As pain, be it acute or chronic, can severely restrict the 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.

WHO Pain Relief Ladder

In 1986, the World Health Organization (WHO) proposed a plan for the treatment of chronic pain. It is based on the administration of oral analgesics (painkillers) according to their potency: First, weaker analgesics are used, and in the absence of the desired effect stronger analgesics are recommended. Coanalgesics (see below) can be administered at each level of pain. Initially only used to treat pain arising from tumors, they are now
utilized in the treatment of other forms of chronic pain as well.

Level 1: Non-Opioid Analgesics

Non-opioid analgesics used to treat the 1st WHO level of pain include paracetamol (4–6 x 500–1000 mg per day), naproxen (2 x 500 mg per day), diclofenac (2 x 50–150 mg per day), and ibuprofen (2-3 x 800 mg per day). However, paracetamol is only slightly effective against bone, soft tissue and tumor pain as it is not an anti-inflammatory medication. Patients with a high risk of gastrointestinal complications are recommended proton pump inhibitors (e.g., omeprazole).

The effects and side effects of non-opioid analgesics are further discussed below.

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

Low-potency opioids along with non-opioid analgesics are recommended for patients with 2nd-degree pain, based on the WHO Pain Relief Ladder. These drugs include dihydrocodeine (2-3 x 60–180 mg per day), tramadol (2-3 x 100–300 mg), and tilidine (2-3 x 100–200 mg per day).

The low-potency opioids will be discussed in detail later. In case of very severe chronic pain, or pain refractory to low-potency opioids, you should switch to pain level 3, but never combine the opioids of levels 2 and 3, which attenuates the pharmacological effect.

N.B. Level 2 and level 3 opioids must not be combined with each other!

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

A combination of non-opioid analgesics and high-potency opioids is recommended for the management of WHO level 3 pain. These include morphine (6 x 5-500 mg p.o. per day), hydromorphone (2-3 x 4–200 mg p.o. per day), buprenorphine (3-4 x 0.2–1.2 mg s.l. per day), fentanyl (0.6–12 mg transdermally), and oxycodone (2-3 x 10–400 mg p.o. per day). Retarded morphine is the medication of choice, whereas non-retarded morphine is primarily indicated 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 incremental doses that should not be decreased; otherwise, the patient runs the risk of opioid accumulation. In the alternative, the dosage should be increased upon experiencing pain during the treatment period.

N.B. 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 ‘Anesthesia’.

<table>
<thead>
<tr>
<th>WHO Levels of Pain</th>
<th>Level 1</th>
<th>Level 2</th>
<th>Level 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-opioid analgesics</td>
<td>Low-potency opioids + non-opioid analgesics</td>
<td>High-potency opioids + non-opioid analgesics</td>
<td></td>
</tr>
</tbody>
</table>
Non-Opioid Analgesics

Non-opioid analgesics are pain medications that inhibit pain without interacting with opioid receptors.

Antipyretic Analgesics as Inhibitors of Cyclooxygenases

Antipyretic analgesics lower fever and alleviate pain by inhibiting cyclooxygenases. Cyclooxygenases are key enzymes catalyzing the synthesis of arachidonic acid derivatives (eicosanoids) such as prostaglandin G2 and prostaglandin H2, which ultimately result in the formation of other prostaglandins, prostacyclins, and thromboxanes in the presence of other enzymes. Along with physiological reactions, these also mediate pathophysiological events, such as fever, inflammation, and pain.

The cyclooxygenases exist 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. COX-1 is thus responsible for many physiological processes.

COX-2, however, is only constitutively present in a few cells (kidney, brain, and vessels).
and is thus primarily an **inducible** enzyme. Its expression is greatly increased in **inflammation, trauma** or **ischemia**, which trigger **pathological** events, such as fever, inflammation, and pain.

The isoenzymes of cyclooxygenases can be inhibited via **selective** and **non-selective** inhibition.

### Non-selective COX Inhibitors

The **non-selective COX** inhibitors include **antipyretic** analgesics with anti-inflammatory effects (acid analgesics, NSAR = non-steroidal antirheumatics) and those without anti-inflammatory effect (**non-acid analgesics**).

