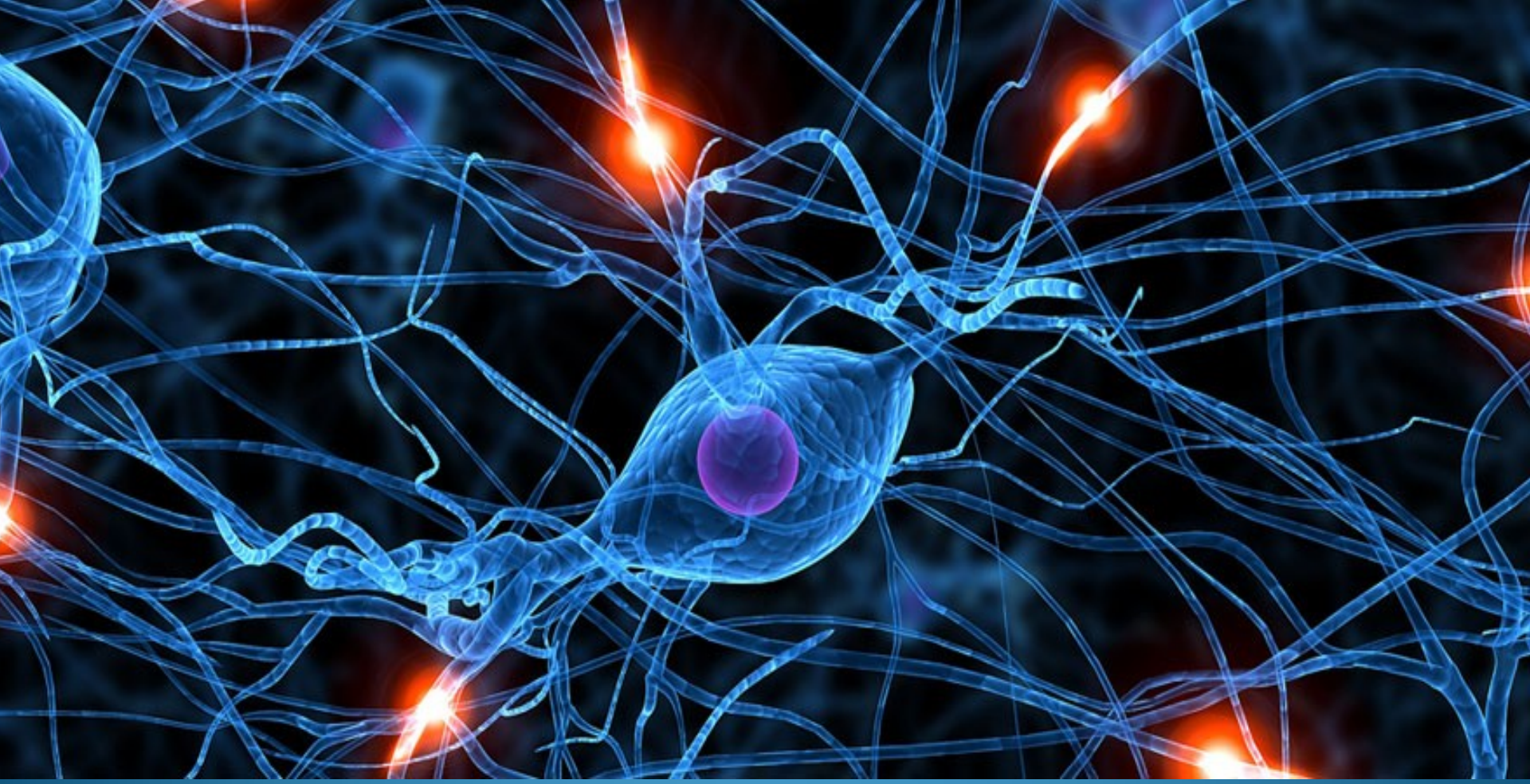
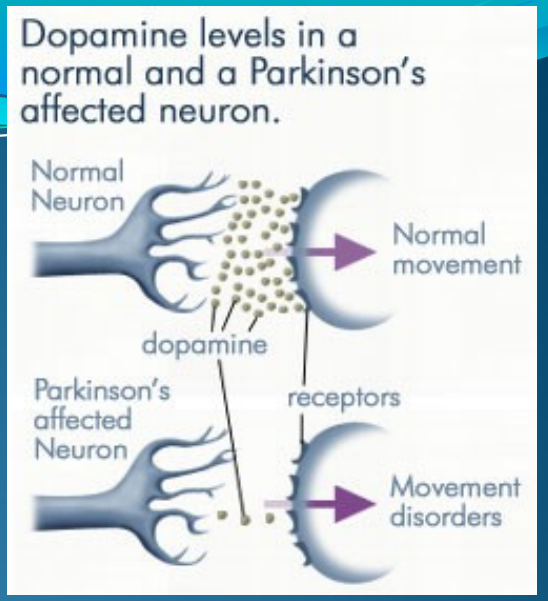


