Skeletal muscle relaxants are pharmacologically active substances which determine the relaxation of skeletal muscles. These drugs are used during surgical procedures to cause paralysis (ie, neuromuscular blockers) or to reduce spasticity in neurologic diseases (ie, spasmyotics). Spasticity is associated with cerebral palsy, multiple sclerosis or stroke and it is characterized by an increase in tonic stretch reflexes, increase in flexor muscle spasms and muscle weakness.

Classification of skeletal muscle relaxants based on the site of action (skeletal muscle, neuromuscular end plate or central nervous system):

1. Direct acting muscle relaxants: Dantrolene
2. Neuromuscular blockers (antagonists of Nm receptors or curare-like substances)
   2.1. nondepolarizing neuromuscular blocking drugs:
       - long acting:
         - isoquinoline derivatives: D-tubocurarine, Doxacurium, Metocurine
         - steroid derivatives: Pancuronium, Pipecuronium
       - other structure: Gallamine
       - intermediate acting:
         - isoquinoline derivatives: Atracurium, Cisatracurium
         - steroid derivatives: Rocuronium, Vecuronium
       - short acting: Mivacurium
   2.2. depolarizing neuromuscular blocking drugs:
       - ultrashort acting: Succinylcholine.
3. Centrally acting muscle relaxants
   3.1. GABA-A receptor agonists (agonists on benzodiazepine BZD1 and BZD2 receptors):
       Diazepam, Clonazepam
   3.2. GABA-B receptor agonist: Baclofen
   3.3. GABA-A and GABA-B receptor agonists: Glycine, Progabid, Idrocilamide
   3.4. Inhibitor of glutamatergic transmitters: Riluzole
   3.5. Antagonists on alpha2 presynaptic receptors: Tizanidine, Dexmedetomidine
   3.6. Antimuscarinic drugs: Chlorzoxazone, Cyclobenzaprine, Chlorphenesin, Mephenesin, Metaxolone, Methocarbamol, Orphenadrine, Carisoprodol
   3.7. Inhibitor of release of acetylcholine: Botulinum toxin

1. DIRECT ACTING MUSCLE RELAXANTS: DANTROLENE

Mechanism of action: block ryanodine receptors from the calcium channels of sarcoplasmic reticulum in the skeletal muscle fibers, which inhibit the release of calcium from the sarcoplasmic reticulum of skeletal muscle.

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1 Ryanodine receptors mediate the release of calcium ions from the sarcoplasmic reticulum, an essential step in skeletal muscle contraction.
Pharmacodynamic effects: inhibition of calcium release in sarcoplasmic reticulum determines skeletal muscle relaxation.

Pharmacokinetics: administration oral or intravenous (in case of emergency).

Indications:
• spasticity (it is an adaptation to pyramidal tract injury in diseases such as hemiplegia, multiple sclerosis, etc.).
• malignant hyperthermia (the syndrome is due to a genetic defect in the sequestration of calcium in the sarcoplasmic reticulum and it is characterised by generalized skeletal muscle contracture, rigidity, severe hyperthermia resulting from skeletal muscle contraction which produce heat, accelerated muscle metabolism, endogenous accumulation of lactic acid metabolic acidosis, and tachycardia).

Adverse effects:
• hepatitis (1-10% of cases are lethal after 60 days of treatment);
• abnormal liver function tests (in chronic administration);
• fatigue and weakness (due to muscle contraction); sedation.

2. NEUROMUSCULAR BLOCKERS
The mechanisms of action, pharmacodynamic effects, pharmacokinetics, indications, contraindications, side effects → See chapter on the pharmacology of SNV, antagonists of acetylcholine.

3. CENTRALLY ACTING MUSCLE RELAXANTS
3.1. GABA-A receptor agonists (agonists on benzodiazepine BZD1 and BZD2 receptors): Diazepam, Clonazepam → See chapter on the benzodiazepines. Particularly, benzodiazepines cause relaxation of skeletal muscles flexors (Clonazepam → in non sedative doses).

3.2. GABA-B receptor agonist: Baclofen
Mechanisms of action:
• agonist on GABA-B;
• inhibition of the release of substance P → analgesic effect.

