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. They are mainly used for their analgesic activity, but it is important to remember that they have many other effects throughout the body. The body also naturally creates its own opioid ligands such as endorphins and enkephalin**.** Currently, there are four known receptor types: **μ, κ, δ and σ**.

For the most part, the terms **opioids** and **opiate** 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	Endorphins
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 act 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**.

The effect on receptor types

The effects on **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 as pure agonists, partial agonists, mixed agonist-antagonist, or pure antagonists:

Pure agonists bind to μ receptors and have maximum effect depending on dosage. Among them are **morphine, fentanyl** and **pethidine**.

Partial agonists, i.e. **buprenorphine**, have a partially agonistic and antagonistic effect. They have a **ceiling effect** meaning that from a certain dose on, increasing the dosage will not increase its effect. This is the result of its very high affinity for the μ receptor with lower intrinsic activity than morphine.

Mixed agonists-antagonists like **pentazocine** are antagonists at the μ receptor and agonists at the κ receptor with high intrinsic activity. Due to their antagonistic effect, they can block agonists from the receptor and reverse their effects.

Pure antagonists are competitive antagonists that bind to and block all opioid receptors. Among them are **naloxone and naltrexone**.

Overview:

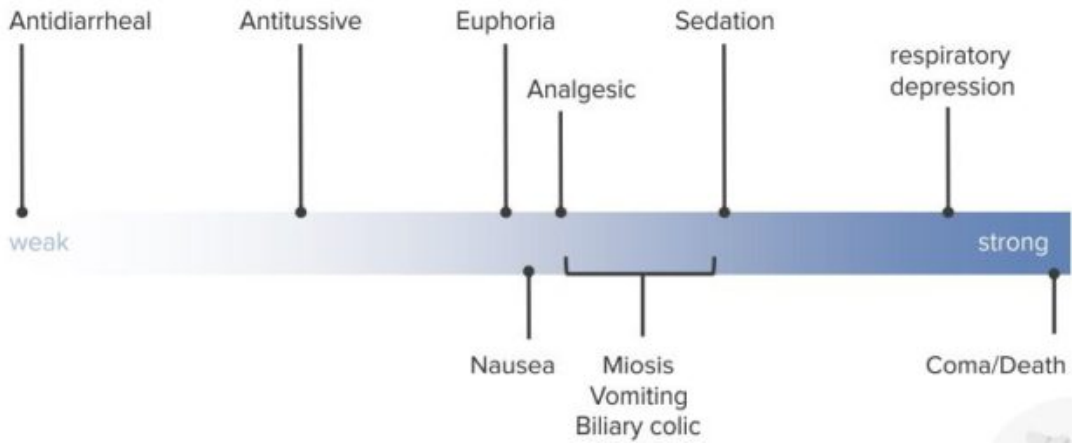
<table>
<tr><th colspan="2">Opioid agonists</th><th>Mixed agonist/antagonists</th><th>Antagonists</th></tr>
<tr><th>Weak agonists</th><th>Strong agonists</th><td rowspan="4">• Nalbuphine
• Buprenorphine</td><td rowspan="4">• Naloxone
• Naltrexone</td></tr>
<tr><td>Propoxyphene</td><td rowspan="3">• Morphine
• Meperidine
• Methadone
• Fentanyl</td></tr>
<tr><th>Moderate agonists</th></tr>
<tr><td>• Codeine
• Oxycodone</td></tr>
</table>

Central and peripheral effects of opioids

Among the central effects of opioids is the **reduction of pain transmission** by stimulating opioid receptors. They activate the descending inhibitory system, spinal **nociceptive impulses** are suppressed and the pain sensation in the limbic system is modulated. Furthermore, opioids have a sedating effect on mental activity and a hypnotic effect. In addition, there are **anxiolytic** and **euphoria-inducing** components. By inhibiting the respiratory center and the cough reflex, opioids cause **respiratory depression and have an antitussive effect**.

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

Peripheral effects include **analgesia**, **delayed gastric emptying** due to **contraction of the pylorus, 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 itching.



“Opioid Analgesics. Effects of Opioids” Image created by Lecturio

Contraindications to and Interactions with Opioids

Relative contraindications to the use of opioids

- Children **under the age of 1 year**
- **Respiratory insufficiency,** i.e. asthma
- **Increased intracranial pressure**
- **Hypotension** or **hypovolemia** due to the blood pressure-reducing effects of the substances
- **Opioid dependence**
- **Gallbladder and urinary tract diseases**– the spastic contraction of the urinary sphincter may lead to urinary retention

- **Pancreatitis** as the sphincter tone is increased and there is a risk of secretion build-up
- **Obstructive and inflammatory gastrointestinal diseases** as the tone of the smooth musculature increases, bringing about the risk of spasms and perforation
- **Ileus** – here is a risk of perforation as well

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

Interactions between opioids and other drugs

There are interactions between opioids and **CNS depressants** such as **hypnotics**, **phenothiazines**, **tranquilizers,** and especially **alcohol**. They enhance the sedating effects of opioids and may lead to 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 type pain**), i.e. in the context of surgeries and tumors. Opioid analgesics are also especially suited for treating pain in cases of **acute myocardial infarction** and **acute pulmonary edema** because of their psycho-sedating effects.