## Overview of pharmacotherapy of:

- Parkinson‘s disease and parkinsonism
- choreatic dyskinesias
- spastic disorders
- *myasthenia gravis*
- Ménière‘s disease

# Parkinson‘s disease




- Degenerative disease of CNS:
  dying of **dopaminergic neurons**
  = dopamine deficit

- Non-specific symptoms: fatigue, depression
- **Specific symptoms**:
  - Resting tremor, stiffness (rigidity) and increased muscle tone, postural impairments
  - Extent of movements is limited, ability to move is slown down
  - Impairment of the movement initiation, akinesia (sudden inability to move)
  - Typical changes in walking, graphomotor skills and facial mimics

- Psychiatric symptoms: cognitive impairment
- Late-onset dyskinesia (night akinesia, morning stiffness, cramps)
- https://www.youtube.com/watch?v=j86omOwx0Hk

- Dopamine (DA) deficit → DA precursor: **LEVODOPA**
- Metabolised by DOPA decarboxylase to DA in CNS
- Used orally several times a day
- **AE:**

  a) ***Metabolism to DA in periphery*** = vomiting, diarrhea, gastric ulcers, hypertension, tachycardia…

  b) ***DA excess*** = hallucinations, agression, psychosis (rarely)

- + **COMT inhibitors** (catechol-O-methyl transferase)
  - entacapone, tolcapone
- + **Peripheral DOPA decarboxylase inhibitors**
  - carbidopa, benserazide

- ***Wearing-off effect*** – quick subsiding of the effect

- Dopamine (DA) deficit → **D receptors agonists**
- Used orally or by TTS
- **AE:** drowsiness, irresistible falling asleep („sleep attacks“)

a) ***Ergoline derivatives*** – bromocriptine, **pergolide**, dihydroergocriptine

- Ergot alkaloids derivatives
- **AE:** fibrotic changes in lungs, heart valves + increased risk of psychiatric AE (psychotic symptoms)

b) ***Non-ergoline drugs*** – ropinirole, **pramipexole**, rotigotine

- Lower risk of psychiatric AE, no fibrotic changes

**Adjuvant therapy of Parkinson's disease:**

- **Selegiline** – MAO B inhibitor (DA degradation enzyme)

- *Anticholinergics:*
  - Relative excess of ACh → worsening of dyskinesia
  - Only for short-term use
  - **Contraindication:** elderly, patients with cognitive deficit
  - **AE:** anticholinergic effects – 3rd lecture
  - **Amantadine** – i.v. infusion in severe acute dyskinesia
  - Biperiden, procyclidine – used orally

# Drug-induced extrapyramidal reactions

- Abnormal reaction of dopaminergic system
  - Imbalance between DA and ACh in CNS
  - Up-regulation of D receptors in basal ganglia
- **Dystonia**, **akathisia**, facial **choreatic movements**
- **Tardive dyskinesia**, parkinsonism

a) **Typical (classical) antipsychotics** – chlorpromazine, levopromazine, prochlorperazine, perfenazine, haloperidol…
   - Approx. 20% pacients !

b) $H_1$ antihistamines of 1st generation – thiethylperazine, prometazine
c) Prokinetic agents – metoklopramid
d) Older antihypertensive – reserpine, α-methyldopa
e) Antivertigo agents – cinnarizine, flunarizine
f) Antiepileptics – phenytoin, carbamazepine
g) Antidepressants – tricyclic AD, trazodone
h) Centrally active muscle relaxant baclofen

**Pharmacotherapy:**

- **Switch to safer drug** (safer antipsychotic etc.)

