Lecture 1
Opioids. Cough suppressants and expectorants.

Pharmacological influence of the central nervous system include the chapters:
I. Opioids
II. Cough suppressants and expectorants
III. Anxiolytics, sedative-hypnotics
IV. Anaesthetics locales and generales
V. Anticonvulsants
VI. Pharmacological influence mental illness
VII. Drugs of abuse inducing euforia and psychotomimetics.

I. Opioids

Terminology
- Opioid is an endogenous or exogenous substance causing effects similar to morphine.
- Opiate (old term) is a drug extracted from the exudate of the poppy.
- Narcotic analgesics or morfiniques act on the CNS depression of the conduction path of the somatosensory pathways, thalamic and medullary crosslinked. They are addictive and create drug. They are producing opiate narcotic sleep.
- Opiod peptides (endogenous opioid peptides) are endogenous substances that act as agonists at opioid receptors; endogenous opioid peptides are included in the enkephalins – endorphins system. Opioid peptides that are produced in the body include: endorphins, enkephalins, dynorphins, endomorphins.

History of Opioids
- Opium is extracted from the juice of poppy seeds (Papaver somniferum). The name “opium” is a Greek word meaning “juice,” or the liquid extracted from the poppy seeds.
  - Papaver somniferum properties have been known for thousands of years and the accounts of its use can be found in ancient Egypt, Greece and documents novels. Smoke "by burning poppy and hemp especially on the rocks" was also known by the ancestors of the Romanians, the Geto-Dacian.
  - Opium is obtained from the opium poppy by incision of the seed pod after the petals have fallen. The white latex flowing turns brown and hardens on contact with air. This gum is sticky brown opium.
- It contains approximately 20 alkaloids, including phénanthrèniques alkaloids such as morphine (10%), codeine (0.5%), thebaine (0.2%) and isoquinoline derivatives such as papaverine and noscapine. Thebaine, papaverine and noscapine are not analgesics. Thebaine is the precursor of several receptor agonist opioids, semi-synthetic derivatives (eg, etorphine, a veterinary officer of 500 -1000 times

Lecturer Cristina GHICIUC, MD, PhD

more potent than morphine, which is more toxic than morphine) and antagonists (naloxone).

- Opium was used alone or combined with alcohol (laudanum is the name of opium combined with alcohol) were used to treat almost all known diseases because it produces relief of pain, sedation, relief from diarrhea and cough suppression. It produces also euphoria.

- Morphine was isolated from opium in 1804 by Sertüner.

  Friedrich Wilhelm Adam Sertüner (1783-1841) was one of the most outstanding chemists which greatly influenced the transformation of pharmaceutical chemistry from alchemy to the status of a recognized branch of science, at the end of 18th century. At the age of twenty-one, in 1803, Sertüner was the first to report some results concerning the substance that was thought to be responsible as "sleep-agent." This substance was isolated by him from the poppy. When other chemists did not accept the report indicating the discovery of morphine, Sertüner turned to experimenting on himself and three friends of him to prove that the substance he isolated was responsible for specific actions of opium. He called the new substance “morphine”, after Morpheus, “the god of sleep and dreams” of the ancient Greeks.

  Sir William Osler (1849-1919) called morphine "God's own medicine" ("The medicine of God"). His contributions to urology are significant and include descriptions of his own episodes of colic and the use of morphine. Morphine remains nowadays the standard of comparison for drugs with a strong analgesic action.

- Morphine and its derivatived are considered the most effective treatment for severe pain.

- For more than 100 years, there were few useful therapeutic agents for analgesia. Morphine has been known to reduce pain with remarkable efficiency and has become the standard drug for treatment.

Natural opioids occur:
1) In the juice of the opium poppy (morphine and codeine)
2) As endogenous endorphins

All other opioids are prepared from either morphine (semisynthetic opioids such as heroin) or they are synthesized from precursor compounds (synthetic opioids such as fentanyl).

