I. ANXYOLITIC – SEDATIVE – HYPNOTIC DRUGS

Terminology

- **Anxiety** is an emotional state in which fear dominates a person's life. Anxiety is defined as apprehensive anticipation of future danger or misfortune, accompanied by a feeling of dysphoria or somatic symptoms of tension\(^1\). It is thus a future-oriented state, motivating the person to avoid the perceived danger; worry may be seen as a cognitive manifestation of anxiety.
  - **Fear**, by contrast, is a basic emotion that is associated with a “fight or flight” response to immediate danger; it typically arises after the exposure, whereas anxiety is apprehension over a potential future danger. Anxiety need not be negative: it may increase vigilance and arousal, and thereby enhance performance and learning.
  - **Anxiety disorders** are relatively evident. The anxious patient appears apprehensive, sweats, and complains of nervousness, palpitations, and faintness; somatic signs include rapid breathing, tachycardia, and labile blood pressure.

- **Anxiolytic drugs** are pharmacologically active substances that reduce anxiety (stress or tension) without reducing mental clarity and improve the capacity of the individual to adapt.

- **Sedative drugs** are pharmacologically active substances that exert a calming effect and reduce anxiety with minimal effect on motor function or mentally. The degree of central nervous system depression caused by a sedative drug should be the minimum consistent with therapeutic efficacy.

- **Hypnotic drugs** are pharmacologically active substances that cause drowsiness and promote the onset and maintenance of a state of sleep. Hypnotic effects involve more pronounced depression of the central nervous system than sedation.

- **Antiseizure Drugs** (antiepileptic drugs) are pharmacologically active substances indicated in the treatment of epilepsy and of seizures of various etiologies (intoxication, metabolic disorders, injuries of the central nervous system etc).

History

- The first benzodiazepine, chlordiazepoxide, was discovered in 1955 by Leo Sternbach and introduced in therapeutics in 1960 under the name of Librium (Hoffmann-La Roche), with anxiolytic properties.
- The first barbiturate, barbituric acid, was discovered in 1863 by Adolf von Baeyer (1835-1917), the Nobel Prize winner in chemistry (1905). In 1913, the second barbiturate, Phenobarbital, was introduced into medical practice

\(^1\) Definition of The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), American Psychiatric Association, Washington, DC, 1994
THE GABA SYSTEM
Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. Gamma-aminobutyric acid (GABA) acts on three groups of receptors: GABA-A, GABA-B and GABA-C.

- GABA-A and GABA-C receptors are ionotropic receptors or ligand-gated ion channels receptors (attached to a chloride channel),
- GABA-B receptors are metabotropic receptors that are G-protein coupled (that act via second messengers).

GABA - A receptor has five specific bindings sites:

- **GABA site**
  - Agonist is GABA → direct opening of chloride channel → inhibitory influx in the CNS (anxiolytic, sedative, hypnotic, skeletal muscle relaxant and anticonvulsant effects);

- **Benzodiazepine site**
  - Function as benzodiazepine receptor. There are two subtypes of benzodiazepine receptor: BDZ1 receptors (Ω1) and BDZ2 receptors (Ω2).
  - Three types of ligands act on benzodiazepine receptors: agonists, competitive antagonists, inverse agonists.
    - **Agonists**:
      - non-selective agonists (act on both BZD1 and BZD2 receptors and produce anxiolytic, sedative, hypnotic, skeletal muscle relaxant and anticonvulsant effects):
        - endogenous (→ endozepines)
        - exogenous (1,4–benzodiazepines, triazolobenzodiazepines);
      - selective agonists on BDZ1 receptors (produce anxiolytic, sedative, hypnotic effects): imidazopyridines
      - act by indirect opening of chloride channel because inhibit the inhibitory protein that bind the mediator GABA on the GABA site → more molecules of GABA will be bound on GABA site → increase in the frequency of chloride channel opening → inhibitory influx in the CNS.
    - Competitive antagonists: imidazobenzodiazepines (Flumazenil)
      - block only the actions of benzodiazepines (used as antidote in benzodiazepine intoxication)
    - Inverse agonists: β – carboline
      - act as negative allosteric modulator of GABA receptor function and produce anxiety and seizures.