  **+**

- Dystonia, akathisia → i.v., p.o. **anticholinergics**
- Tardive dyskinesia → sometimes i.m. **botulinum toxin**
- Parkinsonism → **antiparkinson agents**

- **Benzodiazepines** p.o., i.v. – sedation, muscle relaxation
  - Enhace GABAergic transmission

# Choreatic dyskinesia

= unintentional, involuntary, quick, irregular movements

Causes:

- Huntington‘s chorea (hereditary neurodegenerative disease)
- vascular chorea (ischemia in basal ganglia)
- *chorea minor* (autoimmune disease)

**Pharmacotherapy:**

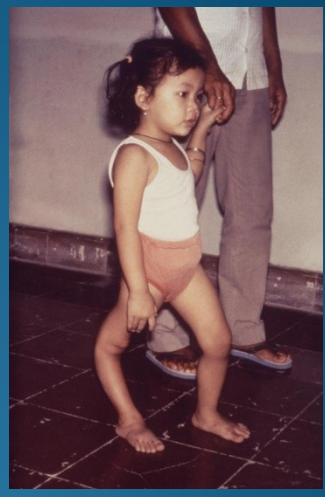
- ***Antipsychotics*** – typical (haloperidol), or atypical (risperidone)
  - Risk of additional extrapyramidal reactions
- Reserpine, tetrabenazine – ↓ levels of DA in CNS
  - Risk of additional extrapyramidal reactions, depression, hypotension
- ***Benzodiazepines*** (clonazepam)
- Amantadine

# Spastic disorders

Caused by damages of motor neurons:

a) *peripheral motor neurons* – ↓ muscle tone, strenght, progressive atrophy of skeletal muscles, long bones and skin

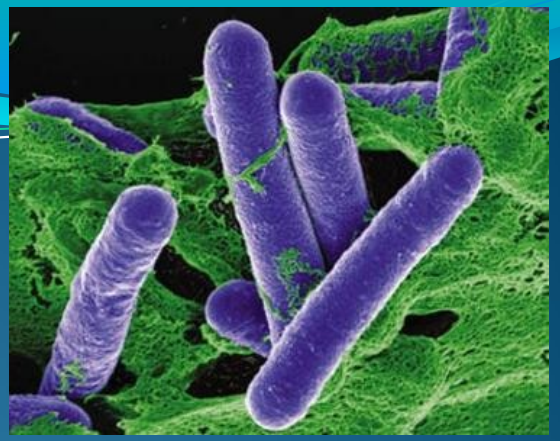
- *poliomyelitis anterior acuta*
- Charcot-Marie-Tooth disease
- *myasthenia gravis*



b) *central motor neurons* – ↑ muscle tone, muscle contractures, limited ability of joints to move, joint dislocations, muscle hypertrophy → atrophy, deformities of long bones

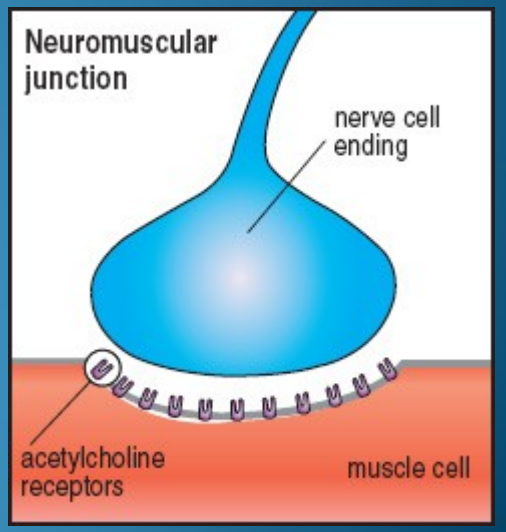
- Cerebral palsy (CP)

