Opioids

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Opioids are a class of substances, which are essential for medical fields like oncology, palliative and emergency medicine because of their analgesic effect. Contrary to many preconceptions, they are safe medications that do not cause dependency or the development of tolerance if used correctly. Obviously, opiate dependence is something physicians deal with time and again in their clinical routine and every physician should be familiar with the fundamentals of the Controlled Substances Act, the withdrawal symptoms as well as how to treat said symptoms.

Definition

Opiates or opioid analgesics are a group of substances that bind to opioid receptors in the nervous system and other tissues. Opiates are mainly used for their analgesic activity, but they have many other effects throughout the body. The body also naturally generates its own opioid ligands such as endorphins and enkephalins**.** Currently, there are 4 known receptor types: **μ, κ, δ** and **σ**.

Most often, the terms **opioids** and **opiates** are used synonymously. Opiates are synthetic drugs derived from opium. The term **opioid** refers to all drugs (synthetic, semi-synthetic, and natural) with properties similar to opium.

Opiate	Opioid	Endorphin
A drug derived from alkaloids of the opium poppy	A class of drugs that includes opiates, synthetic drugs, and opiopeptins that mimic opiates	A naturally occurring peptide that acts on opioid receptors in the body

Mechanism of Action

Central and peripheral opioid receptors are coupled to **inhibitory G-proteins**. The inhibition of **adenylate cyclase activity** lowers Ca^{2+} and results in **hyperpolarization**.

Effects based on receptor types

The effects of binding with **μ receptors** include **supraspinal analgesia**, **respiratory depression**, **miosis,** and **euphoria**.

The effects of **κ receptors** include **spinal analgesia**, **sedation,** and **miosis.**

δ-receptors induce cardiovascular stimulation and **mydriasis,** and can cause **dysphoria** and **hallucinations**.

Classification of agonists and antagonists

Depending on their interaction with the receptors, opioids are classified into **pure agonists, partial agonists, mixed agonist-antagonists**, and **pure antagonists**:

Pure agonists bind to μ receptors and exert maximum effect depending on the dosage. They include **morphine, fentanyl,** and **pethidine**.

Partial agonists, i.e., **buprenorphine**, are associated with partially agonistic and antagonistic effects. They have a **ceiling effect,** which means that the effect plateaus at a certain dosage, and increasing the dosage will not increase its effect. This effect is attributed to the extraordinary affinity of a partial agonist for the μ receptor with lower intrinsic activity than morphine.

Mixed agonist-antagonists such as pentazocine act as antagonists at the μ receptor and agonists at the κ receptor with high intrinsic activity. Due to their antagonistic effect, they prevent the binding of an agonist with the receptor and reverse its pharmacological effects.

Pure antagonists such as naloxone and naltrexone are competitive antagonists that bind to and block all opioid receptors.

Overview

Opioid agonists	Mixed agonist/antagonists	Antagonists

Weak agonists	Strong agonists		
Propoxyphene	• Morphine • Meperidine • Methadone • Fentanyl	• Nalbuphine • Buprenorphine	• Naloxone • Naltrexone
Moderate agonists			
• Codeine • Oxycodone			

Central and peripheral effects of opioids

The central effects of opioids are mediated via **reduction of pain transmission** by stimulating opioid receptors. The opioids activate the descending inhibitory system, suppress the spinal **nociceptive impulses,** and modulate the pain sensation in the limbic system. Furthermore, opioids have a sedating and hypnotic effect. In addition, they **contain anxiolytic** and **euphoria-inducing** components. By inhibiting the respiratory center and the cough reflex, opioids **induce respiratory depression and have an antitussive effect**.

Patients frequently experience nausea and vomiting at the beginning of opioid therapy, due to stimulation of the 'vomiting center' in the **area postrema** at the floor of the **4th ventricle.** Subsequently, however, they inhibit vomiting activity and have an **antiemetic effect**. **Miosis** (pinpoint pupils) is often associated with opioid use. This is caused by the stimulation of the **Edinger-Westphal nucleus** in the midbrain causing the **pupillary sphincter (musculus sphincter pupillae)** to contract.

Peripheral effects include **analgesia**, **delayed gastric emptying** due to **pyloric contraction** and **reduced gastric motility,** and **increased tone** of the smooth musculature of the gastrointestinal tract. In addition, **the tone of the bladder muscle and bladder contractor muscle** is increased. **Histamine** release is also common, causing intense itch.

