MAO inhibitor))
 - **moclobemide** (selective, reversible MAO-A inhibitor) (RIMA)
 - (selegiline (selective, irreversible MAO-B inhibitor))
- Adverse effects:
 - upon abrupt cessation – hypotonia, orthostatic collapse
 - with SSRI – „serotonin syndrome”
(hyperthermia, muscle rigidity, cardiovascular collapse)
 - with tyramine – „cheese reaction”= hypertensive crisis
- Clinical indication:
 - Major depression
 - anxiety, phobias
 - (parkinsonism (selegiline))
- Similar agents: Eprobemide, Toloxatone, Matralindole, etc.

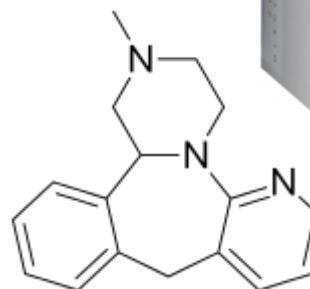


Monoamine receptor antagonists

Tetracyclic substances: **mirtazapine**, **mianserin**, **amoxapine**

- Mechanism of action:

- antagonism on α_2 R, presynaptically
- 5-HT R blocking effect
- H₁R blocking effect
- D₂R blocking effect



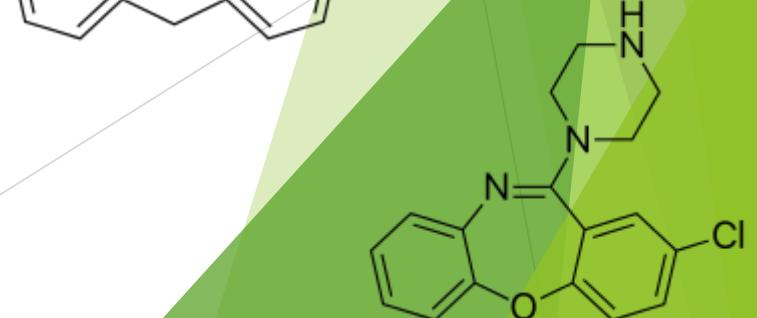
- Adverse effect

- sedation (mirtazapine, mianserin – H₁R blocker)
- pseudoparkinsonism (amoxapine – D₂R blocker)
- bone marrow depression (mianserin) - Regular blood counts are advisable.



- Clinical indication:

- Major depression

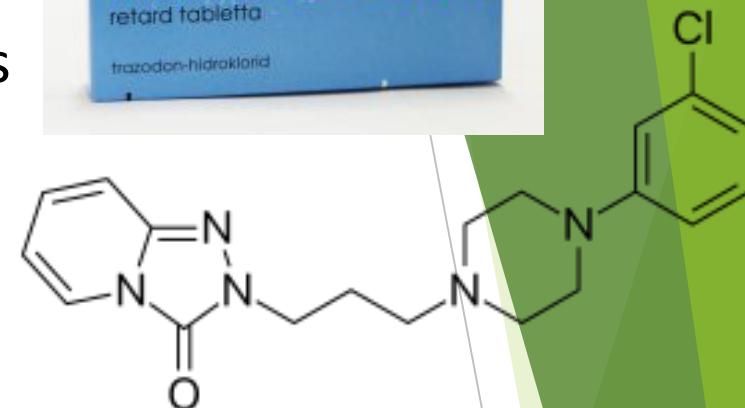


Other Monoamine receptor antagonists

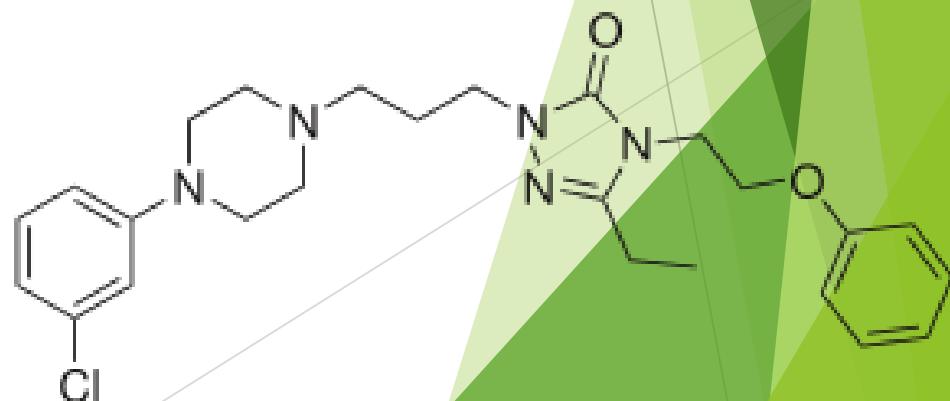
trazodone, nefazodone

- Mechanism of action.:
 - antagonism on 5-HT_{2A} and 5-HT_{2C} receptors
 - inhibition of SERT & NET

→ antidepressant, antipsychotic, antianxiety effect



- Adverse effects:
 - sedation
 - orthostatic hypotension – αR blocking
 - GIT disturbances
- Clinical indication (apart from depression):
 - insomnia (trazodone)



Li⁺



- monovalent cation
- anti-maniac/mood stabilizing agent
- prophylaxis/treatment of bipolar depression
- Mechanism of action.:
 - effects on ion transport
 - substitutes Na⁺ in neural cells
 - action potential caused by Li⁺ is slower, retarded, as pump-out of Li⁺ is slower
 - effects on second messengers
 - inhibition of recycling enzymes converting IP₁ → IP₂
 - effects on neurotransmitters
 - ↑action of serotonin
 - ↓NE, dopamine turnover

Li⁺

- Excretion: kidneys! Substitutes Na⁺, competition:
if more Na⁺ → Li-retention → side effects,
if more Li⁺ → Na⁺ retention → hypertension
- Effective serum cc.: 0,6-0,9 mmol/L; above 1,5mmol/L it is toxic
→ narrow therapeutic window
- Side effects:
 - tremor
 - Inhibits hormone-induced cAMP production
 - uncoupling of TSH receptors → decreased thyroid function
 - Uncoupling of ADH receptors → diabetes insipidus → renal failure, oedema
 - Sinoatrial node depression (Na-Li exchange)
- Clinical indication
 - Bipolar disorders
 - (+ combined with antipsychotics)
 - Schizoaffective disorder
 - Unipolar depression
 - unresponsive cases + SSRIs, TCAs

Pharmacological management of Alzheimer's disease



Alois Alzheimer

Alois Alzheimer

(1864-1915)



German neuropathologist and psychiatrist who described in 1906 the clinical and neuropathological features of a woman aged 51 years, with atrophied cerebral cortex, senile plaques and neurofibrillary tangles.

Alzheimer's disease

► Definition:

- ▶ Progressive dementia, which - beside the impaired cognitive functions – can be characterized by changes in attitude, behavioural disturbances and rapid biological deterioration following dementia

► Epidemiology:

- ▶ It is the 4th death-cause in the developed countries.
- ▶ Alzheimer's affect 5% of patients over 65 years, 20% of over 80 years and 90% of over 95
- ▶ Circa 200 thousand people suffers from the disease in Hungary.

Alzheimer's disease

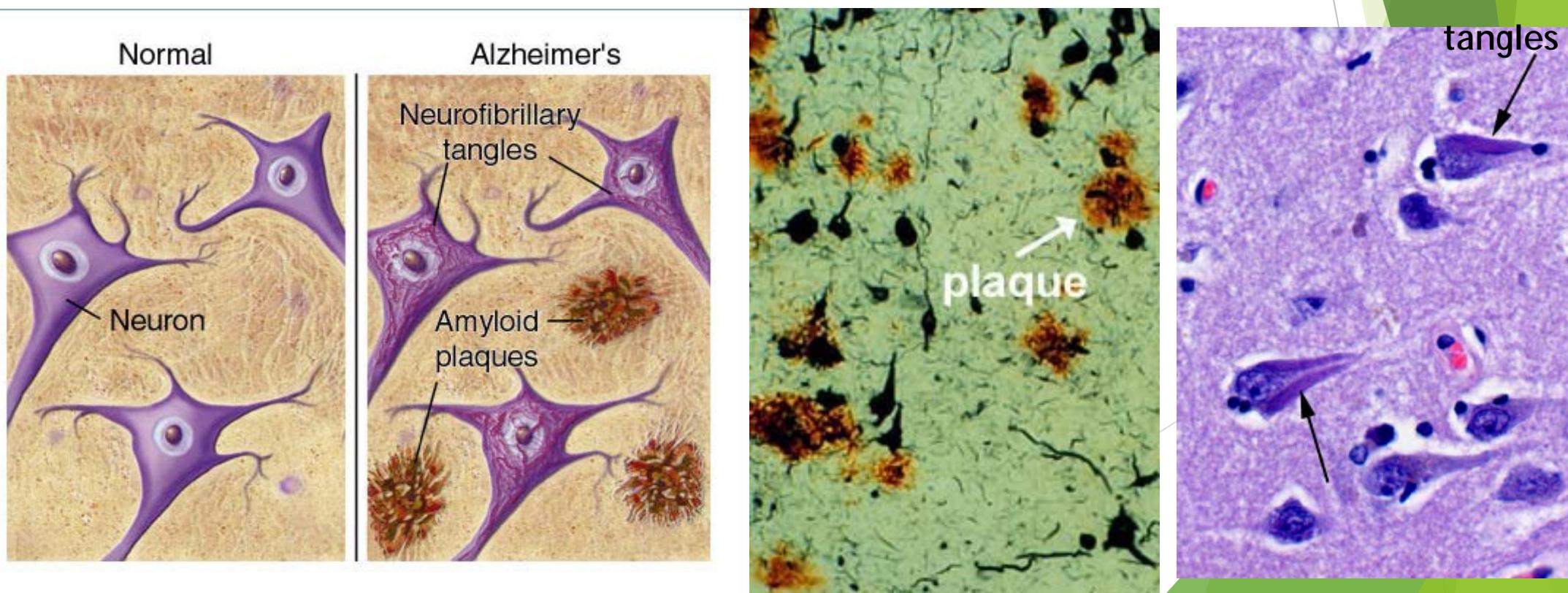
- ▶ Types:
 - ▶ Sporadic form
 - ▶ Common type of Alzheimer's
 - ▶ Affects mostly elderly people
 - ▶ Slightly better prognosis
 - ▶ Familiar;
 - ▶ Very rare: 1-5% of all cases
 - ▶ Genetics and heridity takes part
 - ▶ Usually develops at younger age
 - ▶ Worse prognosis