**Pharmacotherapy is an adjuvant treatment – improves the results of physiotherapy, or enables it to be carried out!**



## Botulinum toxin A

- Polypeptide from *Clostridium botulinum*
- Injected i.m. into the spastic muscles
- Causes **irreversible inhibition of ACh release** in NJs – **peripherally active muscle relaxant** (presynaptically acting)
- **Alleviate pain** associated with spasms
- **Enables muscle growth** – benefit for children with CP
- Administered repeatedly, but sometimes 1 inj. can act even for 12 months
- Reinnervation of muscles – new NJs are created in the muscle → spasms reoccur
- **Improves physiotherapy effects!**



- Spasticity of larger areas → centrally acting muscle relaxants

**BACLOFEN**

- $GABA_B$ agonist – enhances **GABAergic transmission** = inhibits release of excitatory AA (glutamate, aspartate)
- **AE:** drowsiness, confusion, hypotension, muscle weakness
- Progressive **tolerance** – need for higher doses
- **Intrathecal administration** – s.c. pump with catheter inserted into subarachnoideal space = lower doses

**$\alpha_2$ RECEPTOR AGONISTS**

- Activation lead to decrease of neurotransmitter levels in CNS – in spinal cord activation inhibits release of excitatory AA
- **AE:** sedation, xerostomia, bradycardia, hypotension
- **tizanidine**, clonidine

**BENZODIAZEPINES** – clonazepam, tetrazepam, diazepam

Other drugs used in spastic disorders:

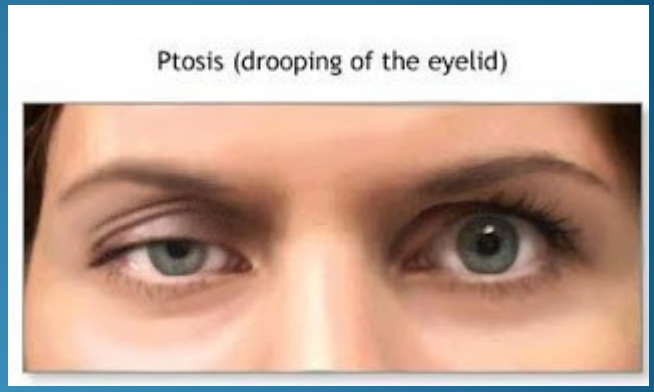
- **dantrolene**
- **gabapentin, lamotrigine** – antiepileptics (GABAergic MoA)
- **riluzole** – amyotrophic lateral sclerosis

**Cannabinoids**

- Mixture of **THC** and **cannabidiol** (oral spray)
- Agonists of **$CB_1$** and **$CB_2$ receptors**, decrease releasing of excitatory AA
- Good therapeutical outcome in 30–40% patients
- **AE:** psychiatric (mood changes, depression, cognitive impairment, appetite changes etc.), GIT AE, off-balance, drowsiness etc.
- Young patients – increased **risk of schizophrenia** or **psychosis development !**

# Myasthenia gravis

- **Autoimmune disease** – autoantibodies aganist $N_M$ receptors of NJs (women > men)
- Fluctuating muscle weakness, patient get tired easily, worsening in afternoon and evening and after muscle strain
- 1st symptoms: **ocular muscles**, ptosis
- Progression: **facial muscles** (facial weakness), **head and neck muscles** (difficulties with chewing, swallowing, speaking etc.)