The WHO ladder governing the use of opioids

The WHO ladder is used for the treatment of chronic pain and was originally created for the **treatment of tumors**. It is, however, also being applied for the treatment of chronic musculoskeletal pain if **NSRA** drugs are contraindicated or if they do not provide sufficient 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 the development of opioid tolerance are promoted 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 substances** if pain peaks occur.

Retarding products are frequently applied as patches that need to be changed every 72 hours. It should be noted that it takes some time for these patches to develop their full effect and that this effect continues on for up to 16 hours after the patch has been removed.

Substances and Their Use with Opioids

Low-potency opioid analgesics

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

If the dosage of low-potency opioids is increased to a certain point, pain relief equal to morphine can be achieved. This is referred to as **maximum attainable response (analgesia)**. Any further increase in dosage would only result in stronger side effects while the analgesic effect cannot be increased. This is not the case with high-potency opioids.

Tramadol has **0.1 to 0.2 times the analgesic potency** of morphine. Its most severe side effects are nausea and vomiting, whereas constipation and respiratory depression rarely occur. The effects of tramadol last four to six hours and it can be taken **orally** or be 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 approximately eight to twelve hours and it is administered **orally**.

The most common side effect of codeine is headache. The most common side effect of dihydrocodeine is constipation.

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

If a normal dose of this product is taken orally, naloxone is inactivated by the **first-pass effect in the liver** and nortilidine becomes effective. If it is injected in an abusive manner, however, naloxone will become effective as the hepatic inactivation of naloxone is delayed. As 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 just like the other low-potency opioids.
Pentazocine and pethidine only play a role in post-operative analgesia. Both have short duration of action and may cause hallucinations. Even though they are mild opioids, they are **subject to the Controlled Substances Act.**

High-potency opioids

Morphine is quickly absorbed after oral administration. The **first-pass effect in the liver is very high** with 30 – 50 %. Furthermore, morphine undergoes conjugation with **glucuronic acid** forming **3-glucuronide** and **6-glucuronide**. While 3-glucuronide has no analgesic effects, the analgesic effect of 6-glucuronide is very high. The half-life is between two and three hours, which is why morphine is administered two to three 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 suitable. 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 the usual administration is **parenteral, transdermal or sublingual.** Due to its high affinity to opioid receptors, it is resistant to antagonism by **naloxone**.

Oxycodone has a similarly good analgesic effect compared 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 to a lesser degree. Stimulating 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. Stimulating the κ receptor causes 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**. Their benefits include good **analgesic efficacy**, low **hemodynamic influence** and **antagonist ability**. Furthermore, there is **no liver or kidney toxicity** and they do not trigger **malignant hyperthermia**. Even though they improve the tolerance of endotracheal intubation, they may lead to t**horax rigidity,** causing problems with assisted ventilation.

They reduce respiratory center CO_2 sensitivity leading to respiratory depression. This can result in **hypercapnia** with significant **increase in cerebral perfusion and intracranial blood volume**. Another side effect of opioids is **increased tone of the bronchial musculature** resulting in increased respiratory resistance. Other disadvantages regarding anesthesia with opioids are 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	Hepatics metabolism, renal excretion	Hepatic metabolism	Metabolism via plasma esterases, renal excretion
Remarks:	Highly lipophilic	Not as highly lipophilic = less likely to accumulate – suitable for short procedures	Similar to fentanyl	Continuous administration is necessary due to its short half-life – suitable for total intravenous anesthesia in combination with propofol

Note: Fentanyl, alfentanil, sufentanil, and remifentanil are not considered narcotics as they do not cause a general depression of neuronal activity.

Treatment of Dyspnea with Opioids in Palliative Medicine

A commonly observed problem during the terminal stage of many diseases is **dyspnea.** And 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 canceled out either completely via pure antagonists such as **naloxone,** or partially via mixed agonists-antagonists such as **nalbuphine**.

Antagonists are used in order to eliminate 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 cancel out the respiratory depression while maintaining analgesia. There is the **risk of tachycardia and increase in blood pressure**. Naloxone has a **short duration of action of 30 minutes,** after which **respiratory depression may rebound.** Patients must be carefully monitored for a sufficient period of time after the antagonist administration.

