Drugs in pain therapy

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Types of drugs

1. **Nonsteroidal anti-inflammatory drugs (NSAIDs)**
   - These drugs reduce inflammation and relieve pain.
   - Examples include aspirin, ibuprofen, and naproxen.
2. **Acetaminophen**
   - This is a pain reliever that is often used for mild to moderate pain.
   - It is not an anti-inflammatory medication, and works by blocking pain signals in the brain.
3. **Opioids**
   - These are powerful painkillers that are often used for severe pain.
   - They work by binding to opioid receptors in the brain and spinal cord, reducing the perception of pain.
   - Examples include morphine, oxycodone, and hydrocodone.

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Types of drugs

1. **Antidepressants**
   - Certain antidepressant medications, such as tricyclic antidepressants, can be effective in treating chronic pain.
2. **Anticonvulsants**
   - Certain medications used to treat seizures, such as gabapentin and pregabalin, can also be effective in treating chronic pain.

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Nonsteroidal anti-inflammatory drugs (NSAIDs)

- Mechanisms of Action: NSAIDs work by blocking the action of an enzyme called **cyclooxygenase (COX)**, which is responsible for the **production of prostaglandins**.
- **Prostaglandins** are messengers that are involved in inflammation, pain, and fever.

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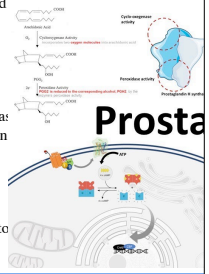
Nonsteroidal anti-inflammatory drugs (NSAIDs)

What's the role of prostaglandins?

- Prostaglandins promote vasodilation (widening of blood vessels) and increase vascular permeability (allowing fluid to leak out of blood vessels) during an inflammatory response.
- They also attract immune cells to the site of inflammation.
- Damaged tissues release inflammatory mediators such as histamine and cytokines, which stimulate the production of prostaglandins.
- They promote the production of more inflammatory mediators, creating a positive feedback loop that amplifies the inflammatory response.
- Excessive production of prostaglandins can contribute to inflammation-related diseases such as arthritis and cardiovascular disease.



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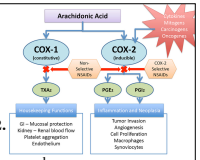
Nonsteroidal anti-inflammatory drugs (NSAIDs)

What's the role of COX?



- Two cyclooxygenase (COX) enzymes: **COX-1 and COX-2.**
- **COX-1** is expressed in many tissues and involved in processes such as maintaining gastric mucosal integrity and regulating blood flow to the kidneys.
- **COX-2** is **induced during an inflammatory response** and is **responsible for the production of prostaglandins** involved in pain and inflammation.
- **COX-1 and COX-2 convert arachidonic acid**, a type of fatty acid, **into prostaglandins.**
- **NSAIDs inhibit the activity of both COX-1 and COX-2, which reduces the production of prostaglandins** and their related symptoms of pain and inflammation.
- Inhibition of COX-1 can also lead to unwanted side effects such as gastrointestinal bleeding and impaired kidney function.

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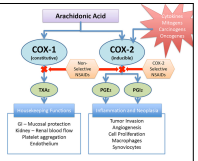
Nonsteroidal anti-inflammatory drugs (NSAIDs)



NSAIDs work by inhibiting the activity of COX enzymes. By inhibiting COX enzymes, NSAIDs reduce the production of prostaglandins

- Varying degrees of selectivity for COX-1 and COX-2.
- Aspirin is a non-selective COX inhibitor, while drugs like celecoxib are more selective for COX-2.
- Inhibition of COX-1 can lead to unwanted side effects such as gastrointestinal bleeding and impaired kidney function, while inhibition of COX-2 may have a protective effect against cancer and cardiovascular disease.
- NSAIDs can also have other effects on the body, such as reducing platelet aggregation (clumping), which can increase the risk of bleeding.
- The effects of COX inhibition on prostaglandin synthesis can vary depending on the dose and duration of NSAID use. Short-term use of NSAIDs may have analgesic (pain-relieving) and anti-inflammatory effects, while long-term use can lead to adverse effects such as gastrointestinal bleeding, kidney damage, and cardiovascular events.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Overview of the therapeutic uses of NSAIDs

- Widely used for their analgesic (pain-relieving), anti-inflammatory, and antipyretic (fever-reducing) effects.
- Commonly used to treat conditions such as osteoarthritis, rheumatoid arthritis, and other forms of inflammatory arthritis by reducing pain, swelling, and stiffness.
- NSAIDs can also be used to **treat mild to moderate pain**, such as headaches, menstrual cramps, and dental pain, and are often used in combination with other pain-relieving medications, such as opioids or acetaminophen.
- NSAIDs are available in various forms, including tablets, capsules, creams, gels, and suppositories, and can be obtained over-the-counter or by prescription depending on the strength and dosage.
- Some NSAIDs, such as aspirin, can also be used as **antiplatelet agents** to reduce the risk of blood clots and stroke.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Side effects

