

Pain Relief – The Pharmacology of Analgesics and Non-Steroid Anti-Inflammatories (NSAIDs)

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As pain, be it acute or chronic, can severely restrict quality of life, humanity has been striving for pain relief since year zero. Painkillers (analgesics) are thus one of the most frequently ingested forms of medication. For that reason, knowledge of the effects and side effects of analgesics is essential during your medical studies and later work as a physician. The following article shall provide you with an overview of the most important painkillers.



The WHO Pain Relief Ladder for Pain Treatment

In 1986, the WHO (World Health Organization) compiled a plan for treating chronic pain, which orders the administration of oral analgesics (painkillers) according to their various potencies: First, apply weaker analgesics, and if the desired effect is not achieved move onto stronger analgesics; coanalgesics (see below) can be administered at each level. These levels of pain, initially only used to treat pain from tumors, are now applied in the treatment of other chronic pains as well.

Level 1: Non-Opioid Analgesics

The **non-opioid analgesics** of the first WHO level of pain include **paracetamol** (4 to 6 x 500 to 1000 mg per day), **naproxen** (2 x 500 mg per day), **diclofenac** (2 x 50 to 150 mg per day) and **ibuprofen** (2 to 3 x 800 mg per day). However, paracetamol is only slightly effective against bone, soft tissue and tumor pain as it is not **antiphlogistic**. Patients with a high risk of **gastrointestinal** complications should also take **proton pump inhibitors** (e.g., **omeprazole**).

The effects and side effects of said substances are described further below in the text.

Level 2: Non-Opioid Analgesics Plus Low-Potency Opioids

Administration of **low-potency opioids** along with the non-opioid analgesics occurs at the second of the WHO levels of pain. These include **dihydrocodeine** (2 to 3 x 60 to 180 mg per day), **tramadol** (2 to 3 x 100 to 300 mg) and **tilidine** (2 to 3 x 100 to 200 mg per day), all of which are administered as a **retarded compound**.

The low-potency opioids will be discussed in detail later. In case of very severe chronic pain, or insufficient effectiveness of low-potency opioids, you should switch to pain level three, but never combine the opioids of levels two and three, as this will weaken the effects of the pharmaceuticals.

Note: Opioids of levels two and three must not be combined with each other!

Level 3: Non-Opioid Analgesics Plus High-Potency Opioids

The third of the WHO levels of pain stipulates a combination of non-opioid analgesics and **high-potency opioids**. These include **morphine** (6 x 5 to 500 mg p.o. per day), **hydromorphone** (2 to 3 x 4 to 200 mg p.o. per day), **buprenorphine** (3 to 4 x 0.2 to 1.2 mg s.l. per day), **fentanyl** (0.6 to 12 mg transdermally) and **oxycodone** (2 to 3 x 10 to 400 mg p.o. per day). **Retarded morphine** is the medication of choice, **non-retarded** is primarily ingested as **required medication** for **breakthrough** or **peak pain**. For dysphagia, severe constipation or other intestinal absorption disorders, fentanyl or buprenorphine may also be administered as a **transdermal** patch (**TTS = transdermal therapeutic system**).

Opioids are ingested at specific increments that should not be shortened as, otherwise, the patient runs the risk of **accumulation** of the agents. Else, the dosage should be increased upon experiencing pain within the interval.

Note: Pain treatment is performed “by the mouth” (oral), “by the ladder” (according to the levels of pain) or “by the clock” (fixed intervals).

The effects and side effects of the high-potency opioids are discussed in the article “[Anaesthesia](#)”.

WHO Levels of Pain		
Level 1	Level 2	Level 3
Non-opioid analgesics	Low-potency opioids + non-opioid analgesics	High-potency opioids + non-opioid analgesics
Coanalgesics and non-medication measures		

Non-Opioid Analgesics

Non-opioid analgesics describe pain medications that do not interact with the **opioid receptors** but rather perform a pain-inhibiting effect in a different manner.

Antipyretic Analgesics as Inhibitors of Cyclooxygenases

Antipyretic analgesics lower fever and alleviate pain by inhibiting the **cyclooxygenases**.