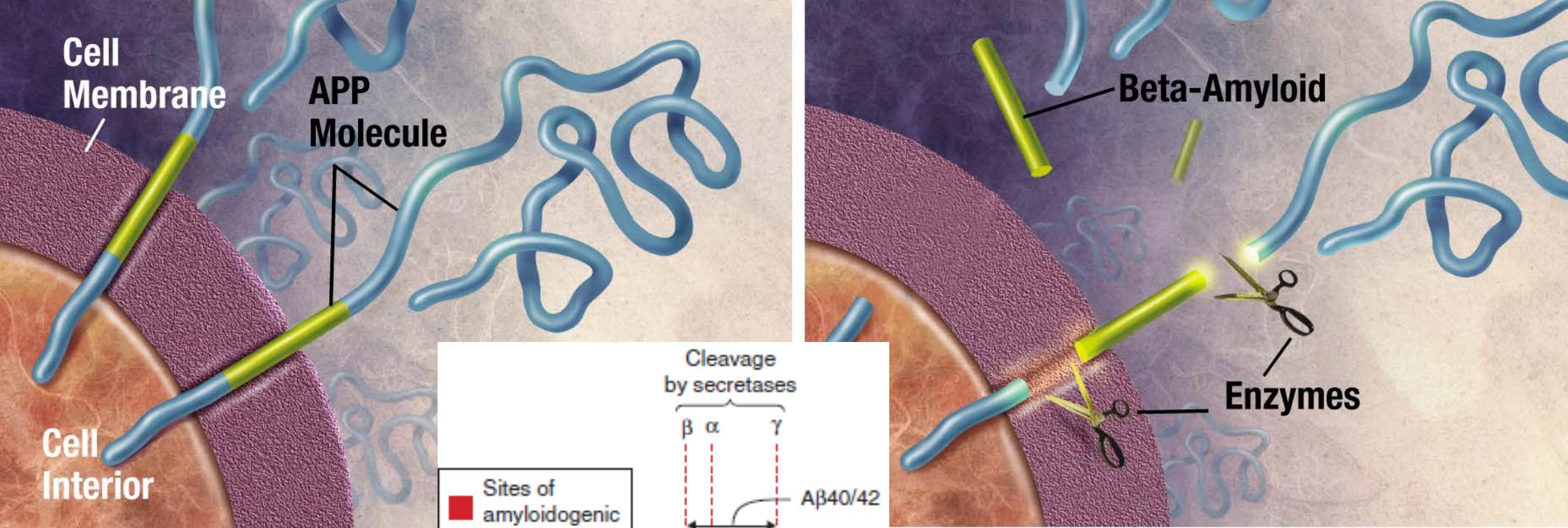
Alzheimer's disease

- ▶ Supposed factors:
 - ▶ Triggering causes are unknown.
 - ▶ Genetics
 - ▶ Dementia is common among first-degree relatives of Alzheimer patients
 - ▶ In case of familiar Alzheimer's point mutation (missense mutation) of presenilin 1, presenilin 2 and amyloid precursor peptide (APP) is detected
 - ▶ presence of Apolipoprotein ε4 allele is also a risk factor
 - ▶ there is no evidence of genetic involvement in sporadic Alzheimer's disease
 - ▶ Viral infection
 - ▶ „slow“ viral infection is also suspected
 - ▶ metabolic disturbances
 - ▶ disturbance in aluminum-metabolism/aluminum intake
 - ▶ despite appropriate dietary intake and good appetite patients lose weight: this suggests general metabolic disturbances (e.g. oxidative processes, lack of Vitamin E etc)
 - ▶ Environmental factors
 - ▶ Social-economic factors
 - ▶ The low level of education, low social status, low income may be involved as risk factors
 - ▶ Immunological differences
 - ▶ there are many immunopathological aspects of Alzheimer's (acute phase reaction, activation of cytokine- and complement-system).

Pathophysiology of Alzheimer's

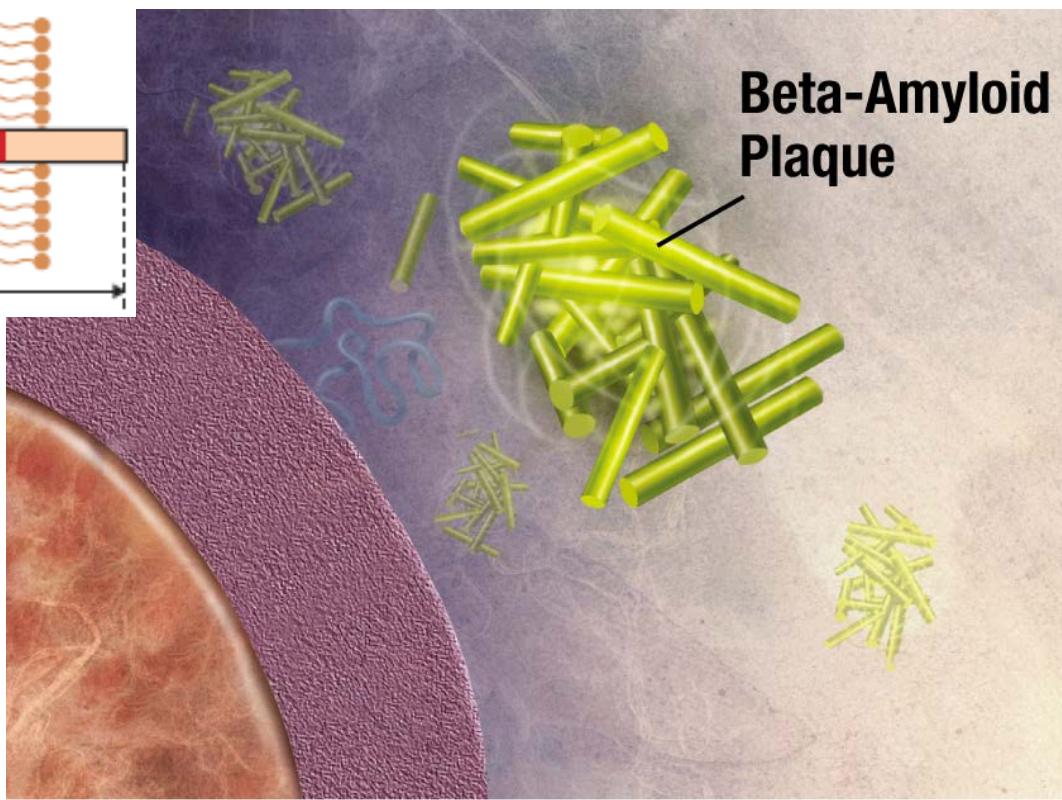
- ▶ Macroscopically
 - ▶ atrophisation of cortex (frontotemporally and parietally)
- ▶ Microscopically
 - ▶ synapses and neurons are lost in the cortex and limbic system due to cell death (mainly apoptosis (necrosis, autophagia)) cholinerg neuron-loss
 - ▶ neurofibrillary tangles (NFTs)
 - ▶ neuritic/senile/amyloid plaques (APs)





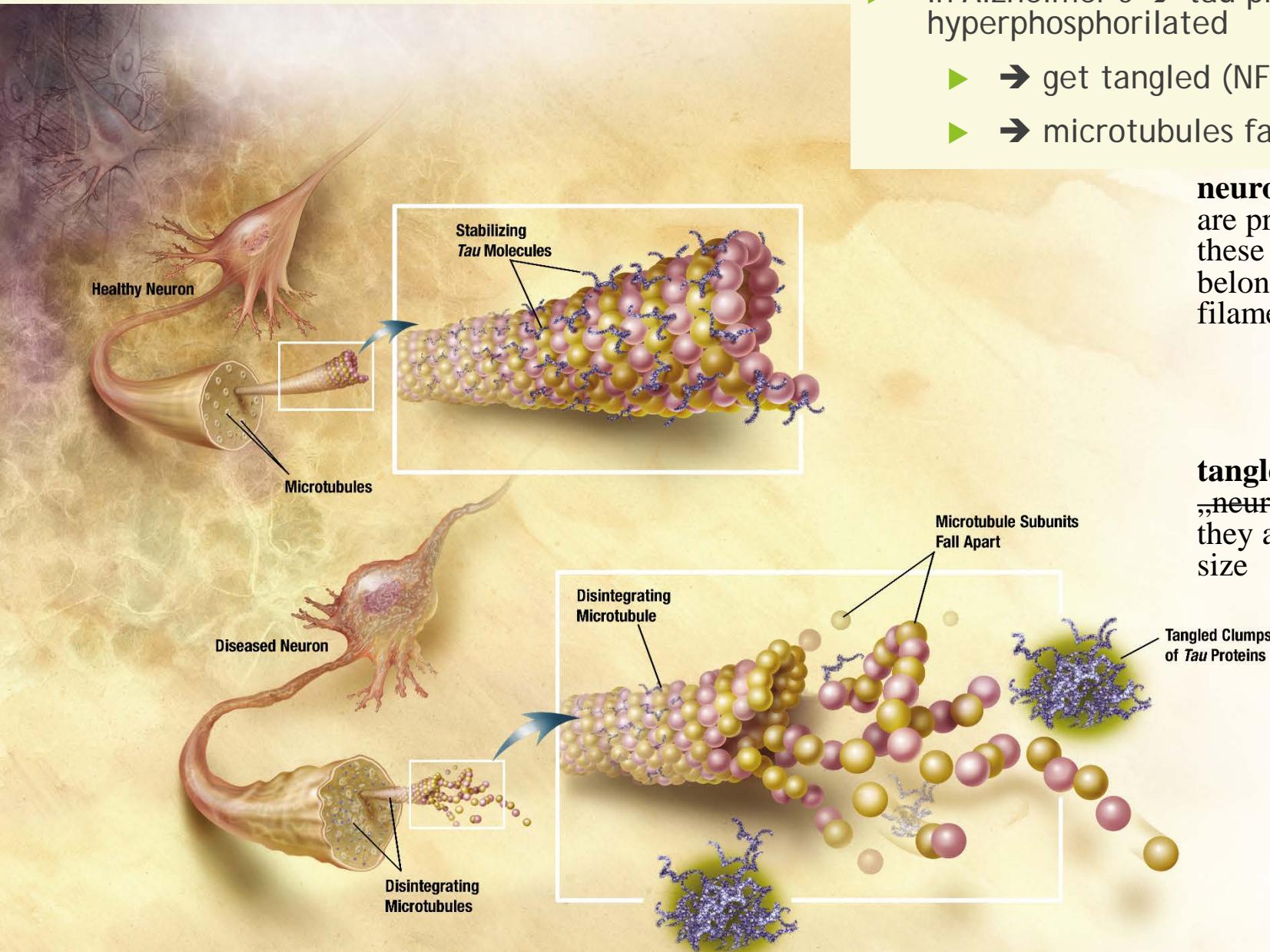
► Amiloid plaques:

- insoluble extracellular deposits
- formed from **amyloid β (A β)** and neurite/axon debris
- amyloid β (39-43 aminoacid peptid) is a fragment of amyloid precursor peptide (APP)
- A β ₄₀<A β ₄₂ are most common and plaque-forming types**
- α -secretase produces soluble sAPP = trophic factor
 β/γ secretases \rightarrow A β \rightarrow plaque



- Neurofibrillary tangles (NFTs):

- ▶ intracellular aggregates
- ▶ formed from hyperphosphorylated τ proteins kinked in dense bundles



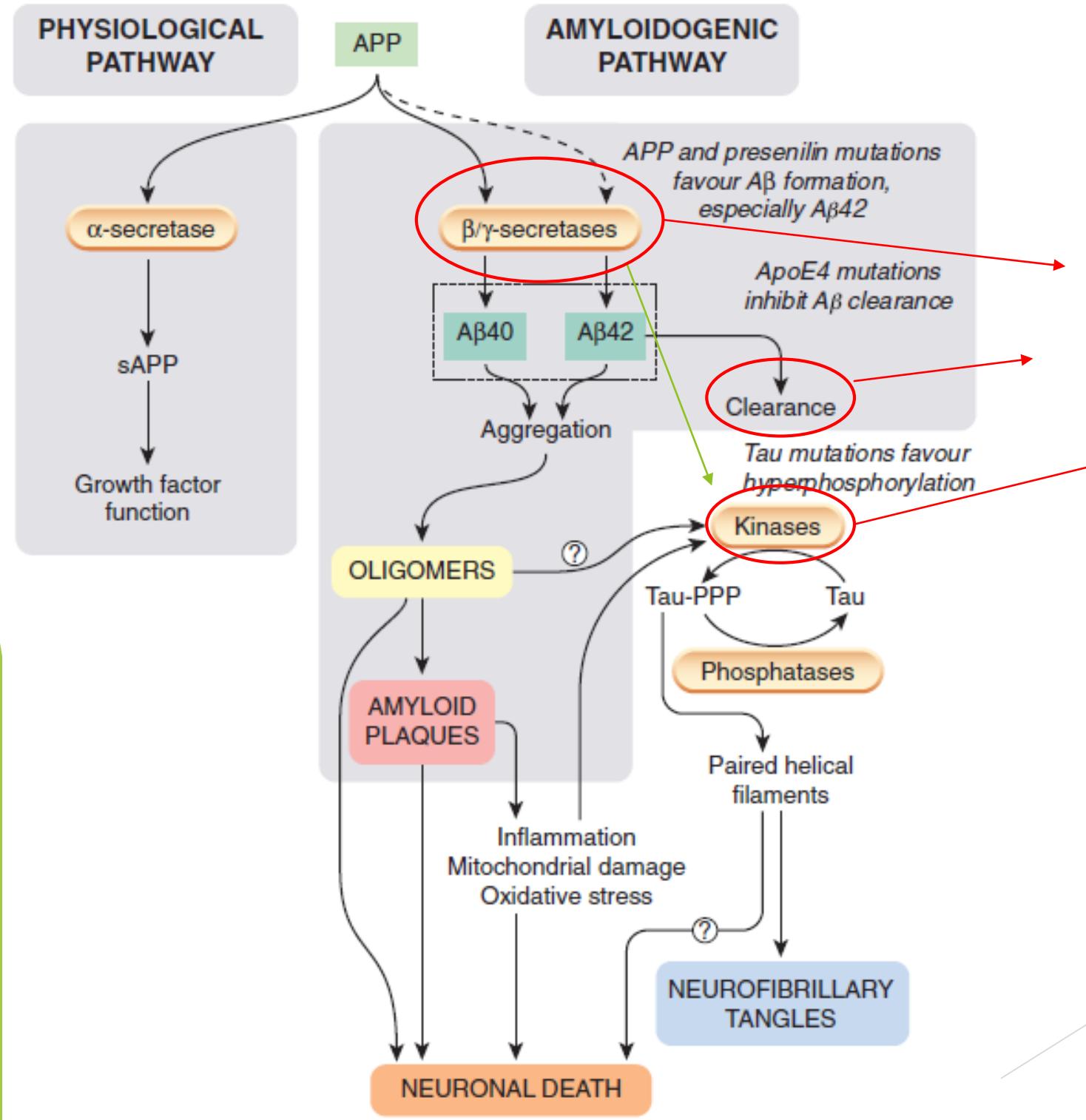
- ▶ tau proteins are present in cells physiologically, stabilizing microtubules (which form the cytoskeleton)
- ▶ In Alzheimer's → tau proteins get abnormally hyperphosphorylated
 - ▶ → get tangled (NFTs)
 - ▶ → microtubules fall apart → cellular death

neurofibrils/neurofilaments:
are present normally in neurons,
these are also cytoskeleton-components,
belonging to the family of intermediate filaments



tangles formed from **tau-proteins**
„**neurofibrils**“ do not exist normally
they are „**neurofibrillar**“ only by their size

Possible New drug targets



Pathophysiology of Alzheimer's

- ▶ **Role of Immune system?**
 - ▶ **immune system** constituents are present near areas of plaque formation
- ▶ **cholinerg processes** are profoundly damaged,
 - ▶ especially a large system of neurons located at the base of the forebrain in the nucleus basalis of Myerly.
 - ▶ this is rather a result than a cause
- ▶ **Serotonerg and noradrenerg** neurons are also lost
 - ▶ serotonerg neurons of the raphe nuclei
 - ▶ noradrenerg cells of the locus coeruleus
 - ▶ whereas MAO-B activity is increased.
- ▶ **Glutamate** and other excitatory amino acid neurotransmitters
 - ▶ neurotoxicity
- ▶ Elevated **cholesterol** levels
 - ▶ Elevated cholesterol levels in brain neurons may alter cell membrane functioning and result in a cascade leading to plaque formation.
- ▶ **Estrogen deficiency**
 - ▶ Estrogen interacts with nerve growth factor, promotes synaptic growth; acts as an antioxidant and may help maintain normal cholinergic transmission

Symptoms of Alzheimer's disease

Cognitive symptoms:

- ▶ memory loss (poor recall and losing items);
- ▶ aphasia (circumlocution and anomia);
- ▶ apraxia; (loss of the ability to execute or carry out learned purposeful movements, despite having the desire and the physical ability to perform the movements)
- ▶ agnosia; (loss of ability to recognize objects, persons, sounds, shapes, or smells while the specific sense is not defective nor is there any significant memory loss)
- ▶ disorientation (impaired perception of time and unable to recognize familiar people);
- ▶ impaired executive function.

Non-cognitive symptoms:

- ▶ affective disorders (anxiety, fear, depression)
- ▶ psychotic symptoms (hallucinations and delusions),
- ▶ disorder of motivation (restlessness, agitation, wandering)
- ▶ behavioural disturbances (change in personality, physical and verbal aggression, combativeness, uncooperativeness)
- ▶ motor hyperactivity, repetitive mannerism and activities (unusual movements)
- ▶ other neurological symptoms (difficulty in walking, vegetative disturbances)

Functional symptoms:

- ▶ Inability to care for self (dressing, bathing, toileting, and eating)

Stages of Cognitive Decline I.

Stage 1	Normal	No subjective or objective change in intellectual functioning.
Stage 2	Forgetfulness	Complaints of losing things or forgetting names of acquaintances. Does not interfere with job or social functioning. Generally a component of normal aging.
Stage 3	Early confusion	Cognitive decline causes interference with work and social functioning. Anomia, difficulty remembering right word in conversation, and recall difficulties are present and noticed by family members. Memory loss may cause anxiety for patient.
Stage 4	Late confusion (early AD)	Patient can no longer manage finances or homemaking activities. Difficulty remembering recent events. Begins to withdrawal from difficult tasks and to give up hobbies. May deny memory problems.

Stages of Cognitive Decline II.

Stage 5	Early dementia (moderate AD)	Patient can no longer survive without assistance. Frequently disoriented with regard to time (date, year, season). Difficulty selecting clothing. Recall for recent events is severely impaired ; may forget some details of past life (e.g., school attended or occupation). Functioning may fluctuate from day to day. Patient generally denies problems. May become suspicious or tearful. Loses ability to drive safely.
Stage 6	Middle dementia (moderately severe AD)	Patients need assistance with activities of daily living (e.g. bathing, dressing, and toileting). Patients experience difficulty interpreting their surroundings; may forget names of family and caregivers; forget most details of past life; have difficulty counting backward from 10. Agitation, paranoia, and delusions are common.
Stage 7	Late dementia	Patients loses ability to speak (may only grunt or scream), walk, and feed self. Incontinent of urine and faeces. Consciousness reduced to stupor or coma.