Pharmacodynamic effects:
• skeletal muscle relaxation;
• analgesia.

Indications:
• spasticity in diseases with lesions of the pyramidal tract (hemiplegia, paresis, multiple sclerosis, etc.).

Adverse effects:
• muscular hypotonia;
• rarely, sedative effect; increase the frequency of seizures in patients with epilepsy; in intrathecal administration → fever, drowsiness, respiratory depression, tolerance (after several months of therapy).

3.3. GABA-A and GABA-B receptor agonists: Glycine, Progabid, Idrocilamide
• reduce spasticity of the skeletal muscles;
• Idrocilamide is indicated in amyotrophic lateral sclerosis.
3.7. INHIBITOR OF GLUTAMATERGIC TRANSMITTERS: RILUZOLE
  
  **Mechanism of action:** inhibition of glutamatergic transmission.
  
  **Pharmacodynamic effects:** reduce spasticity of the skeletal muscles.
  
  **Indications:** amyotrophic lateral sclerosis.

3.5. ANTAGONISTS ON ALPHA2 PRESYNAPTIC RECEPTORS: TIZANIDINE, DEXMEDETOMIDINE - See chapter on medication acting on vegetative system.

3.6. ANTIMUSCARINIC DRUGS: CHLORZOXAZONE, CYCLOBENZAPRINE, CHLORPHENESIN, MEPHENESIN, METAXOLONE, METHOCARBAMOL, ORPHENADRINE, CARISOPRODOL - See chapter on medication acting on vegetative system.

3.7. INHIBITOR OF RELEASE OF ACETYLCHOLINE: BOTULINUM TOXIN - See chapter on medication acting on vegetative system.

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**II. PHARMACOLOGIC MANAGEMENT OF PARKINSONISM**

**Parkinson's disease** is an idiopathic disease with lesions in locus Niger and other extrapyramidal nuclei.

**Parkinsonism** are manifestations similar to Parkinson's disease in cerebral atherosclerosis; after a traumatic brain injury; after viral encephalitis; after parkinsonian drug poisoning (eg, barbiturate intoxication) poisoning mercury, manganese, carbon monoxide, hydrocyanic acid, carbon disulphide.

**Pseudoparkinsonism** is caused by drugs:
- parkinsonian manifestations after chronic blockade of dopamine receptors in the nigrostriatal region → antipsychotics (neuroleptics);
- parkinsonian manifestations after chronic depletion of catecholamines deposits → reserpine.

Parkinsonism has the following important symptoms: bradykinesia (slowness and poverty of movement), muscular rigidity, resting tremor (which usually is reduced during voluntary movement), and an impairment of postural balance.

**Classification of drugs indicated for the treatment of Parkinson's disease (anti-Parkinson drugs)**

1. **Drugs affecting brain dopaminergic system**
   1.1. Dopamine precursor: Levodopa (L-Dopa) associated or not with:
       - inhibitors of peripheral decarboxylase: Carbidopa, Benserazide
       - inhibitors of type B monoaminooxidase (MAO-B): Selegilline, Rasagiline, Lazabemide, Mofegiline
       - inhibitors of cathecolomethyltransferase (COMT): Entacapone, Tolcapone, Nitecapone
   1.2. Dopamine agonists:
       - Ergopeptine: Bromocriptine, Lisuride, Pergolide, Cabergoline
       - Non-ergopeptine: Piribedil; Ropinirole; Apomorfina; Pramipexole; Talipexole.
   1.3. Drugs facilitating dopamine transmission: Amantadine, amphetamines
2. Drugs affecting cholinergic system

2.1. Antimuscarinic drugs:
   - Centrally and peripherally acting: Natural: Atropine, Scopolamine, synthetic derivative: Benztropine
   - Centrally acting: Trihexyphenidyl, Orphenadrine, Biperiden, Procyclidine

2.2. 1<sup>st</sup> generation H1 receptor antagonists: Diphenhydramine

4. Other drug therapies: Vitamin E, neurotrophic factors.

ANTIPARKINSONIAN DRUGS - Drugs affecting brain dopaminergic system

1. SUBSTITUTION OF THE DOPAMINE DEFICIENCY

   ➢ LEVODOPA

   **Mechanisms of action:**
   - levodopa enters the CNS where it enters in the nerve endings of nigrostriatal neurons (functional neurons), where it is converted into dopamine, which acts as an agonist of dopamine receptors.
   