The structure – effect relationship:

- morphine (agonist with high-affinity on \( \mu \) opioid receptors) \( \rightarrow \) codeine (agonist with low affinity on \( \mu \) opioid receptors) \( \rightarrow \) nalbuphine (the \( \mu \) opioid receptor antagonist and agonist opioids);

- Hydromorphone (agonist with high-affinity on \( \mu \) opioid receptors) \( \rightarrow \) oxycodone (agonist with low affinity on \( \mu \) opioid receptors) \( \rightarrow \) buprenorphine (partial agonist of opioid receptors \( \mu \)) \( \rightarrow \) naloxone (antagonist on \( \mu \) opioid receptor).

- The antagonist property is obtained from the replacement of a methyl group to the nitrogen atom by a allyl radical.
ENDOGENOUS OPIOID PEPTIDES (enkephalin - endorphin system)
The endogenous opioid system includes a large number of opioid peptides that are ligands for numerous types of opioid receptors. Three distinct families of classical endogenous opioid peptides have been described: enkephalins, endorphins, and dynorphins. Each family derives from a distinct precursor protein, which is subject to complex cleavages and posttranslational modifications that result in the synthesis of multiple active peptides.

- **Enkephalins family:**
  - The precursor protein is preproenkephalin (which includes 6 copies of methionine-enkephalin and a copy of the leucine-enkephalin).
  - The active products are methionine-enkephalin (met-enkephalin) and leucine-enkephalin (leu-enkephalin), which possess analgesic activity. Met-enkephalin and leu-enkephalin are pentapeptides.

- **Endorphins family:**
  - The precursor protein is prepro-opiomelanocortin (POMC).
  - The active products are:
    - beta-endorphins (are tetrapeptides) which possess analgesic activity,
    - nonopioid peptides such as adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), and beta-lipotropin (beta-LPH).

- **Dynorphins family:**
  - The precursor protein is preprodynorphin (alternatively termed prepro-enkephalin B includes copies of leucine-enkephalin).
  - The active products are:
    - dynorphin A (alternatively termed nociceptin or orphanin FQ) which possess behavioral and pain modulatory properties, has high affinity on opioid receptors and also acts as an agonist at the NMDA receptor. It determines hyperalgesia in a very long time, in case of an inflammatory process. Also acts on the receptor ORL ("orphanin opioid-like subtype receptor-1"), which interferes with the learning process of memory and it opposes the analgesia mediated by µ receptors.
    - dynorphin B,
    - alpha and beta neoendorphins.

More recently were identified 2 additional short peptides, **endomorphin-1** and **endomorphin-2**, which possess a high affinity and selectivity for µ opioid receptors and produce analgesia.

The biological role of endogenous opioid peptides. Endogenous opioid peptides have action as neurotransmitters, neurohormones, immunomodulatory substances:
- regulate the activity of SNV;
- control the emotional tone;
- regulate central integration and interpretation of pain;
- are involved in the process of memorization;
- regulate the GABA system;
- are involved in the mechanism of traumatic shock and septic shock;
- control endocrine activity:
  - stimulate the release of ADH, STH, prolactin;
  - inhibit the release of LH;
- regulate the activity of the immune system: they determine cell proliferation, chemotaxis, production of antibodies Ig.
OPIOID RECEPTORS

Classification

- **Specific receptors:**
  - presynaptic receptors:
    - \( \mu \) (mu): \( \mu_1, \mu_2 \);
    - \( \delta \) (delta): \( \delta_1, \delta_2 \);
    - \( k \) (kappa): \( k_1, k_2, k_3 \);
  - postsynaptic receptors:
    - \( \mu \) (mu): \( \mu_1, \mu_2 \).

- **Nonspecific receptors:**
  - \( \sigma \) (sigma);
  - \( \epsilon \) (epsilon).

Receptors \( \mu \), \( \delta \) and \( k \) are also localized at the spinal level (neurons of the spinal dorsal horn). Agonists of these receptors determine analgesia without the effects mediated supraspinal (nausea and vomiting, respiratory depression, sedation).

On opioid receptors bind:

- Pure Agonist: has affinity for binding and determine a biological effect.
- Pure Antagonist: has affinity for binding but no biological effect; blocks action of endogenous and exogenous ligands.
- Mixed Agonist-Antagonist: produces an agonist effect at one opioid receptor and an antagonist effect at another opioid receptor.
- Partial Agonist: has affinity for binding but low biological effect.