Establishing a diagnosis

Tools of clinical diagnostics:

- ▶ psychometrical examination (MMSE - Mini Mental State Examination(Folstein))
- ▶ Ischaemic scale → to differentiate between Alzheimer's and vascular dementia
- ▶ skull CT, shows atrophy of medio-temporal lobe at early stages
- ▶ MRI shows the disease with 92% safety
- ▶ SPECT also needed for differentiation between Alzheimer's and vascular dementia
- ▶ PET reflects drug effects and status changes of patient
- ▶ markers
 - ▶ genetic; shows probability of the disease (apolipoprotein ε4 allele)
 - ▶ blood counts, skin fibroblasts

Mini Mental State Examination (Folstein)

1.	Orientation	
	What is the year, season, date, day, month?	0 - 5 point
	Where are we: country, city, part of city, number of flat/house, name of the street?	0 - 5 point
2.	Registration	
	Name three objects: one second to say each. Then ask the patient to name all three after you have said them. Give one point for each correct answer. Then repeat them until he learns all three. Count trials and record.	0 - 3 point
3.	Trials	
	Attention and calculation. Serial 7s from 100 backwards: one point for each correct. Stop after five answers. Alternatively spell 'world' backwards.	0 - 5 point
4.	Recall	
	Ask for the three object repeated above. Give one point for each correct.	0 - 3 point
5.	Language	
	Name a pencil and watch.	0 - 2 point
6.	Repeat the following: „No ifs, ands or buts.“	0 - 1 point
7.	Follow a three-stage command: 'Take a paper in your right hand, fold it in half and put it on the floor.'	0 - 1 point
8.	Read and obey the following: Close your eyes.	0 - 1 point
10.	Write a sentence.	0 - 1 point
11.	Copy a design.	0 - 1 point

Total:

30 points

- ▶ **INSTRUCTIONS FOR ADMINISTRATION OF MINI MENTAL STATE EXAMINATION**
 - Orientation**
 - Ask the date. Then ask specifically for parts omitted, for example, 'Can you also tell me what season it is?' Score 1 point for each correct.
 - 2. Ask in turn, 'Can you tell me the name of this place?' (town, country, etc). Score 1 point for each correct.
 - Registration**
 - Ask the patient if you may test his or her memory. Then say the names of three unrelated objects, clearly and slowly, about one second for each. After you have said all three, ask him or her to repeat them. This first repetition determines the score (0-3) but keep saying them until he or she can repeat all three, up to six trials. If he or she does not eventually learn all three, recall cannot be meaningfully tested.
 - Attention and calculation**
 - Ask the patient to begin with 100 and count backwards by 7. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers. If the patient cannot or will not perform this task, ask him or her to spell the word 'world' backwards. The score is the number of letters in correct order, eg dlrow 5, dlowr 3.
 - Recall**
 - Ask the patient if he or she can recall the three words you previously asked him or her to remember. Score 0-3.
 - Language**
 - Naming:* Show the patient a wrist-watch and ask him or her what it is. Repeat for pencil. Score 0-2.
 - Repetition:* Ask the patient to repeat the sentence after you. Allow only one trial. Score 0 or 1.
 - Three-stage command:* Give the patient a piece of plain blank paper and repeat the command. Score 1 point for each part correctly executed.
 - Reading:* On a blank piece of paper, print the sentence 'Close your eyes' in letters large enough for the patient to see clearly. Ask him or her to read it and do what it says. Score 1 point only if he or she actually closes his eyes.
 - Writing:* Give the patient a blank piece of paper and ask him or her to write a sentence for you. Do not dictate a sentence, it is to be written spontaneously. It must contain a subject and verb and be sensible. Correct grammar and punctuation are not necessary.
 - Copying:* On a clean piece of paper, draw intersecting pentagons (as below), each side about one inch and ask him or her to copy it exactly as it is. All ten angles must be present and two must intersect to score 1 point. Tremor and rotation are ignored.
- ▶ A score of 20 or less generally suggests dementia but may also be found in acute confusion, schizophrenia or severe depression. A score of less than 24 may indicate dementia in some patients who are well educated and who do not have any of the above conditions. Serial testing may be of value to demonstrate a decline in cognitive function in borderline cases.



Pharmacotherapy of Alzheimer's disease

- Cholinesterase inhibitors
 - donepezil
 - rivastigmine
 - galanthamine
 - ladostigil
 - tacrine
 - huperzine A
- NMDA antagonists
 - huperzine A
 - memantine
 - ensaculine
- MAO-inhibitors
 - ladostigil
 - bifemelane
 - ergoloid
- neurotroph/growth factor enhancers
 - ladostigil
 - dihexa
 - lateprinim
 - estrogen
- Anti-amyloid antibodies
 - bapineuzumab
- Modifiers of glucose utilization
 - rosiglitazon
(PPAR γ R agonist)
- nACh-R agonists
 - galanthamine
- 5-HT-R antagonists
 - memantine
 - ensaculine
 - pirdine-s (cerla/idalo/*latre)
 - lecozotan
- γ -secretase inhibitors
 - semagacestat*
- Antioxidants
 - Ginkgo biloba extract
 - tocoferol (E-vitamin)
 - ascorbic acid (C-vitamin)
 - estrogen
- Cerebral blood-flow enhancers
 - vinpocetine
 - piracetam
 - pentoxiphylline
- NSAID-s
 - ibuprofen
 - indometacin
- statins
 - pravastatin
 - lovastatin



*Have failed in Phase III studies
(for treatment of Alzheimer's)

Cholinesterase Inhibitors – Donepezil



► Mechanism of action:

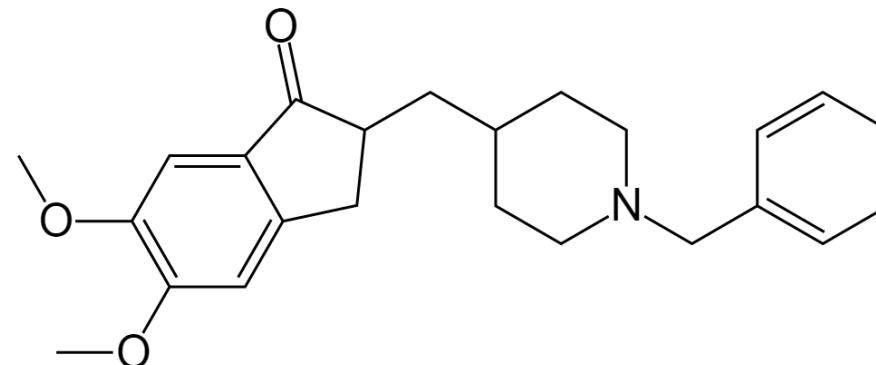
- ▶ specific and reversible inhibitor of acetylcholinesterase
- ▶ 1000-fold less inhibition of peripheral butyrylcholinesterase as well

► Indication:

- ▶ in mild to moderately severe AD (MMSE score 10 to 26).
- ▶ Patients taking donepezil had improved cognition for the first 6 to 9 months, followed by a gradual decline.
- ▶ improves sleep apnoe and gait of Alzheimer patients as well

► Adverse effects:

- ▶ diarrhoea,
- ▶ muscle spasms
- ▶ fatigue
- ▶ nausea, vomiting
- ▶ headache
- ▶ insomnia.



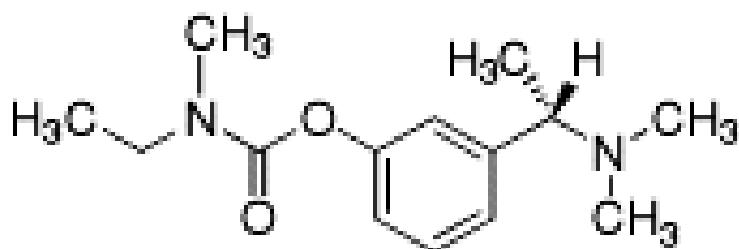
Cholinesterase Inhibitors - Rivastigmine

► Mechanism of action:

- ▶ non-specific acetylcholinesterase and butyrylcholinesterase inhibitor
- ▶ theoretically has central activity and has low activity at the periphery

► Pharmacokinetics:

- ▶ metabolised by the inhibited cholinesterases (not CYP450)
- ▶ transdermal patch also exists



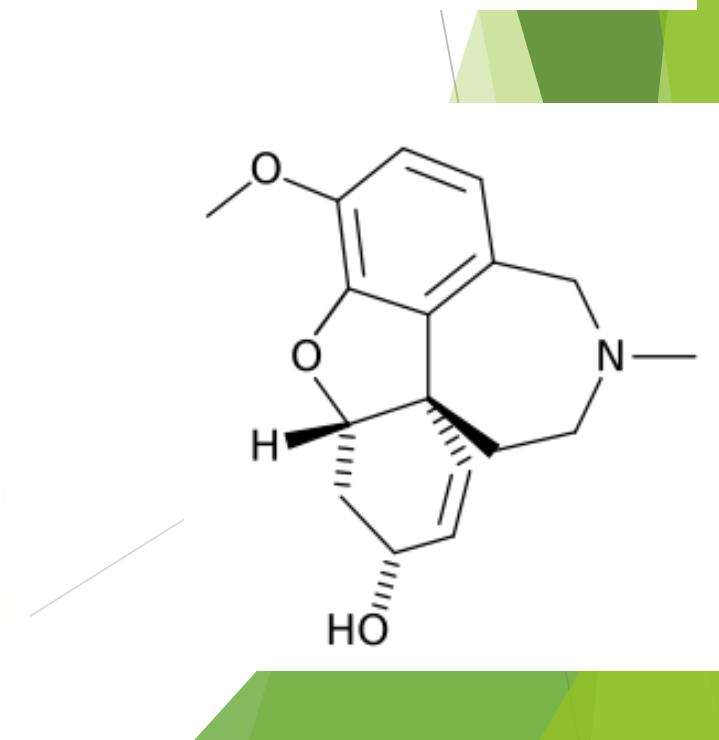
Cholinesterase Inhibitors

Galanthamine

- ▶ It is an alkaloid that may be obtained from the bulbs and flowers of *Galanthus caucasicus* (snowdrop)
- ▶ Mechanism of action:
 - ▶ weak competitive and reversible cholinesterase inhibitor
 - ▶ nACh-receptor agonist as well
- ▶ Pharmacokinetics:
 - ▶ orally well absorbed: bioavailability 80-100%
 - ▶ Plasma protein binding is relatively low (18%)
 - ▶ metabolised by CYP2D6 and CYP3A4
- ▶ Indications:
 - ▶ Alzheimer's and vascular dementia
Galanthamine causes modest cognitive improvement, which lasts about 9 months. (Nivalin®)
- ▶ Adverse effects:
 - ▶ nausea, vomiting,
 - ▶ diarrhoea,
 - ▶ headache,
 - ▶ dizziness.