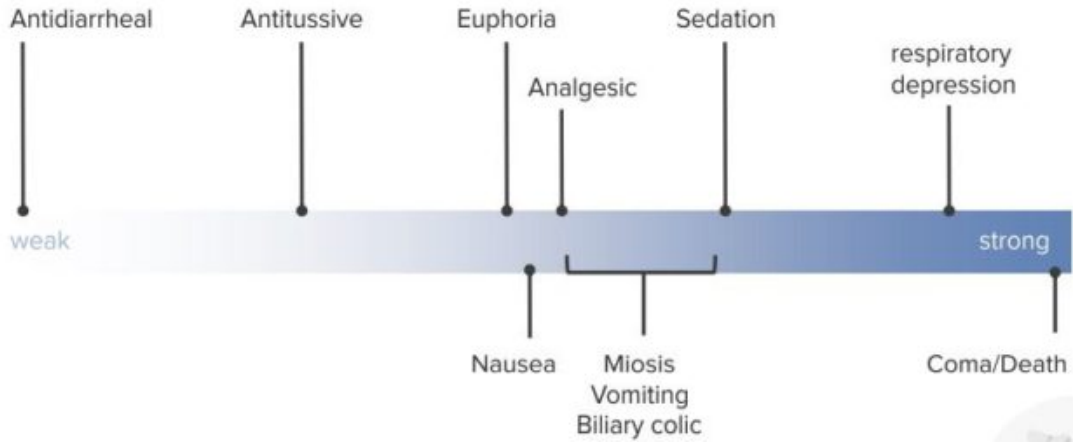

Image: Opioid analgesics. Effects of opioids. By Lecturio

Contraindications to and Interactions with

Opioids

Relative contraindications

- Children **under the age of 1 year**
- **Respiratory insufficiency,** i.e., asthma
- **Increased intracranial pressure**
- **Hypotension** or **hypovolemia** due to the blood-pressure-lowering effects of opioids
- **Opioid dependence**
- **Gallbladder and urinary tract diseases—**spastic contraction of the urinary sphincter may lead to urinary retention
- **Pancreatitis** due to increased sphincter tone along with a risk of secretion build-up
- **Obstructive and inflammatory gastrointestinal diseases** as the tone of the smooth musculature increases, with the associated risk of spasms and perforation
- **Ileus** associated with a risk of perforation

During pregnancy and breastfeeding, the indication must be strictly defined.

Interactions between opioids and other drugs

Opioids **interact with CNS depressants** such as **hypnotics**, **phenothiazines**, **tranquilizers,** and especially **alcohol,** leading to enhanced sedation and life-threatening respiratory depression.

Motility inhibitors enhance the constipating effects of opioids, and cimetidine slows down the break-down of morphine.

Indications for Opioids

Indications for the use of opioids are severe and extreme pain (**nociceptive pain**), i.e., surgical and tumor-related pain. Opioid analgesics are also especially indicated for the treatment of pain in cases of **acute myocardial infarction** and **acute pulmonary edema** because of their psycho-sedative effects.

The World Health Organization (WHO) ladder governing the use of opioids

The WHO ladder is used for the treatment of chronic pain. It was originally created for the **treatment of tumors**. It is, however, also applied for the treatment of chronic musculoskeletal pain if **NSRA** drugs are contraindicated or if they do not provide adequate pain relief.

Step 1	Non-opioid analgesics
Step 2	Non-opioid analgesics plus mild opioids such as tramadol and tilidine
Step 3	Non-opioid analgesics plus strong opioids such as morphine, hydromorphone, and oxycodone
Step 4	Invasive techniques such as epidural injection, peripheral local anesthesia and ganglion block

Dependence and development of opioid tolerance result if opioids are only administered during pain peaks. Therefore, pain management should consist of **basic medication with retarding products** and **on-demand medication with fast-acting agents** if pain peaks occur.

Retarding products are frequently applied as patches that are changed every 72 hours.

These patches take time to manifest their full therapeutic effect, which continues for up to 16 hours after the patch is removed.

Substances and Their Use with Opioids

Low-potency opioid analgesics

Low-potency opioids such as **tilidine, dihydrocodeine, codeine,** and **tramadol** are **regulated under the Controlled Substances Act** and are administered for relief of moderate to severe pain. In comparison to **morphine,** they have lower efficacy, i.e., they have lower **analgesic** (relative) **potency** (RP < 1).

Increasing the dosage of low-potency opioids to a certain point leads to pain relief equivalent to morphine. This phenomenon is referred to as the **maximum attainable response (analgesia)**. In contrast to high-potency opioids, any further increase in the dosage of low-potency opioids only results in stronger side effects without increasing the analgesic effect.