Biological effects mediated by opioid receptors:

- \( \mu \) receptors (mu): spinal and supraspinal analgesia, euphoria, miosis (constricted pupils), respiratory depression, constipation, physical dependence, sedation, modulation of the release of hormones and neurotransmitters.
- receptors \( k \) (kappa) spinal and supraspinal analgesia, dysphoria, miosis, constipation, physical dependence, sedation.
- receptors \( \delta \) (delta): spinal and supraspinal analgesia, modulation of the release of hormones and neurotransmitters.
- receptors \( \sigma \) (sigma): dysphoria, mydriasis, respiratory stimulation, visual hallucinations and auditory hallucinations.
- receptors \( \epsilon \) (epsilon) analgesia.

Opioid Receptor Signaling

- Activation of peripheral nociceptive fibers causes release of substance P and other pain-signaling neurotransmitters from nerve terminals in the dorsal horn of the spinal cord. Release of pain-signaling neurotransmitters is regulated by endogenous endorphins or by exogenous opioid agonists by acting presynaptically to inhibit substance P release, causing analgesia.
- Opioid receptors are coupled to the Gi protein which is coupled to adenylate cyclase → receptor stimulation determines the decrease in the intracellular concentration of cyclic AMP.
- The stimulation of presynaptic \( \mu \) (mu), \( k \) (kappa) and \( \delta \) (delta) receptors:
  - block and inactivate voltage-dependent calcium channels → block the release of excitatory neurotransmitters (acetylcholine, norepinephrine, glutamate, substance P, serotonin);
  - decrease sensitivity of 5-HT3 receptors for serotonin.
- The stimulation of postsynaptic \( \mu \) (mu) receptors:
  - activate potassium channels → determines the postsynaptic neuronal membrane hyperpolarization.
The molecular mechanism of opioid dependence

- Chronic administration of opioids leads to the need of gradually increase of the dose, because it determines tolerance and addiction. Tolerance and addiction involve changing the system of second messengers (cAMP) and changes in intracellular calcium concentrations.

- Acute administration of opioids determines the decrease of the level of intracellular calcium.

- Chronic administration of opiates determines the increase of the level of intracellular calcium. Chronic administration of opiates thus determines the decrease in the activity of adenylate cyclase → cAMP → decrease the phosphorylation of intracellular proteins → modification of DNA → stimulation of early genes, c-fos and c-jun → gene transcription → syntheses of proteins (eg, the synthesis of G protein coupling) → "up - regulation" of opioid receptors → the need to increase the dose. On the other hand, increasing the concentration of agonist determines "down - regulation" opioid receptors → decrease in the number of receptors → the need to increase the dose.

- In young and healthy persons, addiction is quick due to activation gene c-fos and c-jun (genes involved in transcription of certain proteins such as protein G). In people with chronic pain dependence does not occur or occurs late during the regular administration due to impaired production and impaired activity of mediators for genes c-fos and c-jun.
CLASSIFICATION OF OPIOIDS

➢ **agonists of opioid receptors:**
  • **natural alcaloids:**
    o strong agonists: Morphine;
    o mild to moderate agonists: Codeine (Methylmorfine);
  • **semisynthetic derivatives:**
    o strong agonists: Heroine (Diamorphine), Hydromorphone, Oximorfon, Ethylmorphine, Etorphine;
    o mild to moderate agonists: Dihydrocodeine, Oxycodone, Hydrocodone;
  • **synthetic derivatives:**
    o strong agonists:
      ▪ Meperidine,
      ▪ Methadone, Levometadil (Levacetylmethadol),
      ▪ Fentanyl, Alfentanil, Sufentanyl, Remifentanyl, Levorfanol;
    o mild to moderate agonists:
      ▪ Dextromoramide;
      ▪ Levo- and Difenoxinate, Difenoxin,
      ▪ Dextropropoxyphene, Propoxyphene\(^1\);
      ▪ Butorphanol;
      ▪ Loperamide, Difenoxilate, Difenoxin.