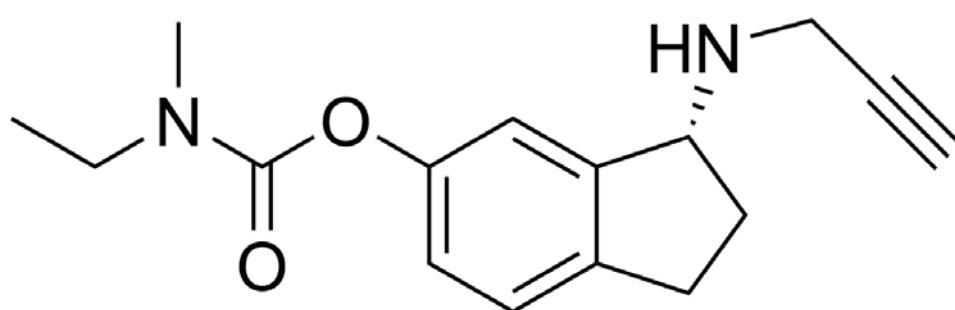


Galanthus caucasicus



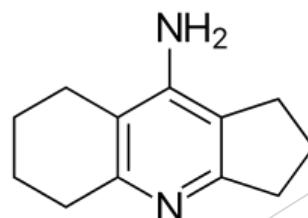
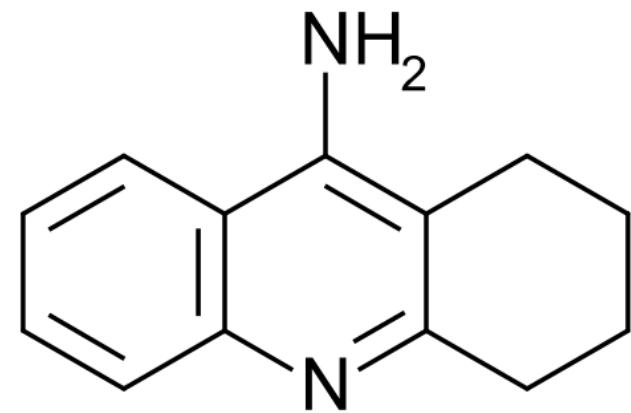
Cholinesterase Inhibitors - Ladostigil

- ▶ Relatively new agent (2000'), experimental compound
- ▶ Mechanism of action:
 - ▶ non-specific, reversible cholinesterase inhibitor
 - ▶ irreversible MAO-B inhibitor
 - ▶ enhances the expression of neurotrophic factors like GDNF (glia) and BDNF
- ▶ Indications:
 - ▶ Alzheimer's disease,
 - ▶ dementia with Lewy-bodies,
 - ▶ Parkinson's disease (although here ACh decrease is needed, but MAO-B inhibitor effect is utilized)
 - ▶ Also has antidepressant effects (due to BDNF increase)
➔ used in comorbid depression following Parkinson's/Alzheimer's disease



Cholinesterase Inhibitors - Tacrine

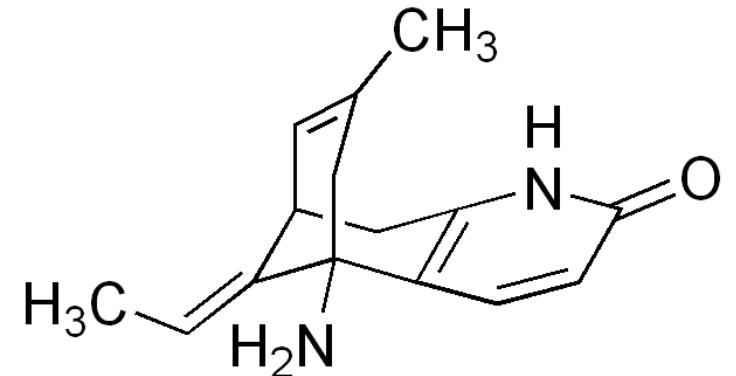
- ▶ first centrally acting cholinesterase inhibitor approved for Alzheimer's disease (Cognex®) (it is withdrawn from market)
- ▶ Mechanism of action:
 - ▶ centrally acting cholinesterase inhibitor
 - ▶ (histamine-N-methyltransferase inhibitor)
- ▶ Pharmacokinetics:
 - ▶ poor bioavailability
 - ▶ metabolised by CYP1A2
 - ▶ its metabolite (hydroxy-tacrine/velnacrine) is also active
- ▶ Adverse effects:
 - ▶ nausea,
 - ▶ diarrhea,
 - ▶ urinary incontinence
 - ▶ Hepatotoxicity



Similar agent still on the market of Russia: ipidacrine (Neiromidin®)

Cholinesterase Inhibitors, NMDA antagonists - Huperzine A

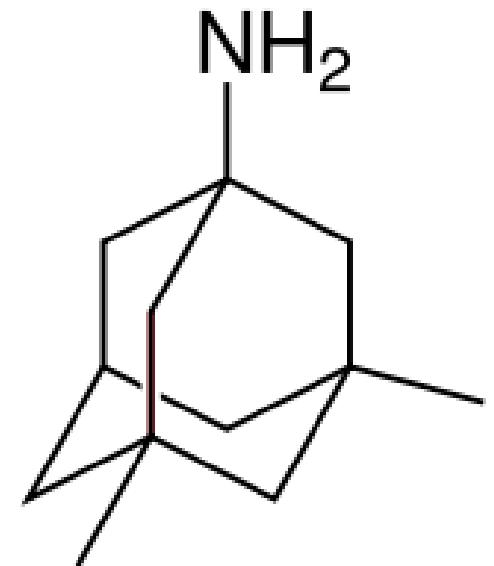
- ▶ Relatively new agent (1990')
- ▶ Found in firmoss/fir clubmoss (Huperzia genus)
- ▶ Mechanism of action:
 - ▶ reversible acetylcholinesterase inhibitor
 - ▶ NMDA receptor antagonist (→ against glutamate excitotoxicity)
- ▶ Adverse effects:
 - ▶ mild cholinergic adverse effects: nausea, vomiting and diarrhea



Huperzia serrata
(toothed clubmoss)

NMDA-antagonists -Memantine

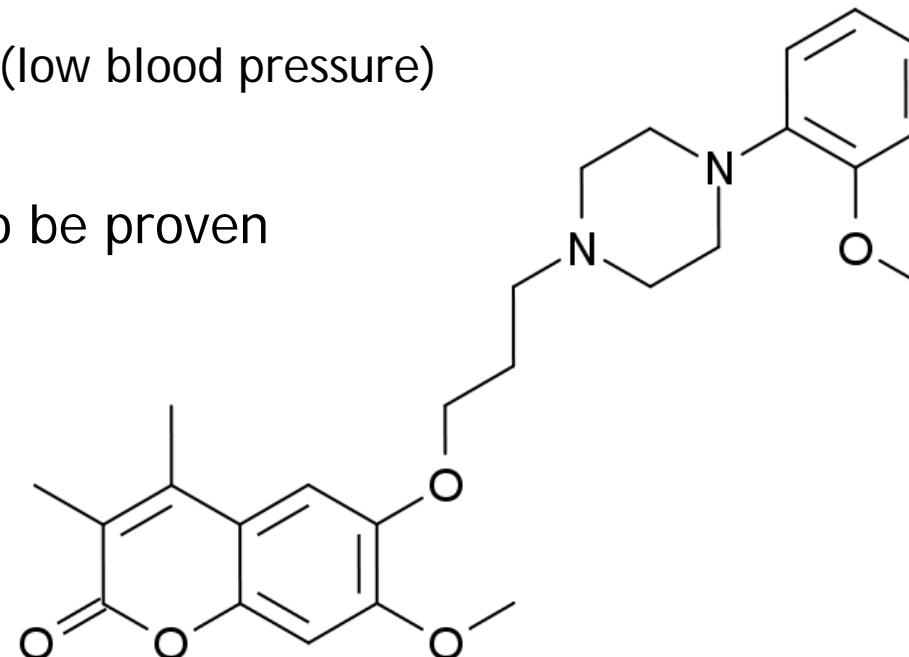
- ▶ Mechanism of action:
 - ▶ NMDA-receptor antagonist
 - ▶ D2-receptor agonist
 - ▶ 5-HT3 rec antagonist
 - ▶ neural-type nACh-rec antagonist (→ initial worsening of cognitive function, later: receptor upregulation → chronic use = cognitive-enhancing)
 - ▶ σ1 receptor agonist
- ▶ Indications:
 - ▶ moderate to severe Alzheimer's disease
 - ▶ dementia with Lewy-bodies
 - ▶ monotherapy or in combination with cholinesterase inhibitors
- ▶ Adverse effects:
 - ▶ constipation,
 - ▶ confusion,
 - ▶ dizziness,
 - ▶ headache,
 - ▶ coughing,
 - ▶ hypertension.