- Severe progression: **myasthenic crisis** – respiratory muscles

- Drugs inducing MG: interferon α
- Drugs worsening MG: aminoglycosides, quinidine, quinine, chloroquine, i.v. $Mg^{2+}$

- Cholinomimetics – **acetylcholine esterase inhibitors**
  = ↑ levels of ACh v synaptic clefts and NJs
  - **pyridostigmine** – p.o. several times a day
  - neostigmine – short-term acting, before muscle strain
  - ambedonium – $N^+$, no central effect

- **AE:** activation of ACh receptors = cholinergic effects:

a) ***muscarinic*** (salivation, sweating, streaming eyes, miosis, blurred vision, nausea, diarrhea, abdominal cramps, bronchospasmus, confusion, restlessness…)

b) ***nicotinic*** (fasciculations)

c) accumulation → ***cholinergic crisis*** = depolarization blockade of ANS ganglia and NJs

- muscle weakness, potentially life-threatening
- therapy: mechanical ventilation + i.v. atropine

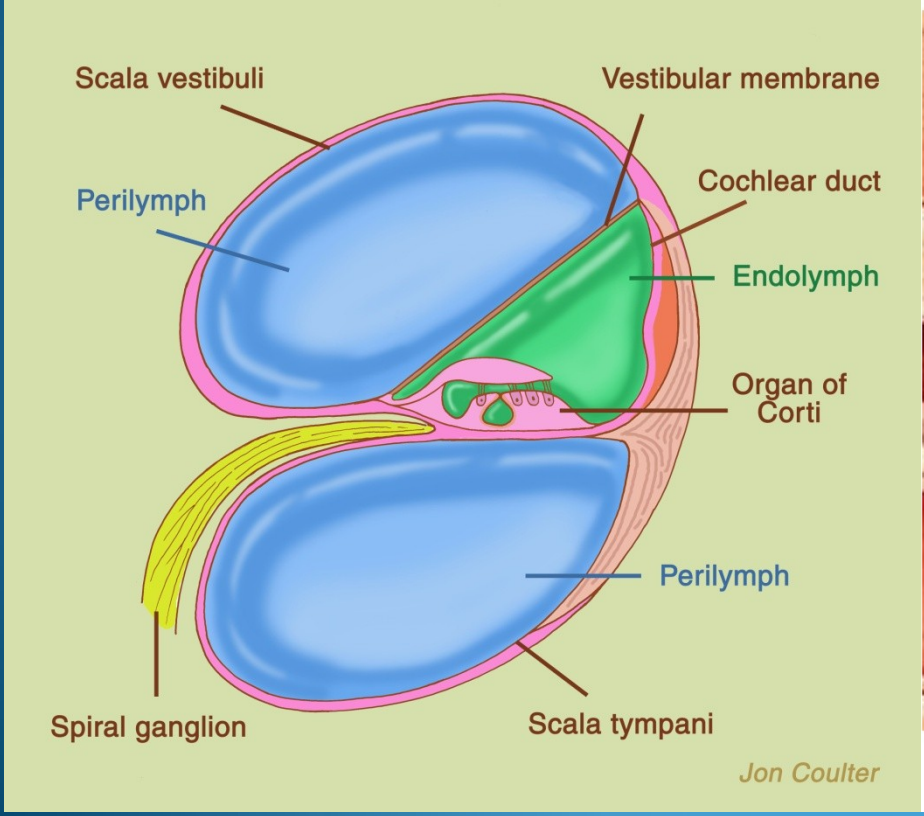
- The cause is autoimmunity → **immunosuppressives**
- Decrease number of B-cells, which produce antibodies
- **AE: non-specific effect** = suppression of overall immune reactions – ↑ infections, risk of sepsis, risk of cancer