The cyclooxygenases are key enzymes in the formation of **arachidonic acid derivatives (eicosanoids)**. Uninhibited, they catalyze the formation of **prostaglandin G₂** and **prostaglandin H₂** from the **arachidonic acid**, which ultimately produce **prostaglandin, prostacyclin** and **thromboxane** due to the effects of other enzymes. Along with **physiological** reactions, these also facilitate **pathophysiological** processes, such as fever, inflammation and pain.

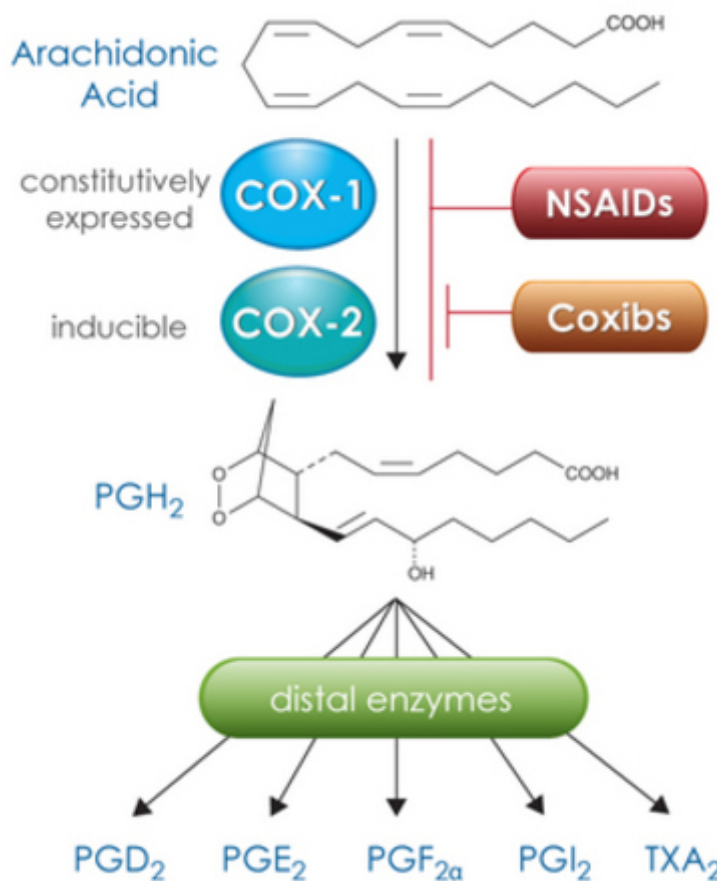


Image: "COX-1 and COX-2 convert arachidonic acid to the intermediate PGH₂, which is then metabolized by specific distal enzymes to produce the different PGs and thromboxane. NSAIDs inhibit both COX forms, while the coxibs selectively inhibit COX-2." by BQUB14-Msanjose. License: [CC-BY-SA-4.0](https://creativecommons.org/licenses/by-sa/4.0/)

The cyclooxygenases are present as isoenzymes **COX-1** and **COX-2**. **COX-1** is **constitutively** expressed in many cells of the human body, including the cells of the gastric mucosa, where it facilitates the **synthesis of PGE₂** (prostaglandin E2) to protect the mucosa. This enzyme is thus responsible for many **physiological** processes.

COX-2, however, is only constitutively present in a few cells (kidney, brain, vessels) and

is thus primarily an **inducible** enzyme. The expression thereof is greatly increased by **inflammations, trauma** or **ischaemia**, so that **pathological** processes (fever, inflammation, pain), among others, are triggered.

Due to the presence of cyclooxygenases as isoenzymes, there are two ways to inhibit these enzymes: **selective** and **non-selective** inhibition.

Non-Selective COX Inhibitors

The **non-selective** inhibitors of the cyclooxygenases include **antipyretic** analgesics with an **antiphlogistical** (inflammation-inhibiting) effect (acid analgesics, NSAR = non-steroidal antiinflammatories) and those with no **antiphlogistical** effect (**non-acid analgesics**).