NMDA-antagonists - Ensaculin

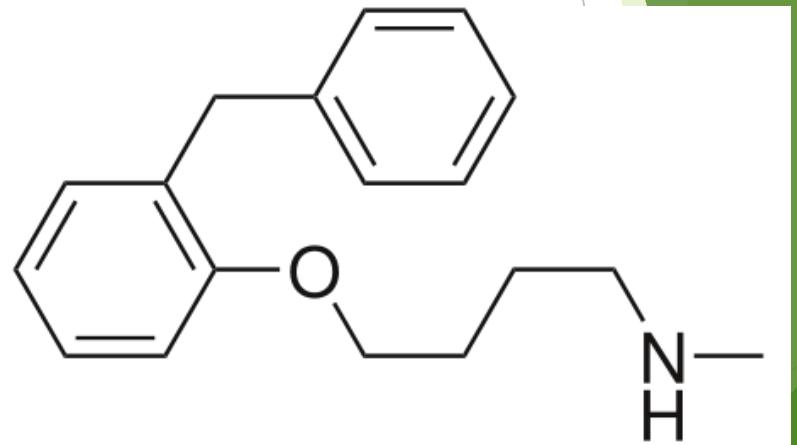
- ▶ relatively new agent (2000's), experimental compound
- ▶ Mechanism of action:
 - ▶ weak NMDA antagonist
 - ▶ 5HT_{1A} agonist
- ▶ Effect:
 - ▶ nootropic
- ▶ adverse effects:
 - ▶ orthostatic hypotension (low blood pressure)

efficacy in humans has yet to be proven



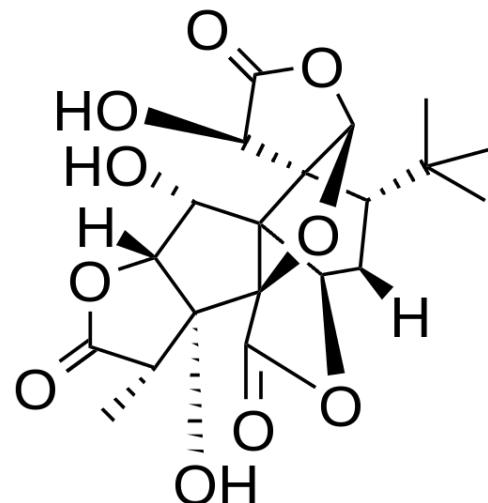
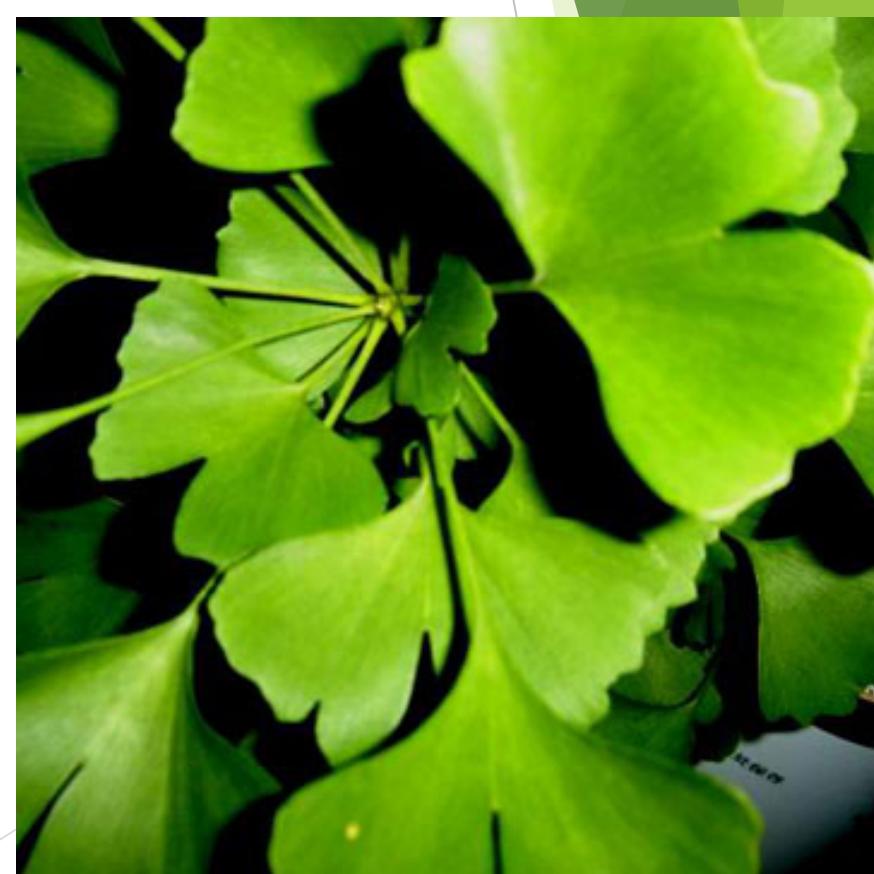
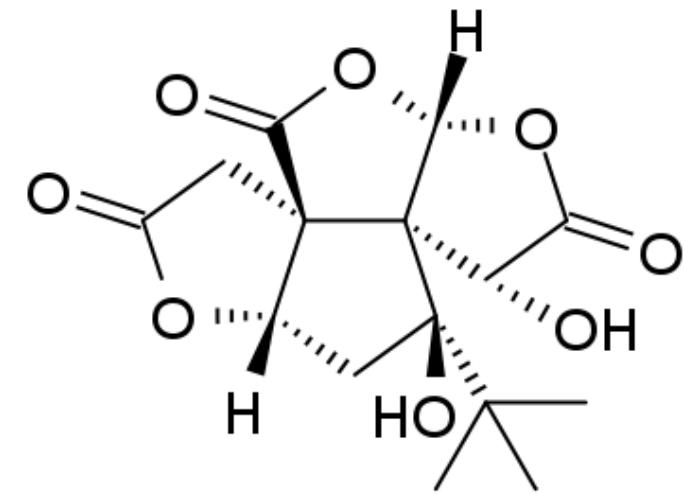
MAO-inhibitors - Bifemelane

- ▶ Tradenames: Alnert®, Celeport®
- ▶ Mechanism of action:
 - ▶ reversible inhibitor of MAO-A
 - ▶ irreversible inhibitor of MAO-B
 - ▶ weak norepinephrine reuptake inhibitor
 - ▶ stimulates cholinerg system in the brain (mechanism unknown)
- ▶ Effects:
 - ▶ antidepressant
 - ▶ nootropic,
 - ▶ neuroprotective,
- ▶ Indications:
 - ▶ depression
 - ▶ senile dementia,
 - ▶ cerebral infarction,
 - ▶ glaucoma (unknown mech.)



Other drugs – *Ginkgo biloba* extract

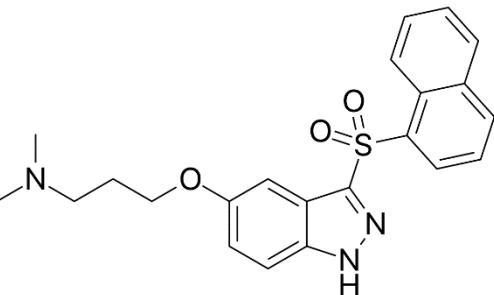
- ▶ **Bilobalide** is a biologically active terpenic trilactone present in *Ginkgo biloba*.
- ▶ Mechanism of action:
 - ▶ negative allosteric modulator at the GABA_A and GABA_A-rho receptors (later is GABA-channel consisting of only rho-subunits)
 - ▶ possibly it is selective for the subunits predominantly implicated in cognitive and memory functioning such as α5
 - ▶ antioxidant
- ▶ **Ginkgolide B** is a diterpenoid trilactone with six five-membered rings
- ▶ Mechanism of action:
 - ▶ antagonist at PAF receptor (→ for treatment of cardiovascular diseases)
 - ▶ non-competitive inhibitor of glycine receptors (→ for treatment of cerebrovascular diseases and migraine)



Other drugs - „-pirdine"s (5-HT-antagonists)

Cerlapirdine

- ▶ as of 2011, it is in phase II clinical trials



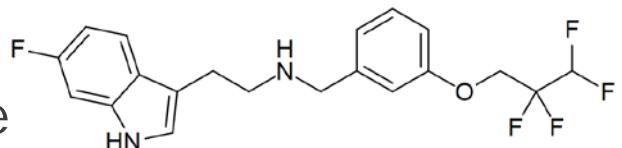
Mechanism of action:

- ▶ selective 5-HT₆ receptor antagonist

Indication:

- ▶ for the treatment of cognitive disorders associated with Alzheimer's disease and schizophrenia

Idalopirdine



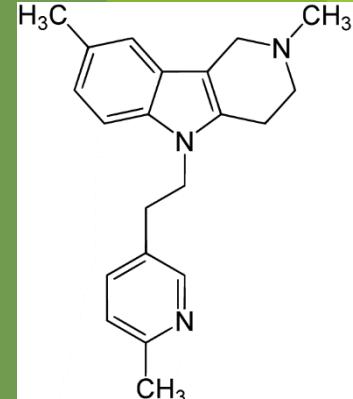
- ▶ Failed in phase III clinical trials

Mechanism of action:

- ▶ potent and selective 5-HT₆ receptor antagonist

Indication:

- ▶ Alzheimer's disease
- ▶ cognitive deficits of schizophrenia



Latrepirdine also known as dimebolin

- ▶ All Phase III trial for latrepirdine in Alzheimer's disease failed

Mechanism of action:

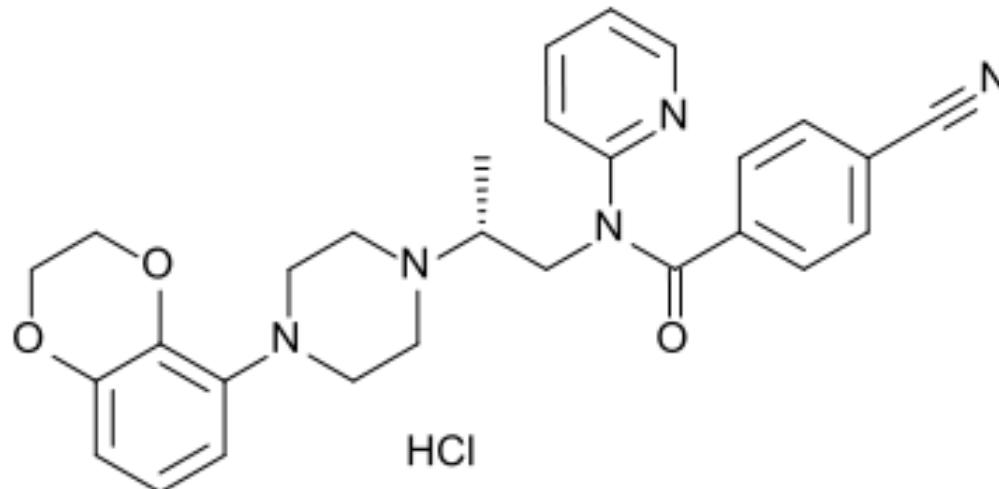
- ▶ inhibition of α-adrenergic, 5-HT_{2C}, 5-HT_{5A}, and 5-HT₆ receptors
- ▶ blocking the action of neurotoxic beta-amyloid proteins
- ▶ inhibiting L-type calcium channels
- ▶ modulating AMPA and NMDA glutamate receptors
- ▶ blocking a novel target that involves mitochondrial pores

Indication:

- ▶ Alzheimer's disease
- ▶ nootropic, neuroprotective effect

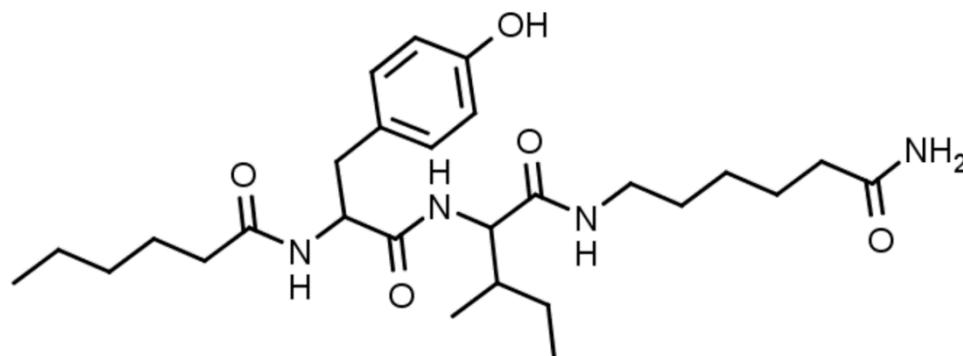
Other drugs - Lecozotan

- ▶ As of June 2008, the first Phase III clinical trial has been completed
- ▶ Mechanism of action:
 - ▶ competitive, selective 5-HT1A receptor antagonist
→ enhances the potassium-stimulated release of acetylcholine and glutamate



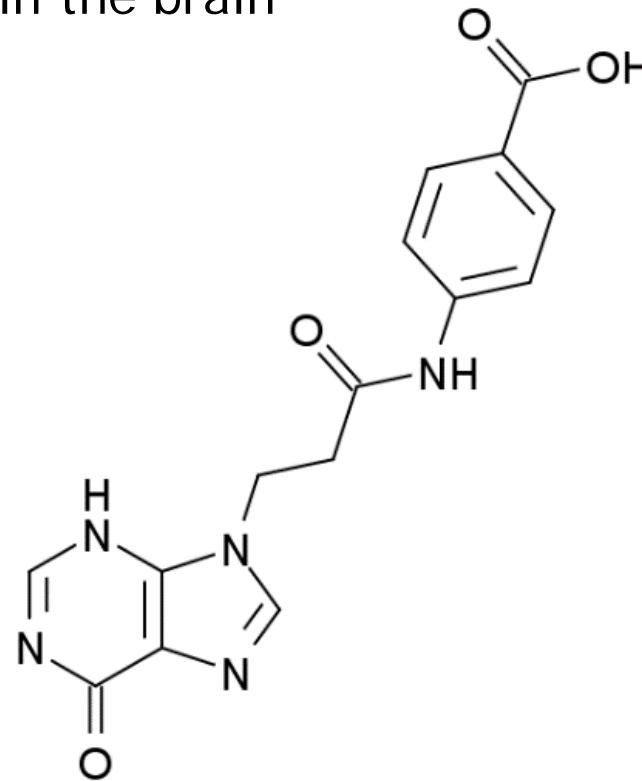
Other drugs - Dihexa

- ▶ very new agent (2010's)
- ▶ Mechanism of action:
 - ▶ binds with high affinity to hepatocyte growth factor (HGF) and potentiates its activity at its receptor
- ▶ In an assay of neurotrophic activity, Dihexa was found to be seven orders of magnitude more potent than brain-derived neurotrophic factor (BDNF).



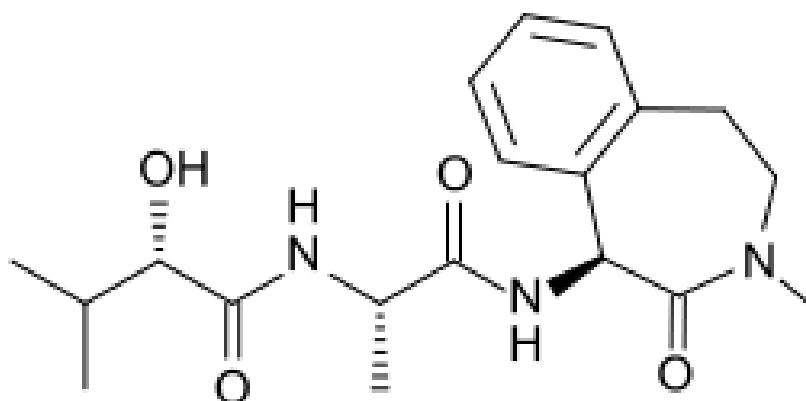
Other drugs - Leteprinim

- ▶ effects:
 - ▶ neuroprotective and nootropic effects.
- ▶ Mechanism of action:
 - ▶ stimulates release of nerve growth factors
→ enhances survival of neurons in the brain
- ▶ Indication:
 - ▶ Alzheimer's disease,
 - ▶ Parkinson's disease
 - ▶ stroke



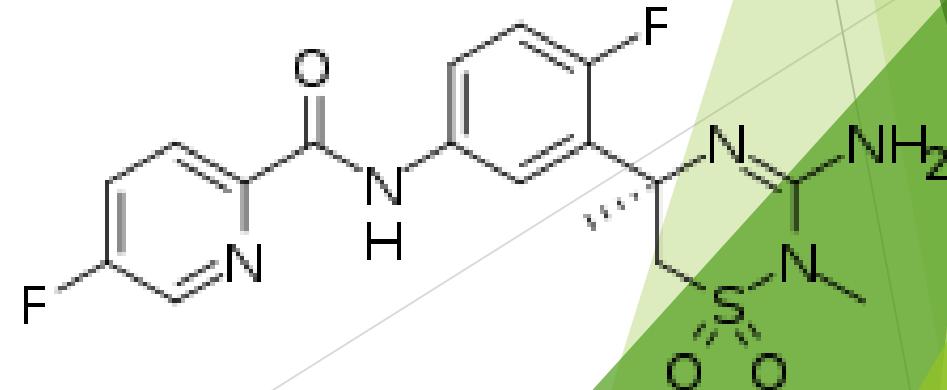
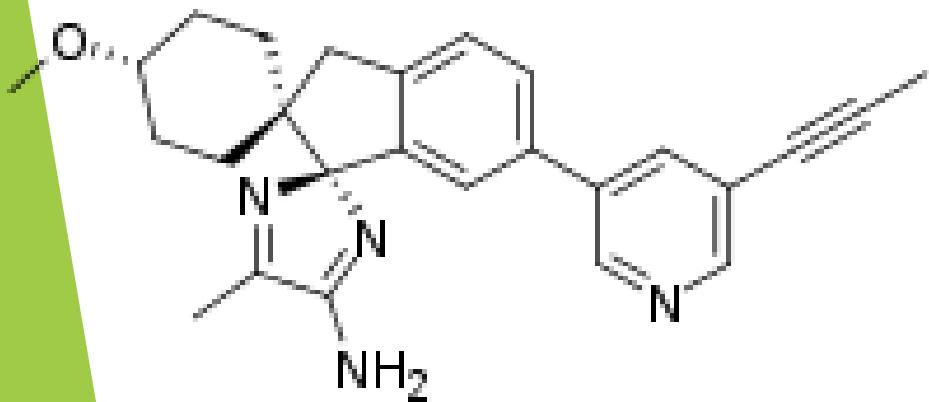
Other drugs - Semagacestat

- ▶ It failed in phase III trials in August 2010 because semagacestat performed worse than the placebo
- ▶ Mechanism of action:
 - ▶ blocks the enzyme γ -secretase
- ▶ Indications:
 - ▶ Alzheimer's disease.



Other drugs – BACE-inhibitors

- ▶ Lanabecestat and verubecestat
- ▶ Mechanism of action:
 - ▶ They block the enzyme β -secretase (beta-site APP cleaving enzyme 1 = BACE)
- ▶ Indications:
 - ▶ early phase of Alzheimer's disease
- ▶ Both lanabecestat and verubecestat failed Phase III in 2018.