Tramadol has **0.1–0.2-fold higher analgesic potency** compared with morphine. However, its most severe side effects are nausea and vomiting, whereas constipation and respiratory depression are rare. The effects of tramadol last 4–6 hours and it can be taken **orally** or administered **intravenously, intramuscularly** or **rectally**.

Dihydrocodeine and **codeine** have a **relative potency of 0.3** and are used as **antitussives,** because of their strong cough suppressant properties. Its effect lasts approx. 8–12 hours and it is administered **orally**.

Headache is the most common side effect of codeine. The most common side effect of dihydrocodeine is constipation.

Tilidine has an **analgesic potency of 0.2** and its effect lasts approx. 3 hours. Tilidine is metabolized to **nortilidine** via hepatic conversion**.** Tilidine is available in fixed combination with the opioid antagonist **naloxone**.

Upon oral intake of a normal dose of tilidine, naloxone is inactivated by **the first-pass effect in the liver** and nortilidine is effective. If it is abused via intravenous administration, however, naloxone is effective as the hepatic inactivation of naloxone is delayed. As an opioid receptor **antagonist**, it prevents the addiction-causing effect as well as the dreaded respiratory depression.

The fixed combination tilidine-naloxone is not subject to the Controlled Substances Act similar to the other low-potency opioids.
Pentazocine and pethidine only mediate postoperative analgesia. Both have a short duration of action and may induce hallucinations. Even though they are mild opioids, they are **subject to the Controlled Substances Act.**

High-potency opioids

Morphine is rapidly absorbed after oral administration. The **hepatic first-pass effect is very high (30–50%**). Furthermore, morphine undergoes conjugation with **glucuronic acid-forming 3-glucuronide** and **6-glucuronide**. While 3-glucuronide has no analgesic effect, the analgesic effect of 6-glucuronide is very high. The half-life varies between 2 and 3 hours, which is why morphine is administered 2–3 times a day. If pain peaks occur, additional morphine solution may be administered.

For patients whose pain cannot be sufficiently relieved by administering oral

morphine, **continuous intrathecal or epidural morphine administration** is indicated. It is applied via a **subcutaneous reservoir** or a **subcutaneous computer-controlled pump**. Indications are, for instance, abdominal metastases and pain in the lower extremities with **syringomyelia**, **spinal tumors,** and **traumatic paraplegia.**

As **buprenorphine** is highly lipophilic, it is well absorbed and is 40 times more potent than morphine. It has, however, poor bioavailability due to its **high first-pass effect,** which is why it administered **parenterally, transdermally or sublingually.** Due to its high affinity for opioid receptors, it is resistant to antagonism by **naloxone**.

Oxycodone exhibits analgesic effect similar to morphine and is especially used in **orthopedics,** i.e., following **partial knee prosthetics.**

Opioids and Anesthesia

Within the context of anesthesia, it is primarily the μ receptor that is responsible for the opioid effects but the κ receptor is also responsible partially. Stimulation of the μ1 receptor leads to pronounced **spinal and supraspinal analgesia** but also to simultaneous respiratory depression via the μ2 receptor. No pure μ1 agonists have been found so far. Stimulation of the κ receptor induces spinal analgesia and **sedating side effects** via receptors in the cortex.

Fentanyl, **alfentanil**, **sufentanil,** and **remifentanil** are pure and selective μ agonists that are used for **intravenous (as well as total intravenous anesthesia (TIVA)) and balanced anesthesia**. They exhibit good **analgesic efficacy**, low **hemodynamic effect,** and **antagonist action**. However, they are not associated with **liver or kidney toxicity** and do not trigger **malignant hyperthermia**. Even though they improve the tolerance to endotracheal intubation, they may cause t**horacic rigidity,** which may interfere with assisted ventilation.

They reduce CO_2 sensitivity in the respiratory center leading to respiratory depression, resulting in **hypercapnia** with a significant **increase in cerebral perfusion and intracranial blood volume**. Another side effect of opioids is **the increased tone of the bronchial musculature** resulting in increased respiratory resistance. Other disadvantages regarding anesthesia with opioids include insufficient reflex reduction, postoperative nausea, and the absence of amnesia with a relatively prolonged wake-up phase.

	Fentanyl	**Alfentanil**	**Sufentanil**	**Remifentanil**
Analgesic potency (morphine = 1)	125	30	1000	450–900
Duration of action	20–30 min.	15–20 min.	30 min.	2–3 min.
Metabolism	Hepatic metabolism, renal excretion	Hepatic metabolism, renal excretion	Hepatic metabolism	Metabolism via plasma esterases, renal excretion

Remarks	Highly lipophilic	Not as highly lipophilic and less likely to accumulate, therefore, indicated for short procedures	Similar to fentanyl	Continuous administration necessary due to short half-life; suitable for total intravenous anesthesia in combination with propofol

N.B. Fentanyl, alfentanil, sufentanil, and remifentanil are not considered narcotics as they do not induce general depression of neuronal activity.