The acid analgesics are thus additionally antiphlogistical as they easily penetrate inflamed tissue—unlike the non-acid analgesics—and can often exercise their effect there. The most important acid analgesics are **acetylsalicylic acid (ASA)**, **ibuprofen** and **diclofenac**, while **paracetamol** and **metamizole** are non-acid analgesics. With the exception of ASA, which irreversibly inhibits cyclooxygenases, all of these substances are competitive inhibitors.

Side effects of non-selective COX inhibitors

As the cyclooxygenases are present in many of the body's cells, they have a wide range of side effects:

- **Gastrointestinal tract:** The most common side effects include dyspeptic symptoms, gastroduodenal ulcers (due to decreased prostaglandin synthesis and increased leukotriene synthesis and accumulation of the acid analgesics in the gastric mucosa); proton pump inhibitors are suitable for prevention.



▪ Gastric Ulcer Antrum

Kidney: Sodium retention (result: increase in preload, edema of the legs), decreased diuresis, hyperkalaemia (result: cardiac arrhythmias); CAVE in patients of advanced age, with **diabetes mellitus** or limited kidney function!

- **CNS:** Headaches, vertigo, hearing and vision impairment.
- **Respiratory tract:** Bronchoconstriction (due to decreased prostaglandin synthesis and increased leukotriene synthesis), analgesic asthma, “aspirin” or “Samter’s triad”: nasal polyp + intrinsic asthma + sinusitis.
- **Pregnancy:** Contraction inhibition with subsequent bradycardia, premature closing of the ductus Botalli.
- **Blood coagulation:** Thrombocyte aggregation inhibition.
- **Hypersensitivity reactions:** Anaphylactic shock, pseudoallergic reactions, skin reactions.

Acetylsalicylic acid (ASA)

ASA is one of the oldest and most well-known painkillers, and its effectiveness **depends on its dosage**:

- From < 30 mg/d: Thrombocyte aggregation inhibition
- Up to 2 to 3 g/d: Analgesic and antipyretic
- 2 to 4 g/d: Antiphlogistic

ASA is thus administered to lower fever and for general states of pain; yet in high doses, it can also be used to treat **acute** and **chronic inflammation** (e.g., **gout, rheumatic fever, osteoarthritis, rheumatoid arthritis**).

The COX-1 (catalyst of **thromboxane** formation in thrombocytes which activates the thrombocyte aggregation inhibition) must be at least 95 % inhibited for **thrombocyte aggregation inhibition** to be present. This is only the case with the acid analgesics, whereby ASA is the only analgesic that **irreversibly** inhibits the cyclooxygenases via **acetylation**. As **thrombocytes** have no nucleus and thus cannot emulate COX-1; the thrombocyte aggregation inhibition lasts for eight to ten days (corresponds to the lifespan of the platelets) and can be used therapeutically: prophylaxis of **thromboses** and **embolisms**, treating **CHD, PAD** and **cerebrovascular diseases** as well as **secondary prophylaxis** of **heart attack** or **stroke**.