- **Barbiturate site**
  - agonists are barbiturates and ethanol; are GABA-mimetics;
  - act by direct opening of chloride channel → prolong the opening of the chloride channel → inhibitory influx in the CNS;

- **Anesthetic steroids site**
  - agonists are general anesthetics volatile liquids, general anesthetics with intravenous administration → indirect opening of chloride channel (similar to benzodiazepines) → inhibitory influx in the CNS.

- **Picrotoxinic site**
  - competitive antagonist is picrotoxin → determines excitatory effects in the CNS.
CLASSIFICATION OF ANXYOLITIC – SEDATIVE – HYPNOTIC DRUGS

1. Drugs with anxyolitic – sedative – hypnotic effect
   - **Barbiturates:**
     - **Oxibarbiturates** (classification according to the duration of action):
       - long-acting (8-12 hours): Phenobarbital
       - intermediate-acting (4-6 hours): Amobarbital, Butabarbital
       - short-acting (3 hours): Cyclobarbital, Pentobarbital, Secobarbital
     - **Thiobarbiturates** (very short-acting 10-20 min): Hexobarbital, Thiopental, Methohexital, Thiamilal
   - **Benzodiazepines:**
     - **1-4 benzodiazepines** (classification according to half-life):
       - long-acting: Diazepam, Chlordiazepoxide, Clorazepate, Prazepam, Flurazepam
       - intermediate-acting: Nitrazepam, Flunitrazepam, Temazepam, Clonazepam, Halazepam, Quazepam
       - short-acting: Oxazepam, Lorazepam
     - **triazolobenzodiazepines** (classification according to half-life):
       - intermediate-acting: Alprazolam, Estazolam
       - short-acting: Midazolam, Triazolam
   - **Imidazopiridines**: Alpidem, Zolpidem, Zaleplon, Zopicone, Eszopiclone,
   - **Alcohols / aldehydes**: Chloral hydrate, Trichloroethanol, Paraldehyde
   - **Quinazolones**: Methaqualone
   - **Carbamates**: Ethinamate, Meprobamate
   - **Piperidindiones**: Glutethimide, Methyprilon
   - **Acyclic ureides**: Bromisoval, Carbromal
   - **Bromides**: salts of sodium, potassium, ammonium, calcium (in monotherapy/association)
   - **Other structures**:
     - L-Tryptophane
     - **H1 receptor antagonists 1st generation**:
       - Ethanolamines:Diphenhydramine, Doxylamine;
       - Ethylaminediamines: Pyrilamine;
       - Phenothiazines: Promethazine;
       - Piperazines: Hydroxyzine;
     - Antagonists on H1 and 5-HT receptors: Cyproheptadine
     - Ethchlorvynol
     - products from plants

2. Anxyolitic drugs without sedative effect:
   - **Serotonin receptor 5HT1A agonists**: Buspirone, Ipsapirone, Gepirone, Tandospirone

3. Treatment of psychomotor agitation:
   - **Diazepam**,
   - **Scopolamine**,  
   - **Neuroleptic drugs**,  
   - **Magnezium sulfate (parenteral administration)**

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2 Drugs with anti-anxiety effect (anxiolytics), calming effect (sedatives), sleep-inducing effect (hypnotics).

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BARBITURATES

Classification

- **Oxibarbiturates** (classification according to the duration of action):
  - long-acting (8-12 hours): Phenobarbital
  - intermediate-acting (4-6 hours): Amobarbital, Butabarbital
  - short-acting (3 hours): Secobarbital, Cyclobarbital, Pentobarbital
- **Thiobarbiturates** (very short-acting 10-20 min): Hexobarbital, Thiopental, Methohexital, Thiamylal

**Mechanism of action:**
- agonists on barbituric segment of the GABA-A;
- increase the release of GABA;
- inhibit the GABA reuptake;
- reduce the release of excitatory neurotransmitters: norepinephrine, acetylcholine;
- interfere with calcium entry into brain synaptosomes;
- increase the permeability of neuronal membranes;
- inhibit the pyruvate oxidation;
- determine the uncoupling of oxidative phosphorylation.