Nalbuphine is a mixed agonist-antagonist meaning its intrinsic activity at the μ receptor is significantly less than that of pure agonists used for anesthesia. Its analgesic effect, on the other hand, is mainly mediated by its agonist activity at the κ-receptors and its duration of action is approximately two to three hours.

Opioid Overdose

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

Note: because opioid abuse is frequently combined with alcohol, sedatives or psycho-stimulants, the symptoms may not always be clear (you may be dealing with miosis for instance), naloxone may be used as a diagnostic tool when the cause of toxicity is unknown.

Opiate Withdrawal Syndrome

Heroin

Opiate dependence with withdrawal symptoms commonly develop with heroin use but also occur with prescription opioid use.

The cause of opioid dependence is the **development of tolerance**. The reason for the adjustment to these drugs is pharmacodynamic tolerance based on **increased adenylyl cyclase activity.** Signs of developing tolerance are an individual’s diminished response to the drug as well as the shortened duration of action that has to be compensated by increasing the dosage.

Withdrawal symptoms include **bone pain and muscle aches**, **fever, tachycardia, insomnia,** and **psychosomatic restlessness**. Atypical symptoms, however, are symptoms of psychosis and delirium.

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

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 that accompanies drug use. In most cases, the replacement drug is **methadone**.

Methadone is a synthetic **racemate**, only the L-form is effective (**levomethadone)**. Due to its long half-life of 24 – 48 hours, there is no typical "rush" effect, which is why it is so suitable for replacement therapy.

Levo-alpha-acetylmethadol or **LAAM** has an even longer half-life and does not have to be taken more than three times per week. The benefits are fewer fluctuations minimizing 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 into the brain as its epithelial cells immediately pump it back into the blood. Loperamide increases the pendulum movement of the gastrointestinal muscles and inhibits GI propulsion. Furthermore, it may reduce loss of enteral fluids.

An indication for loperamide is a temporary measure in cases of **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 cancelled out by naloxone.

Loperamide is contraindicated in children under the age of two as central morphine-like side effects have been observed and there have been some reports of **ileus**.

Racecadotril, on the other hand, is suitable and has been approved for the treatment of babies and infants with diarrhea. It is administered orally and inhibits the break-down 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.

Review Questions

The answers are below the references.

1. **A 45-year old man is found unconscious by a passer-by. She alarms emergency personnel. The emergency physician examines the man and finds pinpoint pupils and several abscessed track marks in the crook of his right arm and on his right hand. The respiratory rate is only three breaths per minute. As the physician suspects opioid intoxication, he administers naloxone and the man comes to relatively fast. He is stable. How should the physician proceed next?**

1. The man should be taken to the hospital because of the short half-time of
2. Titrated naloxone administration should be continued until the man has sobered up completely and can go home.
3. The man's wishes should be respected and he should be left alone.

4. The police should be notified because of the unlawful possession and use of
5. The man should be intubated as he may immediately relapse into respiratory

2. **A 20-year-old man is involved in a bad car accident. The emergency physician arrives on scene and administers intravenous fentanyl to relieve the pain. As the circumstances of the accident are unclear, emergency personnel conduct a sweat test for drugs five minutes later. All fields are negative, even the one for opiates. What is the reason for this field to be negative even though the patient has received fentanyl?**

1. Fentanyl does not yet show up in sweat after five minutes.
2. The test must be faulty.
3. Fentanyl is not an opiate.
4. Due to its high lipophilia, fentanyl does not transfer into sweat.
5. The patient has to undergo drug replacement therapy with naloxone.

3. **What does the term ceiling effect describe with regard to administering partial opioid receptor agonists such as buprenorphine?**

1. From a certain dose on, the antagonistic effect exceeds the agonistic effect.
2. The effect is always the same, independent of the dose given.
3. From a certain dose on, increasing the dosage will not increase the effect.
4. Psychotic symptoms occur during replacement therapy if the dosage is too
5. Individual dosing, only the constipating effect of buprenorphine is cancelled out by the antagonistic component.

References

Adler, M. W. (1993). *Opioids: 2 104,2 / contrib. M.W. Adler*.

Akil, H., Herz, A., & Simon, E. J. (1993). *Opioids*. (Handbook of experimental pharmacology.) Berlin: Springer.

Alberta Alcohol and Drug Abuse Commission. (2004). *Opioids*. Edmonton: AADAC.

Hulse, Sim, M., Hulse, G., & Martin, J. (2004). *Opioids*. Oxford University Press.

Pfeiffer, A. (1991). Psychotomimetic Effects of Opioids. *Neurobiology of Opioids*, 351-362. doi:10.1007/978-3-642-46660-1_21

Correct answers: 1A, 2C, 3C

Notes