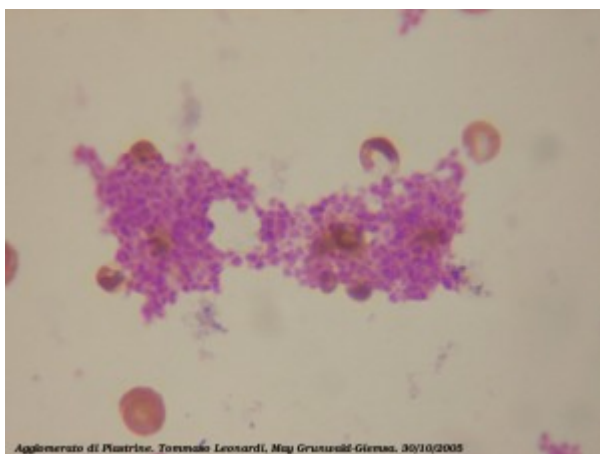


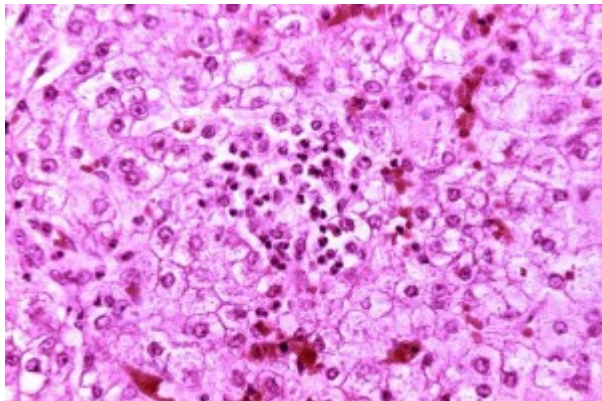
Image: “Platelets clumping from a blood smear. May Grunwald-Giemsa. Light Microscopy, oil immersion 100x.” by Tleopardi.
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CAVE: ASA must be discontinued at least seven days before an operation as otherwise there is a greater tendency to bleed!

The side effects of ASA correspond to the general side effects of the non-selective COX inhibitors, whereby the **gastrointestinal** symptoms take priority.

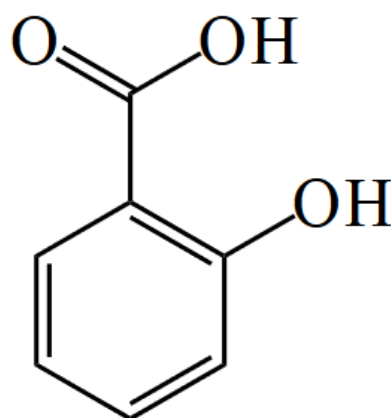
The “**aspirin triad**” (also known as **Samter’s triad**) may appear as a special hypersensitivity reaction to ASA (but also other NSAR), which results in **nasal polyps (polyposis nasi)**, **asthma** and **sinusitis**. **Bronchoconstriction** stemming from an imbalance between **bronchodilatory prostaglandins** and **bronchoconstricting leukotrienes** results in so-called **analgesic asthma**. There is also a greater **risk of bleeding** from ingestion of ASA due to thrombocyte aggregation inhibition.

Note: Samter’s triad and analgesic asthma are side effects of ASA.



Reyes syndrome liver-histology

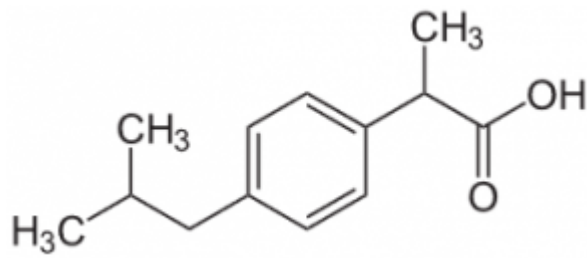
Another special side effect of ASA is **Reye’s syndrome**, which can appear as a result of an infection (chickenpox, influenza) in children under 16. This results in **encephalopathy** and **fatty liver cell degeneration**. This is symptomatically expressed by vomiting, unconsciousness, cerebral edema and spasms as well as increased ammonia levels, increased transaminases and coagulation disorders as a sign of **liver insufficiency**. With a **lethality rate** of 25 to 50%, ASA should thus only be used conservatively in children.



Skeletal formula of salicylic acid

Separating **acetyl** from ASA results in **salicylic acid**, which is expelled **renally**. As this has an **acidic pH value**, expulsion can be accelerated via **alkalisation** of the urine (e.g., by administering bicarbonate). For instance, this is required in the event of intoxication with ASA.