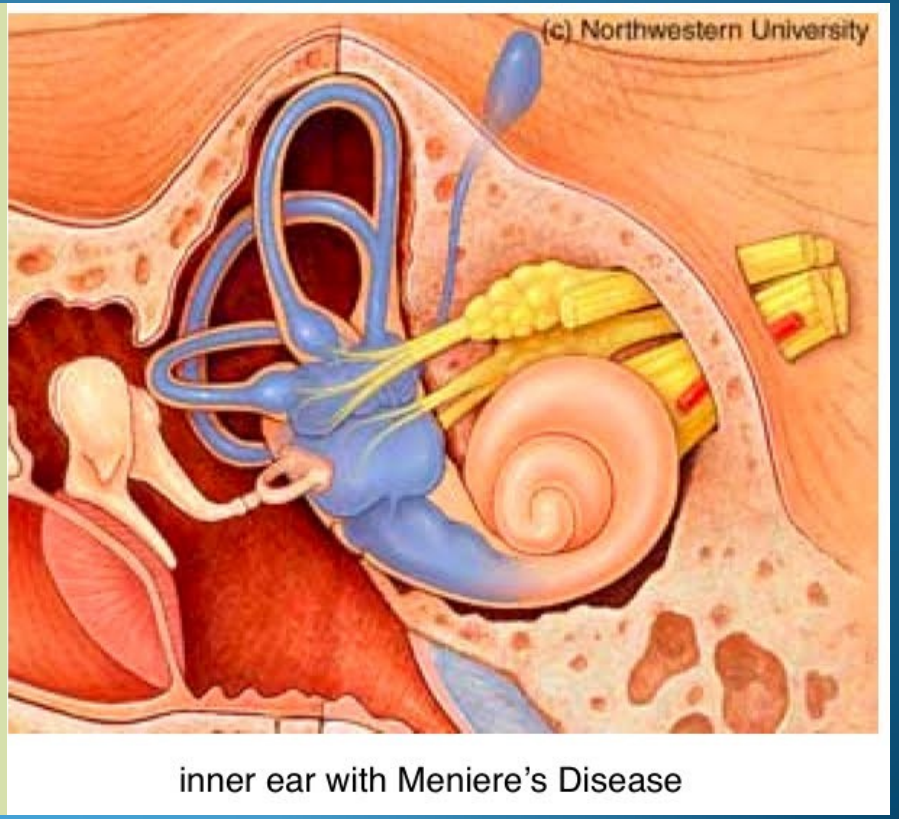
- **Glucocorticoids** (prednisone, prednisolone, methylprednisolone)
  - Titration dose, the **lowest efficient dose** is used
  - **Long-term** oral therapy with **typical AE** (stomach, adipose tissue, diabetes, bone structure…)
- **Azathioprine** – stops proliferation of lymphocytes
  - Combination with corticoids – enables lower doses

- Other immunosupressives: cyclosporin, mycophenolate, methotrexate, tacrolimus

# Ménière's disease

- Disease of the inner ear – **endolymphatic hydrops**
- Accumulation of endolymph + distended endolymphatic space
- **Acute attack:** microrupture of vestibular membrane between endolymphatic and perilymphatic space
  - Dizziness (vertigo), nystagmus, tinnitus, hearing loss…




inner ear with Meniere's Disease

## BETAHISTINE

- $H_3$ receptor antagonist
  - CNS, receptors of negative feedback
  - Regulate histaminergic transmission
  - Antagonism = ↑ release of histamine
- Vasodilation in the inner ear – better microcirculation
- Long-term use (lifelong), orally

## CINNARIZINE

- $H_1$ receptor antagonist + T-type **$Ca^{2+}$ channel blockator**
- Antivertigo and prophylactic effect
- Used orally

## Cerebral vasodilators and hemorheologics

- Improve circulation in CNS
- Increase erythrocytes deformability, reduce blood viscosity
- Mild antitrombotic, antiinflammatory and antioxidative effect
- Used orally, i.v. in acute cases
- **Standardized extract from *Ginkgo biloba***
- **Vinpocetine**
- **Pentoxifylline**


## Other drugs used for prophylaxis

- Glucocorticoids, diuretics – antiedema effects

- Acute attack of Ménière‘s disease – nausea, vomiting, dizziness, hearing loss, tinnitus, feeling of the pressure in the ear…

**Antiemetic/antivertigo drugs:**

- **$H_1$ antihistamines of 1st generation**
  - cross BBB, central effects
  - used also for the treatment of **motion sickness**
  - embramine, moxastine, dimenhydrinate…
  - **AE:** drowsiness, attention (vigilance) deficit
- **thiethylperazine** – $D_2$ receptor antagonist (suppositories)
- **cinnarizine + $H_1$ antihistamines**