➢ **partial agonists of opioid receptors:** Buprenorphine, Tramadol;

➢ **agonists-antagonists of opioid receptors:**
  ▪ Pentazocine, Dezocine,
  ▪ Nalorphine, Nalbufine,
  ▪ Butorphanol;

➢ **competitive antagonists of opioid receptors:**
  • central acting: Naloxone, Naltrexone, Nalmefene;
  • periferal acting: Alvimopan.

PHARMACOKINETICS

➢ **Routes of administration of opioids**
  • Natural morphine and semi-synthetic opiates are administered only by injection: s.c. or i.v.
  • Synthetic opiates:
    o parenteral route – s.c., i.v.;
    o oral - capsules, tablets, coated tablets (eg, MS Contin ®);
    o transdermal patches (eg, MST);
    o intrarectally;
    o epidural;
    o nasal (nasal spray);
    o sublingual;
    o as subcutaneous pump = PCA ("patient - controlled - analgesia").

The maximum initial partial dose of morphine is 20 mg; the daily dose is 60 mg per day.

---

\(^1\) Used as cough suppressant; was recently withdrawn from market in some countries.

\(^2\) Used as analgesic, some combinations containing Dextropropoxifen were withdrawn from market because of dose-related cardiac conduction abnormalities.
Absorption:
- The effect of a given dose is less after oral than after parenteral administration for natural and semi-synthetic opiates because they present a significant first-pass metabolism in the liver (first pass effect). This is why natural (morphine) and semi-synthetic opiates are administered only by injection (sc or iv).
- Codeine and oxycodone are drugs partially protected against the first pass effect, due to the methyl of aromatic hydroxyl at C3.

Distribution:
- Opioids cross the blood-brain barrier (for heroin is faster) and the placental barrier.
- Opiates are concentrated in the milk and gall bladder.

Metabolism in the liver:
- Morphine is metabolized to:
  - morphine - 6 - glucuronide (the metabolite has stronger analgesic effect than morphine);
  - morphine - 3 - glucuronide (the metabolite has a toxic effect on the CNS).
- Codeine is metabolized to morphine in a ratio of 10%.
- Heroin is metabolized to morphine in a ratio of 100%.
- Types of reactions:
  - opiates with free hydroxyl groups (eg, morphine, levorphanol) are metabolized by conjugation with glucuronic acid.
  - esters (eg, heroin, remifentanil) are metabolized by tissue esterases.
  - hepatic oxidative metabolism is the metabolic pathway for alfentanil, sufentanil, fentanyl.

Elimination: mainly through kidney and partially in bile (natural opiates and semi-synthetic).

PHARMACODYNAMIC EFFECTS OF MORPHINE AND OTHER OPIOIDS

Effects on CNS:
- Analgesia - opioids affect two components of pain (Morphine determines a more powerful effect on the continues, spinoreticular chronic pain and determines less effect on acute, intermittent spinothermalic pain);
- Euphoria, tranquility (due to the action on µ receptors from diencephalon and frontal cortex)
  - sometimes may occur dysphoria;
- Sedation (especially the elderly);
- Miosis;
- Truncal rigidity (due to the action on µ receptors from spinal cord);
- Respiratory depression and decrease sensitivity of the respiratory centers to variations of carbon dioxide concentrations;
- Inhibition of cough center (→ explains the indication for dry cough and contraindications in productive cough);
- Induction of nausea and vomiting (these effects are more pronounced for patients which are moving).

---

3 Pain is subjective and it is defined as a sensory and emotional experience. The first component of pain is the sensory input to the central nervous system (CNS) that results in recognition of the sensation of pain. The second component is the reactive (subjective) component with role in the interpretation of the pain.
Periphera1 effects:
- cardiovascular system: bradycardia, hypotension (the effects are more pronounced in patients with these symptoms before treatment);
- increase of intracranial pressure;
- respiratory tract: increase bronchial muscle tone, reduce bronchial secretions;
- digestive tract: increase gastrointestinal muscle tone, decrease gastrointestinal peristalsis (→ explains constipation), spasm of Oddi sphincter (→ explains the pancreatic reflux;
- urogenital: increase urogenital muscle tone and decrease urogenital peristalsis, spasm of the sphincter of the urinary bladder, inhibition of uterine contractions (→ explains the contraindications during labor);
- stimulate histamine release (cause bronchospasm → explains the contraindication in bronchial asthma or COPD; cause hypotension → explains the contraindication in low blood pressure; anaphylactic shock or other allergic reactions);
- endocrine system: stimulate the release of ADH, STH, prolactin, inhibition of LH release;
- immune system: chemotaxis of PMN, T cell proliferation, production of Ig.