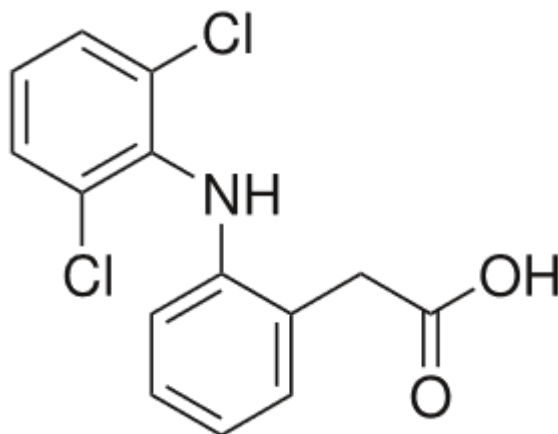
Ibuprofen



Ibuprofen

Another example of an NSAR is **ibuprofen**, which functions as a **reversible inhibitor** of cyclooxygenases. Just like ASA it is **analgesic**, **antipyretic** and **antiphlogistic** in higher doses (single dose: max. 800 mg, maximum daily dosage 2400 mg). Unlike the other acid analgesics, its gastrointestinal side effects are rather minor, which makes it more gastrally tolerable. Another advantage is that it **does not accumulate** after multiple ingestions, making an overdose unlikely. Simultaneous ingestion of ASA and ibuprofen lowers the inhibiting effect of ASA on **thrombocyte aggregation** as the substances compete for the catalytic center of the COX-1.

Diclofenac

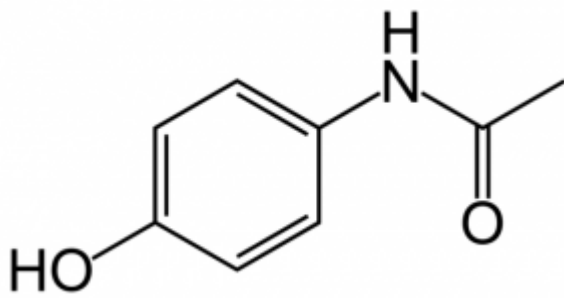


Diclofenac

The NSAR **diclofenac** alleviates pain more effectively than ASA or ibuprofen. The side effects correspond to the characteristically undesired effects of the non-selective COX inhibitors, with **gastrointestinal discomfort** being the most significant.

Paracetamol

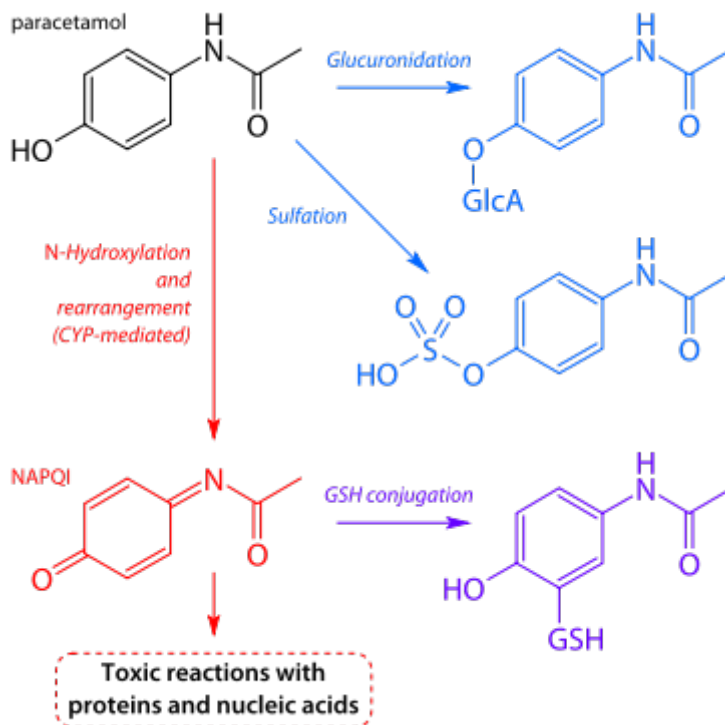
Paracetamol is the most frequently used **analgesic** and **antipyretic**. Because of its low side effect profile (only very few gastrointestinal side effects), it is the **medication of choice** for pain and fever in **children** and is also permitted for use by **pregnant women**. Unlike the acid analgesics, it is **not antiphlogistic** and can be administered as juice, tablets, suppositories or an injection.