**Pharmacodynamic effects**

- CNS (cortex, hypothalamus, thalamus, limbic system)
  - influence both stages of the sleep (particularly the slow wave sleep and determine residual somnolence after waking).
  - reduce the oxygen consumption in the brain (10% during sleep and 50% during the narcosis).
  - determine anticonvulsant effects.
  - determine addiction.
- Respiratory tract
  - decrease the respiratory rate (which is similar to the physiological sleep).
  - high doses → respiratory depression and suppress the sensitivity of the respiratory centers to changes in the concentration of carbon dioxide.
- Cardiovascular system
  - decrease cardiac activity (similar to the physiological sleep).
  - high doses → depression of vasomotor center (vasodilation, hypotension).
- Digestive system: decrease the motility and secretory activity.
- Urogenital tract: decrease the motility of the urinary bladder and the frequency of uterine contractions.
- Stimulate the release of ADH.

**Pharmacokinetics**

- Barbiturates are lipophilic drugs that readily cross blood-brain barrier.
- Absorption: mainly duodeno-jejunal, but also in the stomach.
- Distribution → widely throughout the body; binding to plasma proteins is variable (eg. Phenobarbital - 98% Thiamylal <5%). Thiobarbiturates are highly lipophilic → pass very quickly blood-brain barrier → very rapid distribution into the brain → hypnotic effect → followed by distribution to other organs (adipose tissue, muscles, heart, kidney, liver) → decrease the plasma concentration. This is called **redistribution of the drug**: redistribution accounts for the short duration of action of these drugs, a feature useful in recovery from anesthesia.
• Metabolism: for oxybarbiturates → in the liver; for thiobarbiturates → in the liver, kidneys, brain etc.; barbiturates are enzyme inducers of drug metabolism of other drugs and of their metabolism (autoinduction).
• Elimination: mainly through kidneys, but also in milk, saliva, urine.
• Alkalization of urine determines the acceleration of renal elimination.

Indications:
• oxybarbituriques (indications are dose-dependent):
  o sedatives;
  o hypnotic;
  o anticonvulsants (tonic-clonic epilepsy, partial epilepsy, juvenile myoclonic epilepsy, status epilepticus);
  o Phenobarbital is indicated also in neonatal jaundice (because accelerate bilirubin metabolism);
• thiobarbiturates: intravenous general anesthesia.

Adverse effects:
• addiction and withdrawal syndrome;
• residual drowsiness in the morning, after waking;
• increased reaction time (determine stimulation of motor incoordination);
• reduce the capacity of concentration and learning;
• phenomenon of paradoxical excitement;
• decrease respiratory rate;
• decrease cardiac activity (decrease cardiac output, arrhythmias, hypotension);
• decrease digestive secretory activity and digestive and urinary bladder motility;
• reduce the frequency of uterine contractions;
• immunological reactions type I;
• acute crisis of porphyrinuria;
• hemolysis in patients with G6PDH deficiency.

Contraindications:
• absolute contraindications:
  o heart failure, angina, hypovolemia, shock;
  o status asthmaticus;
  o G6PDH deficiency; acute intermittent porphyria;
• relative contraindications:
  o severe renal failure;
  o severe liver failure;
  o pregnancy, breastfeeding;
  o children with psychomotor agitation;
  o Parkinson's disease;
  o acute adrenal insufficiency; valvular lesions; sepsis.

Warning: doses of barbiturates should be reduced in old patients and children, in patients suffering from bronchial asthma, hypotension.

3 Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymatic disorder of red blood cells in humans. The G6PD enzyme catalyzes the first step in the pentose phosphate pathway, leading to antioxidants that protect cells against oxidative damage. A G6PD-deficient patient lacks the protection against oxidative stresses from certain drugs, metabolic conditions, infections, and ingestion of fava beans.
4 Porphyria is a hereditary disorder due to reduction in enzyme activity of heme synthesis system, resulting in accumulation of heme precursors. Acute intermittent porphyria is characterized by a hereditary deficiency of hepatic porphobilinogen deaminase (PBGD) activity.
BENZODIAZEPINES

Classification

- **1-4 benzodiazepines** (classification according to half-life):
  - long-acting: Diazepam, Chlordiazepoxide, Clorazepate, Flurazepam
  - intermediate-acting: Nitrazepam, Flunitrazepam, Temazepam, Clonazepam, Halazepam, Quazepam
  - short-acting: Oxazepam, Lorazepam

- **triazolobenzodiazepines** (classification according to half-life):
  - intermediate-acting: Alprazolam, Estazolam
  - short-acting: Midazolam, Triazolam

Mechanism of action:

- nonselective agonists segments BZD1 = BZD2;
- inhibition of the release of serotonin in the synapse.