Treatment of Dyspnea with Opioids in Palliative Medicine

Dyspnea is a common challenge during the terminal stages of many diseases. Opioids may be administered for symptomatic relief. Drugs such as morphine are administered **nasally** or **subcutaneously**.

Antagonizing Opioids

The receptor-specific opioid effects may be competitively inhibited either completely via pure antagonists such as **naloxone,** or partially via mixed agonist-antagonists such as **nalbuphine**.

Antagonists are used to eliminate the opioid-induced respiratory depression due to an absolute or relative overdose or in the context of postoperative reversal of opioid effects.

The administration of **naloxone** should be **titrated** in order to rule out respiratory depression while maintaining analgesia. There is a **risk of tachycardia and an increase in blood pressure**. Naloxone has a **short duration of action of 30 minutes,** after which **respiratory depression may recur.** Patients must be carefully monitored for a sufficient period of time after the antagonist administration.

Nalbuphine is a mixed agonist-antagonist with its intrinsic activity at the μ receptor that is significantly less than that of pure agonists used for anesthesia. Its analgesic effect, however, is mainly mediated by its agonist activity at the κ-receptors and its duration of action is approx. 2–3 hours.

Opioid Overdose

The **triad** of symptoms associated with classic opioid overdose includes**: respiratory depression with a respiratory rate of 2–4 breaths per minute, coma, and miosis**. Immediate treatment is essential in the form of **assisted ventilation** and **titrated administration of the antagonist** naloxone.

N.B. Because opioid abuse is frequently combined with alcohol, sedatives or psycho-stimulants, the symptoms may not always be obvious (for e.g., miosis). Naloxone may be used as a diagnostic tool when the cause of toxicity is unknown.

Opiate Withdrawal Syndrome

Heroin

Opiate dependence with withdrawal symptoms develops generally with heroin use but may also occur with prescription opioid use.

Opioid dependence is **caused by the development of tolerance**. Pharmacodynamic tolerance is based on **increased adenylyl cyclase activity.** Signs of tolerance include

diminished response to the drug as well as the shortened duration of action that is compensated by increasing the dosage.

Withdrawal symptoms include **bone pain and muscle aches**, **fever, tachycardia, insomnia,** and **psychosomatic restlessness**. However, atypical symptoms involve psychosis and delirium.

Withdrawal symptoms are treated with **sedating benzodiazepines** with long half-life such as **diazepam** and **sedating tricyclic antidepressants**. Ultra-rapid detoxification (URD) that occurs under anesthesia with high doses of opiate antagonists such as **naloxone** and **naltrexone** is disputed.

Opiate Replacement Therapy

For many opiate addicts, replacement therapy may facilitate psychosocial integration, reduce criminal activity for the purpose of obtaining drugs and lower the risk of acquiring HIV and hepatitis following drug use. In most cases, the replacement drug is **methadone**.

Methadone is a synthetic **racemate**, and only the L-form is effective (**levomethadone)**. Due to its long half-life of 24–48 hours, there is no typical 'rush' effect, and therefore appropriate for replacement therapy.

Levo-alpha-acetylmethadol (**LAAM)** has an even longer half-life and does not require administration more than 3 times per week. The benefits are fewer fluctuations, which minimize the risk of withdrawal symptoms, and better bridging weekends as daily physician-patient contact is not necessary.

Peripheral Opioids

Loperamide does not cross the blood-brain barrier as the epithelial cells immediately pump it back into the blood. Loperamide increases the oscillatory movement of the gastrointestinal muscles and inhibits GI propulsion. Further, it may reduce the loss of enteral fluids.

Loperamide is indicated as a temporary treatment for **traveler's diarrhea,** caused by either a viral or bacterial infection. It is not, however, indicated in cases of functional diarrhea due to toxins produced by bacteria. The **antidiarrheal effect** of loperamide is neutralized by naloxone.

Loperamide is contraindicated in children under the age of 2 years due to central morphine-like side effects in addition to **ileus**.

Racecadotril, however, is approved for the treatment of diarrhea in newborns, infants, and toddlers. It is administered orally and inhibits the breakdown of **enkephalins,** thus reducing the secretion of water and sodium in the intestinal epithelium.

Fun fact: Opium tincture used to be the standard remedy for traveler's diarrhea but is no longer used because of the Controlled Substances Act.

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Notes