Paracetamol is mainly metabolized in the **liver** by **glucuronidation** and **sulfation**. **Reactive intermediate products**, among others, form upon breakdown of the medication, and these are inactivated by **linkage** to **glutathione**. In the event of an **overdose** of paracetamol (> 7.5 g per day), the

glutathione reserves are exhausted, the **reactive metabolites** are no longer inactivated and bind with liver cell proteins. This results in **liver cell necrosis** with risk of **liver failure**. The sulfhydryl group donor **N-acetylcysteine** is a life-saving **antidote**.

Note: Paracetamol is hepatotoxic in excess doses!

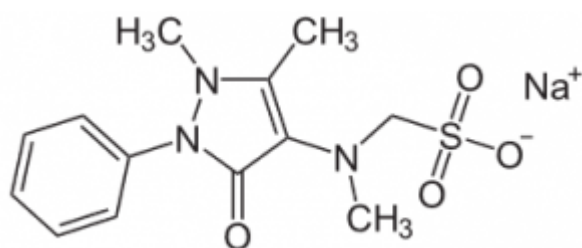


Paracetamol metabolism

Due to the **potential liver toxicity**, paracetamol should not be administered to patients with severe **liver dysfunction**, **glucose-6-phosphate-dehydrogenase deficiency** (decreased glutathione reserves!) and **alcoholism**.

An overdose of paracetamol may also have a toxic effect on the kidneys.

Metamizole



Metamizole

The **pyrazolone derivative metamizole** is also known as **novaminsulfon** and is the most effective non-opioid analgesic. In addition to its **analgesic** and **antipyretic** potency, it is the only **spasmolytic (anticonvulsive)** non-opioid analgesic and is thus administered to counter very severe pain, tumorous pain, colics and high fever.

It may be administered **orally, rectally** or **intravenously**, but too rapid an IV injection may result in a **shock reaction** with a possibly **lethal** result.

CAVE: Always slowly inject metamizole intravenously (< 1 ml/min)!

Gastrointestinal side effects rarely arise after ingestion of metamizole. However, various **oversensitivity reactions** such as **leukopenia, exanthema** and minor to severe **anaphylactic** reactions (see above) do occur.

Agranulocytosis, in which antibodies are formed to target **granulocytes**, is the most severe side effect. This results in cytotoxic immune reactions with high fever, sore throat, difficulties swallowing, **mucosal ulcers** in the mouth, pharynx and less commonly in the genitals and anal region and, ultimately, a systemic reaction with **sepsis** and possible death. Should there be suspicion of agranulocytosis, administration of metamizole must immediately be discontinued. This is followed by administration of **antibiotics** and perhaps also **transfusion** of granulocytes. In order to prevent agranulocytosis, or to treat it in time, **regular blood samples** are required during long-term treatment with metamizole.

Note: An important side effect of metamizole is agranulocytosis.

It is primarily metabolized in the liver and expelled through the kidneys.

Contraindications for the administration of metamizole include **acute hepatic porphyria** and hereditary **glucose-6-phosphate dehydrogenase deficiency**.

Note: Due to the life-threatening side effects of metamizole, a very strong indication has to be present!

List of the Most Common Non-Selective COX Inhibitors

Agent	Dosage (p.o.)	Duration of effect & administration	Effect	Side effect	Contraindication
ASA (acidic)	0.5 to 1 g; max. daily dose: 6 g	6 to 8 h, half life 15 min.; oral, IV.	Analgesic, antipyretic, antiphlogistic, thrombocyte aggregation inhibition	Analgesic asthma, Samter's triad, elevated risk of bleeding, Reye's syndrome, gastrointestinal complaints	Pregnancy (esp. 3rd trimester), duodenal ulcers, hemorrhagic diathesis, renal insufficiency
Ibuprofen (acidic)	Analgesic: 200 to 400 mg; max. daily dose: 1200 mg	Up to. 6 h, half life 2 h; oral, rectal, IV, topical, dermal	Analgesic, antipyretic, antiphlogistic	Headaches, vertigo, tinnitus, gastrointestinal complaints (although more tolerable than other NSAR or ASA)	See ASA