Differences between various benzodiazepines exist based on:

- pharmacodynamic characteristics: certain molecules have a dominating effect (eg, anticonvulsive effect) relatively more important than other effects.
- pharmacokinetic characteristics: onset and duration of action explain differences between their therapeutic uses.

Pharmacodynamic effects

- CNS (cortex, hypothalamus, limbic system, the cerebellar cortex, spinal)
  - influence both phases of sleep (no residual somnolence).
  - anticonvulsant effects.
  - skeletal muscle relaxant effects.
  - addiction.
- Respiratory tract: only large doses decrease respiratory rate (it is not influenced the sensitivity of the respiratory center to CO2 variations), respiratory acidosis.
- Cardiovascular system: decrease the force of contraction of the left ventricle → decrease cardiac output. Only large doses → depression vasomotor of center (hypotension, reflex increase in peripheral resistance and heart rate).
  - The cardiovascular effects are not significant in triazolobenzodiazepines.
- Digestive system: only large doses → decrease in gastrointestinal motility.

Pharmacokinetics

- Benzodiazepines are lipophilic drugs that readily cross the physiological barriers.
- Absorption: duodeno-jejunal.
- Metabolism: in the liver. Some benzodiazepines are biotransformed into active metabolites (eg, Diazepam is metabolized to nordiazepam, oxazepam, temazepam).
- Benzodiazepines present enterohepatic circuit, effect of first-pass metabolism.
- Elimination: mainly in the kidneys, but also in milk and in bile.

Indications:

- anxiolytics;
- sedatives;
- hypnotic;
- anticonvulsants;
- skeletal muscle relaxants.

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5Long-acting benzodiazepines are associated with daytime sedation, cognitive and psychomotor impairment particularly in the elderly [explains increase of falls, hip fractures], preferred when need of daytime sedation. Intermediate and short-acting benzodiazepines are more efficacious in inducing sleep during the first night of administration.
Adverse effects:
- addiction and withdrawal syndrome (short-acting benzodiazepines have an earlier onset of withdrawal symptoms, long-acting benzodiazepines have a later onset);
- increased reaction time determine exogenous stimulation of motor incoordination;
- phenomenon of paradoxical excitement;
- decrease the force of contraction of the left ventricle → decrease cardiac output, and the heart rate, arterial hypotension (for 1,4 - benzodiazepines);
- decrease the gastrointestinal motility;
- immunological reactions type I;
- hepatotoxicity.

The antidote in acute intoxication with benzodiazepines is Flumazenil.

Contraindications:
- severe heart failure;
- severe renal insufficiency;
- severe hepatic insufficiency;
- pregnancy, breastfeeding.

Benzodiazepines should be administered with caution in old patients (doses are reduced).

IMIDAZOPYRIDINES: ALPIDEM, ZOLPIDEM, ZALEPLON, ZOPILICONE, ESZOPLICONE

Mechanism of action: selective agonists on segments BZD1 of GABA-A receptor.

Pharmacodynamic effects: effects anxiolytics, sedatives, hypnotics.

Indications: anxiolytics; sedatives; hypnotics.

Adverse effects: severe hepatotoxicity.

Contraindications are similar to those of benzodiazepines.

ALCOHOLS / ALDEHYDES: CHLORAL HYDRATE

Pharmacodynamic effects: effects anxiolytics, sedatives, hypnotics.

Indications: anxiolytics; sedatives; hypnotics.

Adverse effects and contraindications are similar to those of barbiturates.

THE QUINAZOLINONES: METHAQUALONE

Indications: anxiolytics; sedatives; hypnotics.

Adverse effects and contraindications are similar to those of barbiturates.

These drugs determine adiction.