   **Pharmacodynamic effects** (Levodopa determine these effects in patients with Parkinson's disease. Levodopa does not affect muscle tone or motility in healthy man):
   - improvement of akinesia, bradykinesia;
   - improve the muscle stiffness;
   - improvement of motor function (the facial expression, speech, writing, reading etc);
   - improve the mental functions;
   - remove the apathy, depression;
   - it renews the interest of patients for themselves and for the environment.

   **Pharmacokinetics:**
   - Levodopa crosses the blood-brain barrier; dopamine does not cross the blood-brain barrier;
   - approximately 95% of the administered L-Dopa is decarboxylated and converted to dopamine in periphery → only 1% of the administered dose enters the brain → it is needed association with inhibitors of enzymes involved in the metabolism of dopamine.

   **Adverse effects:**
   - early onset adverse:
     - anorexia, nausea, vomiting → nausea and vomiting are treated with domperidone (peripheral D2 receptor antagonist), which does not cross the blood-brain barrier;
     - orthostatic hypotension → treated with midodrine (a α1 adrenergic stimulant), which does not cross the blood-brain barrier;
     - transient tachyarrhythmias → treated with β1-blockers;
     - hypertension → occurs in the presence of MAOI, in patients treated with sympathomimetics or in patients with Parkinson's disease treated with high doses of levodopa;
     - taste changes.
   - late onset adverse effects:
     - after 3-4 months of treatment → abnormal involuntary movements (in 80% of patients after one year of treatment);
     - fluctuations of effect → "on - off effect";
     - neurovegetative dystonia;
psychiatric disturbances (hallucinations, nightmares, delirium, mania, depression);
- insomnia;
- sexual excitation (due to the action on the diencephalic region).

- Sudden interruption of the administration of levodopa → withdrawal syndrome which is equivalent to the neuroleptic malignant syndrome:
  - Initial: muscle rigidity, high fever, leukocytosis (the latest two effects require a differential diagnosis with infectious diseases);
  - Late: autonomic nervous system instability with changes in blood pressure and pulse rate, increase in creatine kinase (reflecting muscle damage).

**INHIBITORS OF PERIPHERAL DECARBOXYLASE (DDC INHIBITOR): BENSERAZIDE, CARBIDOPA**

*Mechanisms of action:* inhibition of dopa decarboxylase in periphery.
*Pharmacokinetics:* do not cross the blood-brain barrier → these drugs determine efficient concentration of L-Dopa in the brain.
*Indications:* association to L-dopa treatment.

**INHIBITORS OF TYPE B MONOAMINOOXIDASE (MAO-B): SELEGILINE, RASAGILINE, LAZABEMIDE, MOFEGILINE**

*Mechanisms of action:* inhibition of MAO-B.
*Pharmacodynamic effects:* MAO-B effectively prolong the duration of action of L-Dopa. The advantage of MAO-B → do not determine hypertensive accidents when administered with foods containing tyramine.

*Pharmacological characteristics of selegiline*
  - *Pharmacokinetics* → the drug rapidly crosses the blood-brain barrier, T1/2 = 40 hours, but the therapeutic effect is being extended in relation to the "turnover" of MAO.
  - *Pharmacodynamic effects* → determines a reduced antiparkinsonian effect and effectively prolongs the duration of action of L-Dopa;
  - *Contraindications* → association with antidepressants inhibiting serotonin reuptake, because the association may determine the serotonin syndrome.
  - Some studies indicate a high risk of mortality after administration of selegiline.

**INHIBITORS OF CATECHOL-O-METHYLTRANSFERASE (ICOMT): TOLCAPONE, NITECAPONE, ENTACAPONE**

- Entacapone and nitecapone act exclusively at the peripheral level (at the COMT from digestive tract, liver, and plasma);
- Tolcapone is the only ICOMT that crosses the blood-brain barrier → the drug also determines the inhibition of peripheral and central COMT.