Other drugs - Ergoloid

Tradename: Hydergin

mixture of dihydrogenated ergot alkaloids

► Mechanism of action:

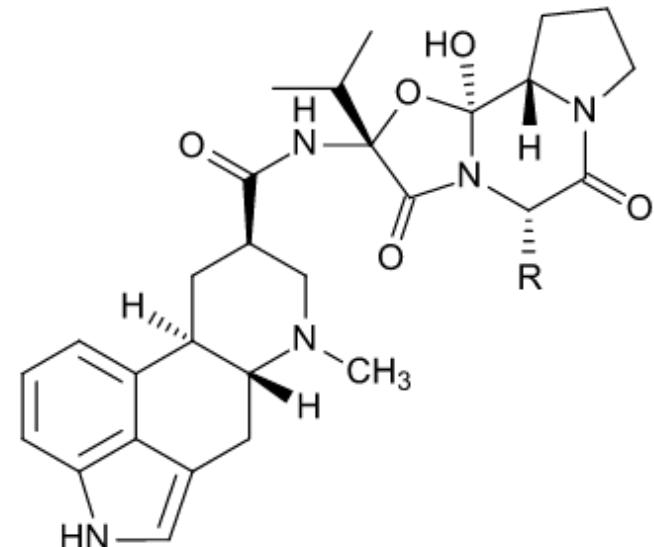
- stimulates dopaminergic (and serotonergic) receptors
- inhibition of alpha-adrenoreceptors
- inhibition of MAO (questioned)

► Indications:

- Alzheimer's and other types of dementia
- recovery after stroke

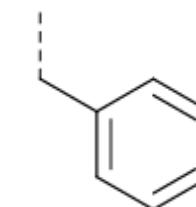
► Adverse effects:

- nausea
- gastrointestinal disturbances
- orthostatic hypotension

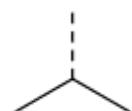


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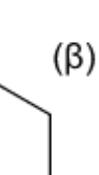
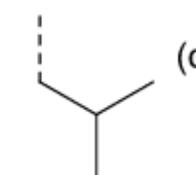
-cristine:



-cornine:



-cryptine:

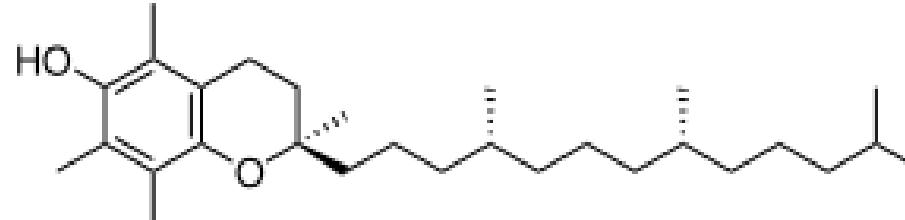


Other drugs - antioxidants

antioxidants have been studied in AD on the basis of pathophysiology theories involving free radicals

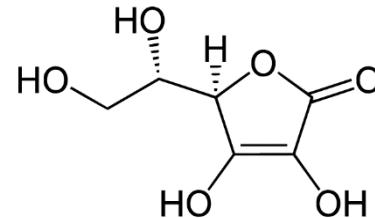
Vitamin E (tocopherol)

- ▶ antioxidant
- ▶ for complementary therapy



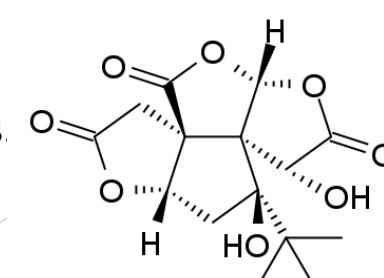
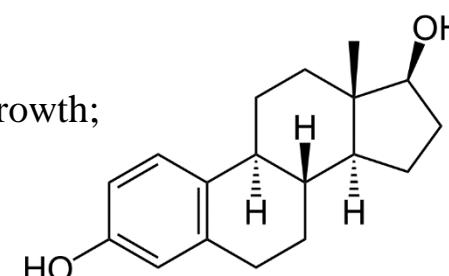
Vitamin C (ascorbic acid)

- ▶ antioxidant



Estrogen.

- ▶ Mechanism of action:
 - ▶ Estrogen interacts with nerve growth factor, promotes synaptic growth;
 - ▶ antioxidant
 - ▶ may help maintain normal cholinergic transmission
- ▶ Bilobalid (from *Ginkgo biloba*) also has antioxidant properties.



Other drugs – cerebral blood-flow enhancers

Vinpocetine (Cavinton)

- ▶ semisynthetic derivative alkaloid of vincamine, an extract from the periwinkle (plant) *Vinca minor*.

Hungarian discovery!

▶ Effects:

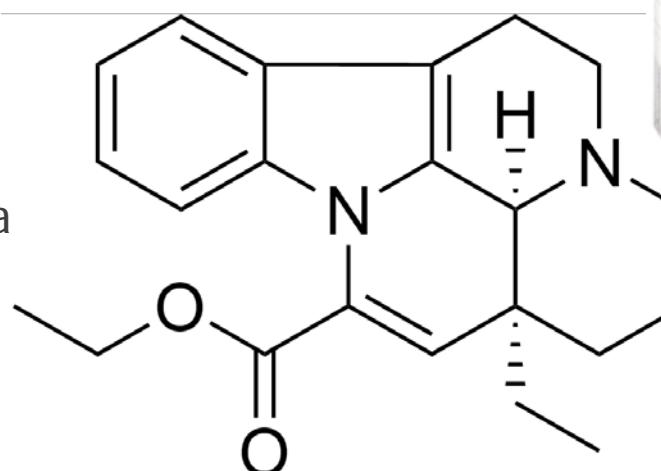
- ▶ enhances cerebral blood-flow
- ▶ neuroprotective effects

▶ Mechanism of action:

- ▶ selectively inhibits voltage-sensitive Na⁺ channels
→ decreased Ca²⁺ influx → less excitotoxicity = neuroprotection
- ▶ PDE₁ inhibitor → cerebral vasodilator effect = cerebral blood-flow enhancer

Indications:

- ▶ Alzheimer's and other types of dementia
- ▶ stroke recovery



Other drugs – cerebral blood-flow enhancers

Piracetam

► Mechanism of action:

- ▶ exact mechanism is unknown
- ▶ positive allosteric modulator of the AMPA receptor
- ▶ improves the functioning of mACh-rec (positive allosteric modulator?)
- ▶ inhibits platelet aggregation
- ▶ enhances blood-cell deformability
→ used in blood-flow disorders e.g. Raynaud-syndrome

► Indications:

- ▶ Alzheimer's and other types of dementia
- ▶ tinnitus, vertigo - blood-flow disorder of inner ear
- ▶ Raynaud-syndrome

Pentoxifylline

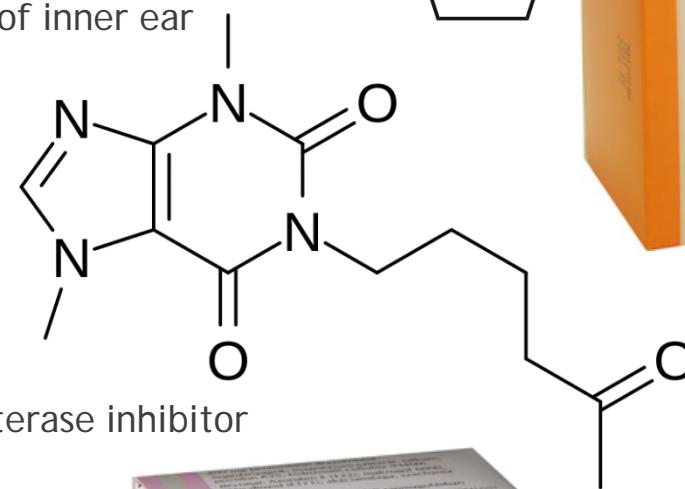
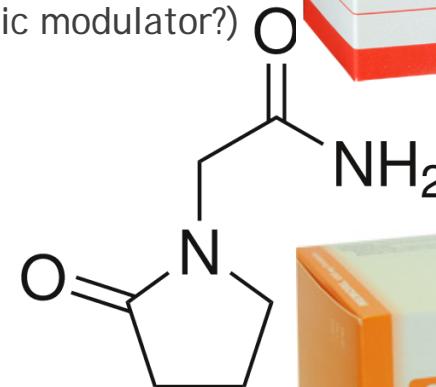
► Pentoxifylline is a xanthine derivative.

► Mechanism of action:

- ▶ competitive nonselective phosphodiesterase inhibitor
- ▶ adenosine A₂-rec antagonist
- ▶ improves red blood cell deformability

► Indications:

- ▶ peripheral artery/vascular disease
- ▶ Raynaud-syndrome



Other drugs

The mechanism of action in Alzheimer's disease is unknown.

NSAIDs

- ▶ Regular NSAID use ➔ lower incidence of AD in epidemiologic studies.
- ▶ Ibuprofen and indometacin, but not aspirin
- ▶ Explanation: Role of Immune system in Alzheimer's disease?
 - ▶ immune system constituents are present near areas of plaque formation

Statins (HMG-CoA reductase inhibitors)

- ▶ Statins were associated with lower prevalence of AD.
- ▶ Pravastatin and lovastatin, but not simvastatin,
- ▶ Explanation: Elevated cholesterol may lead to Alzheimer's?
 - ▶ Elevated cholesterol levels in brain neurons may alter cell membrane functioning and result in the cascade leading to plaque formation.

Approved in US

► Cholinesterase Inhibitors

- ▶ Donepezil (Aricept®) (for mild, moderate, severe AD)
 - ▶ Rivastigmine (Exelon®)(oral & patch) (for mild to moderate AD)
 - ▶ Galanthamine (Razadyne®, Razadyne ER®) (for mild to moderate AD)



► NMDA-antagonist

- ▶ Memantine (Namenda®)
(from moderate to severe AD)



► Fixed Combination

- ▶ Memantine/donepezil (Namzaric®)
(from moderate to severe AD)
 - ▶ (for patients already stabilized on donepezil)



► Food supplements approved for Alzheimer

- #### ► Caprylidene (Axona)

- ▶ Caprylidene is a prescription medical food that is metabolized into ketone bodies.
The brain can use these ketone bodies for energy when its ability to process glucose is impaired, which brain-imaging scans suggest is the case in AD.



„There is insufficient evidence to recommend other pharmacological treatments for Alzheimer’s Disease patients in general.”