Diclofenac (acidic)	25 to 150 mg	Up to 6 h, half life 1 to 2 h; oral, rectal, IV, transdermal, as gel and as eye drops	Analgesic, antipyretic, antiphlogistic	Gastrointestinal complaints	See ASA
Paracetamol (non-acidic)	Adults: 0.5 to 1.0 g, children: 10 to 15 mg/kg KG; max. daily dose: 4 to 6 g	6 to 8 h, half life 2 h; oral, rectal, IV	Analgesic, antipyretic	Minor, can thus be used in children and pregnant women, CAVE: overdose leads to liver toxicity	Severe impairment of liver function, glucose-6-phosphate dehydrogenase deficiency
Metamizole (non-acidic)	0.5 to 1 g; max. daily dose: 4 g	6 to 8 h; oral, rectal, IV	Analgesic, antipyretic, spasmolytic	Leukopenia, agranulocytosis, exanthema, anaphylaxis, shock, hypotension	Hepatic porphyria, glucose-6-phosphate dehydrogenase deficiency

Selective COX-2 Inhibitors

Selective COX-2 inhibitors, also known as **coxibs**, selectively inhibit COX-2 as the name implies. The gastroprotective prostaglandin-producing COX-1 is not inhibited, which leads to a reduced **side effect profile** with only rare incidence of **gastrointestinal** complaints.

Celecoxib (p.o.) and **Etoricoxib** (p.o.) are available as substances for treating **arthrosis** and **rheumatoid arthritis** and **parecoxib** (IV, i.m.) for treating **post-operative** pain. However, the coxibs are not without side effects: Long-term use thereof may lead to **thrombotic cardiovascular events (heart attack or stroke)**. For that reason, the objective should be a low dosage and a brief treatment period.

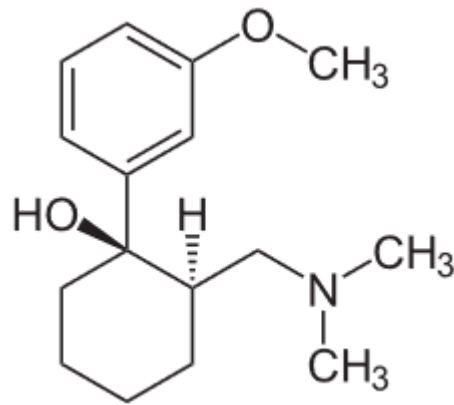
Note: The cardiovascular risk of coxibs increases with dosage and duration! Selective COX-2 inhibitors should not be administered to patients with oversensitivity toward coxibs or sulfonamides, inflammatory intestinal diseases, CHD, PAD, stroke, cardiac insufficiency, gastroduodenal ulcers or severe liver and kidney dysfunction.

Low-Potency Opioid Analgesics

Opioids are discussed in more detail in the article "[Anaesthesia](#)"; yet a brief overview of the low-potency opioids is provided below.

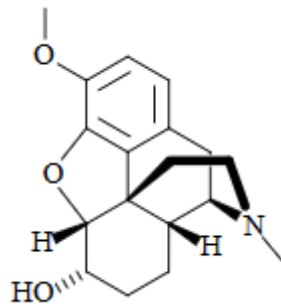
The **low-potency opioids tilidine, dihydrocodeine, codeine** and **tramadol** are designed to alleviate moderately severe to severe pain. Compared to the reference substance **morphine**, they are less effective, meaning that they have a lower **analgesic** (relative) **potency** (RP < 1).

If the dosage of **low-potency opioids** is raised to a certain point, the same level of pain relief as **morphine** can be achieved. This is referred to as **maximum achievable analgesia**. Each additional **dosage increase** would then only lead to amplification of the side effects, while the analgesic effect can no longer be enhanced. This is not the case with high-potency opioids.



Tramadol

Tramadol has **0.1 to 0.2 times the analgesic potency** of morphine. Its major side effects are nausea and vomiting, while constipation and hypoventilation occur only rarely. It has a **duration of action** of four to six hours and can be applied **orally, intravenously, intramuscularly** or **rectally**.