*Pharmacokinetics:*
  - increase the bioavailability of L-dopa;
  - T1/2 of elimination increases without increasing plasma concentration;
  - highly bound on plasma proteins; metabolism in the liver by glucuronidation;
*Indications* → reduce the symptoms of "on - off effect" of Levodopa.
*Adverse effects:* similar to those caused by L-dopa (nausea, orthostatic hypotension, dyskinesias);
  - other adverse effects: diarrhea, abdominal pain, discoloration of urine.
2. DOPAMINE AGONISTS

Mechanisms of action:
- **ERGOPEPTINES**
  - Bromocriptine → agonist on D2 receptor and antagonist on α=D1=5-HT2;
  - Pergolide → agonist on D2 = D1 receptor;
  - Lisuride → agonist on D2 receptor, partial agonist on D1, interfere with 5-HT2 receptors;
  - Cabergoline → agonist on D2 receptor;
- **NON ERGOPEPTINES**:  
  - Piribedil → agonist on D2 receptor and low agonist on D3 = D1 receptors;
  - Ropinirole → agonist on D2 = D3 = D4 receptors;
  - Apomorphine → agonist on D2 = D3 = D4 receptors;
  - Talipexole → agonist on D2 = D3 = D4 receptors;
  - Pramipexole → agonist on D2 = D3 = D4 receptors.

The benefits of dopamine agonists:
- stimulation of dopamine receptors is more stable compared to the L-Dopa;
- there is a good relationship between dose and effect;
- reduce the severity of "off" periods.

**Contraindications of agonists of dopamine receptors:**
- psychoses;
- glaucoma;
- breastfeeding;
- melanoma and other pigmented skin lesions;
- pseudoparkinsonism caused by neuroleptics;
- pregnancy;
- cardiovascular disease;
- peptic ulcer;
- liver failure;
- kidney failure.

**Adverse effects of agonists of dopamine receptors:**
- psychiatric disorders (hallucinations, nightmares, delirium, mania, depression);
- "dopaminergic psychosis" (hallucinations, particularly visual hallucinations), due to the excessive stimulation of mesolimbic dopamine receptors, these effects are also caused by interfering with serotonergic transmission.

**Particularities of some dopamine agonists**
- **BROMOCRIPTINE** adverse effects:
  - hallucinations;
  - hypotension;
  - circulatory disorders induced by cold;
  - rarely dyskinesias.
- **Lisuride, Terguride** determine less frequently tardive dyskinesia.
- **Pergolide** side effects → induce "on - off effect".
- **Cabergoline** determine a very stable dopaminergic stimulation.
ANTIPARKINSONIAN DRUGS - *drugs affecting cholinergic system*

1. **ANTIMUSCARINIC DRUGS** improve salivation.

*Indications:*
- adjuvant treatment of Parkinson's disease;
- the centrally acting anticholinergic drugs are the only effective treatment of pseudoparkinsonism.

The mechanisms of action, pharmacodynamic effects, pharmacokinetics, indications, cons-indications, side effects → See in the chapter on the pharmacology of SNV.

The central anticholinergic drugs may determine the onset of "dopaminergic psychosis" (particularly visual hallucinations).

2. **1\textsuperscript{st} GENERATION H\textsubscript{1} RECEPTOR ANTAGONISTS**

The mechanisms of action, pharmacodynamic effects, pharmacokinetics, indications, cons-indications, side effects → See in the chapter of autacoids.

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**III. THE TREATMENT OF TREMOR ("TREMOR")**

Tremor consists of a rhythmic oscillatory movement around a joint. Types of tremor:
- postural tremor occurs during maintenance of sustained posture
- intention tremor occur during movement.

1. Treatment of postural tremor (physiological): Propranolol
2. Treatment of essential tremor: Propranolol, Metoprolol
3. Other treatments:
   - anticonvulsants → Primidone;
   - small amounts of alcohol;
   - benzodiazepines:
     - 1.4 – benzodiazepines: diazepam, chlordiazepoxide;
     - Triazolobenzodiazepines: alprazolam.