Acid analgesics are thus more anti-inflammatory than the non-acid analgesics. They easily penetrate the inflamed tissue resulting in effective pain relief. 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 medications are competitive inhibitors.

#### Side effects of non-selective COX inhibitors

The cyclooxygenases exist in multiple cells of the body, and therefore, exhibit a wide range of side effects:

- **Gastrointestinal tract**: The most common side effects include dyspepsia and gastroduodenal ulcers due to decreased prostaglandin synthesis and increased leukotriene synthesis as well as accumulation of acid analgesics in the gastric mucosa. Proton pump inhibitors are indicated for the prevention of side effects.

  ![Image: Gastric ulcer antrum. By Med_Chaos, License: Public domain](image)

- **Kidney**: Sodium retention leading to increased cardiac preload and edema of the legs, decreased diuresis, and hyperkalemia resulting in cardiac arrhythmias, warrants cardiopulmonary risk evaluation in adult patients undergoing abdominal or visceral surgery (CAVE), especially in patients at an
advanced age, with diabetes mellitus or limited kidney function.

- **CNS**: CNS side effects include headaches, vertigo, hearing and vision impairment.
- **Respiratory tract**: Respiratory side effects include bronchoconstriction (due to decreased prostaglandin synthesis and increased leukotriene synthesis), analgesic asthma, ‘aspirin’ or ‘Samter’s triad’: nasal polyp + intrinsic asthma + sinusitis.
- **Pregnancy**: Pregnancy-related side effects include contraction inhibition with subsequent bradytoca, premature closing of the ductus Botalli.
- **Blood coagulation**: Coagulatory defects include inhibition of thrombocyte aggregation.
- **Hypersensitivity reactions**: COX treatment may trigger anaphylactic shock, pseudo allergic reactions, and skin reactions.

**Acetylsalicylic acid (ASA)**

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

- From < 30 mg/d: thrombocyte aggregation inhibition
- Up to 2-3 g/d: analgesic and antipyretic
- 2-4 g/d: anti-inflammatory

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

Thrombocyte aggregation is inhibited when the COX-1 is inhibited at least 95%. ASA is the only analgesic that irreversibly inhibits the cyclooxygenases via acetylation. As thrombocytes have no nucleus and thus cannot synthesize new COX-1, the inhibition of thrombocyte aggregation lasts for 8-10 days (corresponding to platelet lifespan) and can be used in the prophylaxis of thromboses and embolisms, treatment of CHD, PAD and cerebrovascular diseases as well as secondary prophylaxis of heart attack or stroke.

ASA must be discontinued at least 7 days before surgery to reduce the risk of
intraoperative bleeding.

The side effects of ASA resemble the general side effects of non-selective COX inhibitors and include gastrointestinal symptoms predominantly.

‘Aspirin triad’ (also known as Samter’s triad) may manifest in response to ASA (but also other NSAR), defined by nasal polyps (polyposis nasi), asthma and sinusitis. Bronchoconstriction due to an imbalance between bronchodilatory prostaglandins and bronchoconstriction leukotrienes results in so-called analgesic asthma. The risk of bleeding is increased following treatment with ASA due to thrombocyte aggregation inhibition.

N.B. Samter’s triad and analgesic asthma are side effects of ASA.

Reye’s syndrome is another side effect associated with ASA treatment, which can occur as a result of infection (chickenpox or influenza) in children under 16. It results in encephalopathy and fatty liver cell degeneration. The clinical manifestations include vomiting, unconsciousness, cerebral edema, and spasm as well as increased levels of ammonia, transaminases, and coagulation disorders as a sign of liver insufficiency. ASA treatment is associated with a lethality rate of 25-50%, and therefore, should only be used conservatively in children.

Separating acetyl from ASA results in salicylic acid, which is expelled renally. Salicylic acid has an acidic pH, and thus its elimination can be accelerated via alkalization of the urine (e.g., by administering bicarbonate), especially in the event of intoxication with
ASA.