CARBAMATES: ETHINAMATE, MEPROBAMATE

Pharmacodynamic effects: effects anxiolytics, sedatives, hypnotics, these drugs do not affect REM sleep.

Indications: anxiolytics; sedatives; hypnotics.

Adverse effects and contraindications are similar to those of barbiturates.

These drugs determine adiction.

PIPERIDINEDIONES: GLUTETHIMIDE, METHYPYRON

Pharmacodynamic effects: effects anxiolytics, sedatives, hypnotics (these medications do not determine the residual sleepiness), anticonvulsant, anticholinergic effects.

These drugs are enzyme inducers metabolism of vitamin D, warfarin and barbiturates.
These drugs are concentrated in milk and bile. They present enterohepatic circulation. 
**Indications:** anxiolytics; sedatives; hypnotics. 
**Adverse effects** and **contraindications** are similar to those of barbiturates. 
These drugs determine addiction.

**ACYCLIC UREIDES: BROMISOVAL, CARBROMAL**

**Indications:** sedative. 
**Adverse effects:** bromism. These drugs have low therapeutic index. 
**Contraindications** are similar to those of barbiturates.

**BROMIDES: SALTS WITH SODIUM, POTASSIUM, AMMONIUM, CALCIUM**

**Mechanism of action:** replacement of the chloride from the extracellular fluid. 
**Pharmacodynamic effects:** sedative effects, hypnotics, anticonvulsants. 

**Indications:**
- sedatives; 
- hypnotic; 
- anticonvulsants in patients with G6PDH deficiency (it is treatment of choice). 

**Adverse effects:**
- bromism: digestive symptoms (nausea, vomiting), CNS symptoms (drowsiness, irritability, tremors, ataxia, hallucinations, mania, delirium, psychoses, slurred speech, memory impairment), conjunctivitis, skin rashes and folliculitis/toxic epidermal necrolysis (particularly after long-term treatment); 
- immunological reactions type I ("rash").

**NON-SEDATING ANXIOLYTICS:** Buspirone, Ipsapirone, Gepirone, Tandospirone 

**Mechanism of action:** partial agonists of the 5 HT1A. 
**Pharmacodynamic effects:** anxiolytic effects without sedation. 
**Pharmacokinetics:** have short-term action, present enterohepatic circulation and first-pass effect. 
**Indications:** anxiolytic (not efficient for panic attacks). 
**Adverse effects:** tachycardia, nervousness, paresthesia, confusional states, gastrointestinal, miosis (dose-dependent), increase blood pressure when are associated with MAO inhibitors. 
These drugs do not determine addiction. 
**Contraindications:** heart rhythm disorders.

**THE TREATMENT OF AGITATION:** Diazepam; Scopolamine; Neuroleptics; Magnesium sulfate 

**Parenteral Magnesium sulfate**

**Indications:** arrhythmias (torsade de pointes, arrhythmias associated with hypokalaemia), eclampsia, premature labor, hypertensive encephalopathy, seizures, tetanus. 
**Adverse effects:** flushing of the skin, hypotension (due to vasodilation), respiratory depression and loss of deep tendon reflexes (both due to neuromuscular blockade).
II. LOCAL ANESTHETICS

Local anesthetics are pharmacologically active substances that are applied locally and block temporarily and reversibly the transmission of action potentials in the membranes of excitable cells (neurons, muscle cells, gustatory corpuscles etc.).

Classification depending on the structure of local anesthetics:

1. **Esters:**
   - Natural sources: Cocaine
   - Synthetic: Benzocaine, Tetracaine, Procaine (Novocain), Chloroprocaine, Proparacaine

2. **Amides:** Lidocaine (Xylocaine), Mepivacaine, Articaine, Ropivacaine, Bupivacaine, Levobupivacaine, Prilocaine, Etidocaine

3. **Other structures:** Ethylchloride.

Classification depending on the duration of action:

- Short acting (20-60 minutes): Benzocaine, Procaine, Chloroprocaine, Proparacaine;
- Intermediate acting (1-2 h): Lidocaine (Xylocaine), Mepivacaine, Prilocaine, Cocaine;
- Long acting (> 3 h): Articaine, Ropivacaine, Bupivacaine, Levobupivacaine, Etidocaine, Tetracaine, Ethylchloride.