Miosis, truncal rigidity and constipation are pharmacodynamic effects of opioids for which no tolerance develop in chronic administration. These effects are pathognomonic signs in chronic opiates consumers.

INDICATIONS, CONTRAINDICATIONS, ADVERSE EFFECTS OF OPIOIDS

MORPHINE

Indications:
- analgesia:
  - cancer pain,
  - other chronic pain (degenerative rheumatic disease, rheumatoid arthritis),
  - visceral pain (renal / ureteral / biliary colicative pain - Meperidine is preferred because of its atropine-like effects → Meperidine does not cause nausea, vomiting, spasm of the sphincter of Oddi)
  - pain in myocardial infarction (Meperidine is preferred because of its atropine-like effects → Meperidine does not cause nausea, vomiting, spasm of the sphincter of Oddi, bradycardia, marked hypotension);
- acute pulmonary edema;
- pre-anesthesia, intraoperative (general anesthesia), post-operative, neuroleptanalgesia (Fentanyl is preferred, associated with Droperidol/Haloperidol).

Adverse reactions:
- respiratory depression;
- bradycardia, hypotension;
- nausea, vomiting;
- constipation;
- spasm of Oddi sphincter and pancreatic and bile reflux;
- acute retention of urine;

---

4 Furosemide, morphine, and nitroglycerin have historically been the baseline standard for drug therapy in CPE management. Most current textbooks and official guidelines advise the use of morphine as one of the first-line treatments for patients in acute cardiogenic pulmonary oedema.

Lecturer Cristina GHICIUC, MD, PhD
• immunological reactions type I;
• addiction.

**Contraindications:**

• absolute contraindications:
  o bronchial asthma;
  o chronic obstructive pulmonary disease (COPD);
  o labor, pregnancy, breastfeeding;
  o acute abdominal pain;
  o severe heart failure, cardiac arrhythmias, bradycardia, atrioventricular block;
  o intracranial hypertension;

• relative contraindications: kidney failure, liver failure.

- **CODEINE**
  **Indications:**
  • cough suppressant (the treatment of choice for dry cough and itchy);
  • analgesia: dentistry, oral surgery, maxillofacial surgery etc.
  The drug has addictive potential.
  **Contraindications:** productive cough.

- **DIHYDROCODEINE**
  **Indications:** analgesia (treatment of choice).
  The drug has the addictive potential higher than morphine.

- **MEPERIDINE**
  This drug also has atropine effects → does not cause nausea, vomiting, spasm of the sphincter of Oddi, bradycardia, marked hypotension.
  **Indications:** analgesic
  • visceral pain (renal colic, ureteral colic, biliary colic),
  • chronic degenerative rheumatism,
  • rheumatoid arthritis,
  • pain in myocardial infarction (particularly in myocardial infarction with hypotension or bradycardia).

- **METHADONE**
  Methadone has a longer duration of action than morphine, it determines low euphoric effects and lower intensity abstinence syndrome compared to morphine.
  **Indications:** treatment of opioid dependence (replace opiates that caused the addiction).

- **FENTANYL AND ITS DERIVATIVES (ALFENTANIL, SUFENTANIL, REMIFENTANIL)**
  Fentanyl determine analgesic effect of 80-100 times more potent than morphine, but it is also more toxic than morphine.
  These derivatives have rapid and short duration action.
  Remifentanil is very effective in rectal administration or in the form of transdermal patches.
  **Indications:**
  • neuroleptanalgesia (Fentanyl is associated with Droperidol or Haloperidol);
  • general anesthesia.

- **DEXTROMORAMIDE**
  It is an analgesic for oral administration, more powerful and shorter action than morphine. It can cause orthostatic hypotension.