Ibuprofen

Another example of an NSAR is **ibuprofen**, which acts as a **reversible inhibitor** of cyclooxygenases. Similar to ASA, it is **analgesic**, **antipyretic** and **anti-inflammatory** when administered 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 increases its gastric tolerance. Further, it **does not accumulate** after multiple doses, making an overdose unlikely. Simultaneous ingestion of ASA and ibuprofen lowers the inhibition of ASA on **thrombocyte aggregation** as the substances compete for the catalytic center of the COX-1.

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 (very few gastrointestinal side effects), it is the **medication of choice** for pain and fever in **children** and **pregnant women**. Unlike acid analgesics, it is **not** **anti-inflammatory** and can be administered as juice, tablets, suppositories or an injection.
Paracetamol is mainly metabolized in the **liver** via **glucuronidation** and **sulfation**. It breaks down into **reactive intermediates**, which are inactivated by **linkage** to **glutathione**. In the event of an **overdose** of paracetamol (> 7.5 g per day), the glutathione reserves are exhausted, and the **reactive metabolites** are no longer inactivated or bind with liver cell proteins, resulting in **liver cell necrosis** with the risk of **liver failure**. The sulfhydryl group donor **N-acetylcysteine** is a life-saving **antidote**.

**N.B.** Paracetamol is hepatotoxic when administered in excess doses!

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, also known as Novaminsulfon, 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 manage very severe pain, tumor pain, colic, and high fever.

It may be administered orally, rectally or intravenously. However, rapid IV injection may trigger shock with a lethal outcome.

Always inject intravenous metamizole slowly (< 1 mL/min)!

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

Agranulocytosis, in which antibodies are formed to target granulocytes, is the most severe side effect. It results in cytotoxic immune reactions with high fever, sore throat, difficulties swallowing, mucosal ulcers in the mouth, pharynx, and less commonly the genitals and anal region, and ultimately resulting in a systemic reaction with sepsis and possible death. When agranulocytosis is suspected, treatment with metamizole must be discontinued immediately and followed by the administration of antibiotics and further transfusion of granulocytes. Prevention or prompt treatment of agranulocytosis requires regular blood samples during long-term treatment with metamizole.

N.B. An important side effect of metamizole is agranulocytosis.

Metamizole 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.

N.B. Due to the life-threatening side effects of metamizole, it is not recommended except for very strong indications!

List of the Most Common Non-Selective COX Inhibitors

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosage (p.o.)</th>
<th>Duration of effect &amp; administration</th>
<th>Effect</th>
<th>Side effect</th>
<th>Contraindication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA (acidic)</td>
<td>0.5-1 g; max. daily dose: 6 g</td>
<td>6-8 h, half-life 15 min.; oral, IV.</td>
<td>Analgesic, antipyretic, anti-inflammatory, thrombocyte aggregation inhibition</td>
<td>Analgesic asthma, Samter’s triad, elevated risk of bleeding, Reye’s syndrome, gastrointestinal complaints</td>
<td>Pregnancy (esp. 3rd trimester), duodenal ulcers, hemorrhagic diathesis, renal insufficiency</td>
</tr>
<tr>
<td>Ibuprofen (acidic)</td>
<td>Analgesic: 200–400 mg; max. daily dose: 1200 mg</td>
<td>Up to 6 h, half-life 2 h; oral, rectal, IV, topical, dermal</td>
<td>Analgesic, antipyretic, antiinflammatory</td>
<td>Headaches, vertigo, tinnitus, gastrointestinal complaints (although more tolerable than other NSAR or ASA)</td>
<td>See ASA</td>
</tr>
<tr>
<td>Diclofenac (acidic)</td>
<td>25-150 mg</td>
<td>Up to 6 h, half-life 1-2 h; oral, rectal, IV, transdermal, as gel and as eye drops</td>
<td>Analgesic, antipyretic, anti-inflammatory</td>
<td>Gastrointestinal complaints</td>
<td>See ASA</td>
</tr>
</tbody>
</table>
Paracetamol
(non-acidic)

| Adults: 0.5–1.0 g; children: 10–15 mg/kg KG; max. daily dose: 4–6 g | 6–8 h, half-life 2 h; oral, rectal, IV | Analgesic, antipyretic | Minor, can thus be used in children and pregnant women. However, overdose leads to liver toxicity | Severe impairment of liver function, glucose-6-phosphate dehydrogenase deficiency |

Metamizole
(non-acidic)

| 0.5–1 g; max. daily dose: 4 g | 6–8 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. They do not inhibit the gastroprotective prostaglandin-producing COX-1, which leads to a reduced side effect profile with a rare incidence of gastrointestinal complaints.