Types of local anesthesia:

1. **Topical anesthesia (surface anesthesia)** is anesthesia of mucous membranes (nose, mouth, throat, tracheobronchial, esophagus, genitourinary tract) or skin, produced by direct application of local anesthetics.

2. **Infiltration anesthesia** is the injection of a local anesthetic directly into tissue (superficial as to include only the skin, profound to include deeper structures) without taking into consideration the course of cutaneous nerves.

3. **Nerve Block Anesthesia** is the injection of a local anesthetic into or around individual peripheral nerves or nerve plexuses; produces greater areas of anesthesia than previous techniques.

4. **Intravenous Regional Anesthesia** is the injection of a local anesthetic into a cannulated vein of an extremity which was exsanguinated with an elastic bandage and with a proximally located tourniquet inflated to 100–150 mm Hg above the systolic blood pressure. Complete anesthesia of the limb ensues within 5–10 minutes.

5. **Spinal Anesthesia** (intrathecal anesthesia) is one of the most popular forms of anesthesia and is the injection of local anesthetic in the subarachnoid space into the cerebrospinal fluid (CSF), by penetration of the spinal dura from the lumbar space under the second lumbar vertebra.

6. **Epidural Anesthesia** is the injection of a local anesthetic into the epidural space (also known as "extradural space" or "peridural space", is the space outside the dura mater enveloping the spinal cord).
**Mechanism of action:**
- Local anaesthetics act as Na+ channel-blocking agents: bind on the inner gate of voltage-gated Na+ channels → block Na+ movement through the channels, and thus block the action potential and neural conduction → no new depolarization can be produced = “membrane stabilization”.
- At higher concentrations of drug → local anesthetics can block K+ channels.

There is a differential sensitivity of nerve fibers to local anesthetics: small unmyelinated fibers (mediating pain and temperature sensations) are blocked before the larger myelinated fibers (mediating postural, touch, pressure, and motor information).

Local anesthetics are not water soluble, but their salts with acids are water-soluble and can be injected. Solutions dissociate rapidly after injection → "onium" structure prevents the passage of solutions through physiological membranes, but it is necessary to pass through the membrane to reach the inner gate of sodium channels where the molecules must complete blockage. local anaesthetics penetrate the nerve membrane in the uncharged form and block the action potential from inside the membrane in the charged form, with "N" trivalent. After the passage, the molecules pass again in the form of "onium" to block the inner door of sodium channels. The following factors influence this transformation:
- tissue pH (alkaline pH tissue is favorable) → in inflamed tissue, the acidic pH reduce the effectiveness of anesthetic;
- pH of the substance.

**Pharmacodynamic effects**
- Local anesthetic effect
- Antiarrhythmic effect (Lidocaine is class Ib antiarrhythmic drug)
- Vasodilatatory effect
  - All local anesthetics (except cocaine) are vasodilators → necessary the association of local anesthetics with vasoconstrictor agents. The vasoconstrictors are: adrenaline, norepinephrine, phenylephrine. The synthetic derivative vasopressin is used in patients with contraindications for sympathomimetics.
  - Mepivacaine has the lowest vasodilatatory effect.
  - Advantages of the association of local anesthetics with vasoconstrictors:
    - prolong the effect of local anesthetics because delays the removal of drug from the injection site;
    - reduce the bleeding and congestion of the mucosa → operatory field is clear;
    - prevent the systemic absorption → decrease the probability of CNS toxicity because the blood level of local anesthetic is low;
  - Contraindications of the association with vasoconstrictors: hypertension, tachyarrhythmias, local anesthesia of the extremities such as nose, ears, fingers, penis (because may determine the ischemic tissue necrosis).

**Pharmacokinetics:**
- Bupivacaine passes the feto-placental barrier.
- Metabolism:
  - Local anesthetics with ester structure are hydrolyzed and inactivated primarily by plasma esterases and by hepatic enzymes.
Local anesthetics with amide structure are degraded by the hepatic enzymes.