Dihydrocodeine

Dihydrocodeine and **codeine** have a relative potency of **0.3** and are administered as **antitussives** due to their cough-relieving effect. They are active for approximately eight to twelve hours and are administered **orally**.

Tilidine has an analgesic potency of **0.2** and a duration of action of approximately three hours. Hepatic conversion yields the active metabolite **nortilidine**. **Tilidine** is available in combination with the **opioid-antagonist naloxone**. If a normal dosage of this compound is ingested orally, the naloxone portion is inactivated by the **first-pass effect**, so that nortilidine can exercise its effect. However, if it is improperly injected intravenously, naloxone will exercise its effect: As an **antagonist** to the opioids' receptor, it prevents an **addictive** effect and the feared **hypoventilation**.

Coanalgesics

Medications that usually have a different indication, but actually can alleviate pain in combination with analgesics or even on their own, are administered as **coanalgesics** for **adjuvant pain therapy**. These include the following substances, among others:

- **Antidepressants:** increase in the **serotonin** and **noradrenaline concentration** in the synaptic cleft of the **descending antinociceptive neuronal system**; best analgesic effect with **tricyclic** antidepressants (**amitriptyline, imipramine, clomipramine, doxepin**); application: **chronic** and **neuropathic** pain, lower dosage than necessary for

the antidepressant effect; other substances: **bupropion, venlafaxine, duloxetine.**

- **Anticonvulsants:** blockage of **sodium channels** (**carbamazepine, lamotrigine, topiramate**) and **calcium channels** (**gabapentin, pregabalin**) in the CNS; application: **neuropathic pain** (e.g., **trigeminal neuralgia**).
- **Glucocorticoids:** antiphlogistic, antipyretic and anti-edematous; application: **neuropathic** and **nociceptor pain** (e.g., pain due to **metastases**).
- **Bisphosphonates:** application: treating **osteoporosis** and for osteolytic bone metastases.

Non-Steroid Anti-Inflammatories (NSAIDs)

- ASA and others of same class
- Ibuprofen is a relatively low potency, short acting example of the family
- Inhibit the action of cyclooxygenase enzymes (COX-1 and COX-2) and reduce the production of prostaglandins which are present in inflamed tissues
- Analgesia by reducing prostaglandin synthesis
- Reduce the recruitment of leukocytes which produce inflammatory mediators
- Directly inhibit the release of prostaglandins in the dorsal horn
- Side effects: gastric hemorrhage, platelet dysfunction, renal toxicity

Specific drugs

- ASA — relatively short acting, little negative effect upon kidney
- Acetaminophen — reduces central prostaglandin synthesis — no real anti-inflammatory effect — no renal effects — overdose can cause acute liver failure

Ibuprofen — relatively short acting

- Naproxen, ketorolac (systemic), diclofenac, and others — relatively long acting — all have negative renal and gastric effects — likely also have cardiac effects
- COX-2 inhibitors were introduced with the expectation of fewer side effects (particularly gastric) but caused increased incidence of ischemic cardiac events (myocardial infarctions and death) and were withdrawn from the market

Review Questions

Correct answers can be found below the references.

1. The WHO pain relief ladder...

- ...was developed to treat acute pain.
- ...consists of five different levels that determine the dosage increase of analgesics.
- ...recommends a combination of opioids from levels two and three.
- ...stipulates fixed intervals for high-potency opioids.
- ...categorically excludes coanalgesics as additional medication.

2. Which of the following statements about non-opioid analgesics is true?

- Paracetamol works as a selective COX-2 inhibitor.

- B. Paracetamol and metamizole are antipyretic, analgesic and antiphlogistic.
- C. Metamizole is the first medication of choice for lowering fever and relieving pain in children.
- D. One side effect of parecoxib is Reye's syndrome.
- E. Coxibs can lead to thrombotic cardiovascular events.

3. Which substance does not alleviate pain?

- A. Amitriptyline
- B. Flucloxacillin
- C. Tilidine
- D. Pentagabin
- E. Dihydrocodeine

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Correct answers: 1D, 2E, 3B

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Notes