Celecoxib (p.o.) and Etoricoxib (p.o.) are used to treat arthrosis and rheumatoid arthritis and parecoxib (IV, i.m.) for treatment of post-operative pain. However, long-term use may lead to thrombotic cardiovascular events (heart attack or stroke). Therefore, low dosage and a brief treatment period are recommended.

**N.B.** The cardiovascular risk of coxibs increases with dosage and duration!

Selective COX-2 inhibitors should not be administered to patients with hypersensitivity to 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 ‘Anesthesia’. However, 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 and have a lower analgesic (relative) potency (RP < 1).

Increasing the dosage of low-potency opioids provides a similar level of pain relief as morphine. This phenomenon is referred to as maximum achievable analgesia. Unlike high-potency opioids, each additional dosage increase of low-potency opioids only amplifies the side effects, without enhancing the analgesic effect.
The analgesic potency of tramadol is 0.1–0.2-fold higher than the analgesic potency of morphine. Its major side effects are nausea and vomiting, while constipation and hypoventilation are rare. Its duration of action is 4–6 hours and can be administered orally, intravenously, intramuscularly or rectally.

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 approx. 8–12 hours and are administered orally.

Tilidine has an analgesic potency of 0.2 with a duration of action of nearly 3 hours. Hepatic conversion yields the active metabolite nortilidine. Tilidine is available in combination with the opioid-antagonist naloxone. Oral ingestion of normal dosage of this compound inactivates the naloxone portion via the first-pass effect, to allow the effect of nortilidine. However, when tilidine is improperly injected intravenously, naloxone acts as an antagonist against the opioid receptor and prevents addictive effects and hypoventilation.

Coanalgesics

Medications that usually have a different indication, but actually alleviate pain in combination with analgesics or even act independently, are administered as coanalgesics for adjuvant pain therapy. The list of coanalgesics includes:

- Antidepressants: Antidepressants increase the serotonin and noradrenaline concentration in the synaptic cleft of the descending antinociceptive neuronal system. The optimal analgesic effect is obtained with tricyclic antidepressants (amitriptyline, imipramine, clomipramine,
doxepin). Applications include chronic and neuropathic pain, with a lower dosage than an antidepressant effect. Other substances include bupropion, venlafaxine, and duloxetine.

- **Anticonvulsants:** Anticonvulsants block sodium channels (carbamazepine, lamotrigine, topiramate) and calcium channels (gabapentin, pregabaline) in the CNS. They are used to manage neuropathic pain (e.g., trigeminal neuralgia).
- **Glucocorticoids:** Glucocorticoids are indicated for antiphlogistic, antipyretic and anti-edematous conditions to manage neuropathic and nociceptor pain (e.g., pain due to metastases).
- **Bisphosphonates:** Bisphosphonates are used to treat osteoporosis and osteolytic bone metastases.

### Non-Steroid Anti-Inflammatory Drugs (NSAIDs)

- ASA and other drugs of the same class
- Ibuprofen, a relatively low-potent, short-acting NSAID
- Inhibit the action of COX-1 and COX-2, and reduce the production of prostaglandins in inflamed tissues
- Analgesia via reduced prostaglandin synthesis
- Decrease synthesis of inflammatory mediators by leukocytes
- Directly inhibit the release of prostaglandins in the dorsal horn
- Side effects: gastric hemorrhage, platelet dysfunction, and renal toxicity

#### Specific drugs

- ASA—relatively short-acting, with a little negative effect upon the 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—with negative renal and gastric effects as well as possible cardiac effects
- COX-2 inhibitors: fewer gastric side effects but increased incidence of ischemic cardiac events (myocardial infarctions and death), and therefore, withdrawn from the market

### References