**Indications:**
- local anesthetic for surgery (eye, ear, nose, throat, and cosmetic surgery);
  - Tetracaine is indicated only for topical (surface) anesthesia;
  - Lidocaine is indicated in:
    - topical anesthesia, infiltration anesthesia, nerve block anesthesia, spinal anesthesia, epidural anesthesia;
    - ventricular arrhythmias;
  - Articaine is preferred in dentistry (has a good concentration in bones);
  - Prilocaine is used intravenous regional anesthesia;
  - Ropivacaine, Bupivacaine are used in obstetrics.
- neuropathic pain syndromes (interruption of pathological reflexes);

**Adverse effects:**
- tachyphylaxis (loss of effectiveness) because the repeated injections of a local anesthetic deplete the buffering capacity of the local tissues, especially in areas of limited buffer reserve, such as the cerebrospinal fluid, and induce extracellular acidosis which limit the diffusion of local anesthetic into cells (for local anesthetics with long duration are preferred bupivacaine, ropivacaine, etidocaine).
- irreversible spinal injuries (in spinal anesthesia)
- cardiovascular effects (related to the free concentration of drug)
  - Cocaine: vasoconstrictor effects, hypertension; positive inotropic effect; tachyarrhythmias;
  - Other local anesthetics: arterial hypotension; negative inotropic effect; atrioventricular block; tachyarrhythmias to ventricular fibrillation;
  - Bupivacaine has the highest cardiotoxicity (QRS shortening, myocardial depression, ventricular arrhythmia), Ropivacaine is less cardiotoxic.
- CNS effects are related to the free concentration of drug: drowsiness (most common), restlessness, tremor, tonic-clonic seizures;
- immunological reactions of type I for local anesthetics with ester structure;
- depress contractions of intestine, vascular, and bronchial smooth muscle;
- methemoglobinemia (is a rare but serious complication of local anesthetic prilocaine iv administration).
- side effects caused by stimulants sympathetic vasoconstrictor.
III. GENERAL ANESTHETICS

General anesthetics are pharmacologically active substances that suppress temporarily and reversibly the state of consciousness, sensitivity to pain, somatic, autonomic reflexes.

Classification of general anesthetics

1. Inhalational general anesthetics:
   - gases: Nitrous oxide, Cyclopropane
   - volatile liquids: Halothane, Isoflurane, Enflurane, Desflurane, Sevoflurane, Methoxyflurane, Ethyl ether, Chloroform

2. Intravenous general anesthetics:
   - Thiobarbiturates (very short acting barbiturates): Hexobarbital, Thiopental, Methohexital, Thiamylal, Thiobutabarbitral;
   - benzodiazepines (as adjuncts in anesthesia): Midazolam, Diazepam, Lorazepam;
   - imidazoles: Etomidate
   - steroid structure: Althesin
   - opioid analgesics: Morphine, Fentanyl, Sufentanil, Alfentanil, Remifentanil
   - others: Propofol, Ketamine, Dexmedetomidine, Propanidid.

Preanesthetic medication

- cholinoreceptor-blocking drugs (anticholinergic drugs) → reduce salivary and bronchial secretion, prevent vagal bradycardia and reflex hypotension.
- antihistaminic drugs → antiallergic and antiemetic effects, 1st generation has also sedative effects
- benzodiazepines → anxiolytic-sedative-hypnotic effects
- opioids are analgesic drugs that potentiate analgesic effect of general anesthetics
- neuroleptic drugs
- antiplatelet drugs: Abciximab, Eptifibatide → prevent venous thrombosis.

A good general anesthesia is characterized by:

- good muscle relaxation.
- the depth of general anesthesia is continuously monitored at all time frames.
- installation and recovery of anesthesia must be quick, with fewer adverse effects.
- the general anesthetic should have a high index narcotic.

Stages of general anesthesia using a single general anesthetic:

1. Stage of analgesia:
   - depression of certain cortical and spinal cord areas, of spinothalamic tract;
   - initially analgesia without amnesia (state of consciousness is maintained), later are produced both analgesia and amnesia;

2. Stage of excitement:
   - depression of small inhibitory circuits and amnesia (no consciousness);
   - hyperexcitability (delirium, excitation, vomiting, irregular respirations);

3. Stage of Surgical Anesthesia:
   - depression of ascending reticular activation system (but with the maintenance of the sensitivity of bulbar vegetative centers) and skeletal muscle relaxation;