- **LEVOPROPXYPHENE**
  *Indications:* cough suppressant (dry and itchy cough).
  *Contraindications:* productive cough.

- **LOPERAMIDE, DIPHENOXYLATE, DIFENOXIN**
  These drugs are partial agonists of μ-opioid receptors and don’t cross the blood-brain barrier at antidiarrheal doses.
  *Indications:* diarrhea (acute nonspecific or chronic inflammatory diarrhea).
  *Contraindications:*
  - ulcerative colitis (treatment may induce toxic megacolon);
  - intestinal infections with Shigella spp., Salmonella spp.

- **BUPRENORPHINE**
  *Indications:*
  - acute intoxication with opioids in addicted persons;
  - chronic intoxication with opioids (restore the opioid receptor sensitivity to endogenous opioid peptides after treatment of withdrawal syndrome).

- **TRAMADOL**
  It is a partial agonist on opioid receptors, with low side effects.
  *Indications:* analgesia

- **PENTAZOCINE, NALBUPHINE**
  These are agonists – antagonists on opioid receptors (agonists on k receptors and antagonists on μ receptors). Pentazocine is also agonist on σ opioid receptors.
  *Indications:*
  - Pentazocine → analgesia;
  - Nalorphine → acute intoxication in addicted persons.
  Pentazocine and nalbuphine are good analgesics, but they cause dysphoria, they determine lower addiction.

- **COMPETITIVE ANTAGONISTS OF OPIOID RECEPTORS (NALOXONE, NALTREXONE, NALMEFENE)**
  *Indications:*
  - antidote in acute opiate intoxication for people which are not addicted;
  - post-traumatic spinal cord injury.
II. Cough suppressants and expectorant drugs

COUGH SUPPRESSANTS

Classification:
- **Opioids**: Codeine; Propoxyphen, Levopropoxyphen;
- **Nonopioids**:
  - Oxeladine;
  - Clobutinol;
  - Butamirat;
  - Pentoxiverine, Prenodoxazine, Levodropropizine; Clofedanol.

*Mechanism of action*: inhibition of the cough center (non-opioid drugs do not act on opioid receptors); also determines bronchodilator effects.

*Indications*: as cough suppressant (treatment of dry and itchy cough).

*Contraindications*:
- productive cough (is common for all cough suppressants);
- other contraindications:
  - Oxeladin: children under 16;
  - Clobutinol: kidney failure, liver failure, respiratory failure, bronchial asthma, neuropsychological disorders, pregnancy (first trimester).

EXPECTORANTS

Classification:
- **fluidifiers**: from plants: Liquiritia extracts, Primula roof; Ipeca;
  - Guaiifenesin;
  - ammonium salts (eg, Amonium chloride), Sodium benzoate;
  - sweet juices, tea, candies.
- **mucolytics**: Acetylcisteine, Carbocisteine, Dornaze alfa (Desoxiribonuclease), Erdosteine;
- mixt mechanism (fluidifiers and mucolytics): Bromhexin, Ambroxol (active metabolite of Bromhexin).

**Expectorants which increas the fluidity of bronchial secretions**

*Mechanism of action*: increasing the proportion of water bronchial secretions.

*Indications*: acute and chronic bronchitis.

**Guaiifenesin**
- *Pharmacodynamic effects*: expectorant, skeletal muscle relaxant, sedative, antiseptic, local anesthetic effect.
- *Adverse effects*:
  - gastrointestinal irritation, sedation,
  - false-positive reaction for 5-hydroxyindoleacetic acid in the urine (marker for the diagnosis of carcinoma).
- *Contraindications*: persons performing precise movements.

**Mucolytic expectorant drugs**

*Mechanism of action*: cleavage of the mucin molecule → decrease the viscosity of bronchial secretions.

*Indications*: acute and chronic bronchitis, bronchiectasis, pneumonia, amyloidosis, cystic fibrosis.
• **Adverse reactions:**
  - excessive stimulation of bronchial secretions;
  - **Acetylcysteine:**
    - determines rhinorrhea, stomatitis, nausea;
    - acetylcysteine inactivates penicillins and cephalosporins → these drugs should not be mixed in vitro;
    - metals inactivate acetylcysteine.