- A range of side effects, some of which can be serious.
- **Gastrointestinal problems** (stomach ulcers, bleeding, and perforation)
  - COX-1 producing prostaglandins that protect the stomach lining. Inhibiting COX-1 can reduce the production of protective prostaglandins and increase the bleeding risk.
- **Kidney damage**, particularly if pre-existing renal failure.
  - Prostaglandins play a role in maintaining normal kidney function, and inhibiting COX enzymes can interfere with this process.
- **Cardiovascular events**:
  - Studies suggested long-term high doses use of NSAIDs may increase the risk of heart attack or stroke.
- **Allergic reactions**:
  - Allergic reaction to NSAIDs, ranging from mild symptoms to difficulty breathing or anaphylaxis.
- **Liver damage**: In rare cases, NSAIDs can cause liver damage or liver failure.

Acetaminophen

Side effects

- Acetaminophen, also known as paracetamol, is a commonly used pain reliever and fever reducer.
- It is available **over-the-counter** and in prescription-strength formulations.
- It is used to treat **mild to moderate pain**, such as headaches, toothaches, and menstrual cramps.



Acetaminophen

Mechanism of Action

- Acetaminophen works by inhibiting the production of prostaglandins, which are chemicals in the body that contribute to pain and inflammation.
- Acetaminophen **primarily inhibits COX-2**, which is the form of the enzyme that is most involved in producing prostaglandins that contribute to pain and inflammation.
- Unlike NSAIDs, acetaminophen **does not significantly affect the production of prostaglandins in other parts of the body(** such as maintaining the integrity of the gastrointestinal tract)
- Acetaminophen is also thought to affect other pathways in the body that are involved in **pain perception** and temperature regulation.



Acetaminophen

Mechanism of pain perception

- Acetaminophen activates the **endocannabinoid system**
- By increasing levels of the **endocannabinoid anandamide** which binds to cannabinoid receptors (in the brain) involved in pain regulation.
- Acetaminophen may affect production of **serotonin and norepinephrine**, which are involved in pain **transmission and modulation**.
    - Increase levels of serotonin in the brain, which can have analgesic effects.
    - Decrease levels of norepinephrine, which can reduce the sensation of pain.
- It's important to note that while acetaminophen can provide effective pain relief, it is not as effective at reducing inflammation as NSAIDs.



Acetaminophen

Indications and Dosage

- Acetaminophen is indicated for the treatment of mild to moderate pain and fever.
- The recommended adult dose is 325-1000 mg every 4-6 hours, not to exceed 4000 mg per day.
- The recommended pediatric dose depends on the child's weight (18 mg/kg)



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Acetaminophen

Side effects

- Acetaminophen can lead to liver failure when taken in excessive amounts, either in a single dose or over an extended period of time.
- Liver metabolize acetaminophen, however, when too much is taken can build up in the liver cells.
- It produces a toxic byproduct **N-acetyl-p-benzoquinone imine (NAPQI)**.
- In normal doses process NAPQI quickly and safely, but in cases of acetaminophen overdose, NAPQI can accumulate and cause severe liver damage.
- NAPQI can bind to proteins in the liver cells, causing oxidative stress and cellular damage.



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Opioids

- Class of drugs that are used for the treatment of pain and are among the most powerful analgesics available.
- Opioids act by binding to specific receptors in the central and peripheral nervous systems, including the **μ**, **δ**, and k opioid receptors, to block the transmission of pain signals.
- Opioids can be derived from natural sources, such as the opium poppy, or synthesized in a laboratory, resulting in different chemical structures, pharmacokinetic properties, and potencies.
- Opioids can be classified as **agonists, partial agonists, or antagonists**, depending on their ability to activate or block opioid receptors.



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Type of Opioids

- Classified based on their chemical structure, potency, and pharmacokinetic properties.
- **Natural opiates** derived from **opium poppies** (morphine and codeine). High affinity for μ receptor
- **Semi-synthetic opioids** are chemically modified, include drugs such as **oxycodone and hydrocodone. Higher potency** than natural opiates and are commonly prescribed for **moderate to severe pain.**
- **Synthetic opioids** are **entirely man-made** (fentanyl and methadone). They have a **higher potency than natural or semi-synthetic opioids** and are used for **severe pain** management or in opioid substitution therapy for addiction treatment.
- Administered via various routes (oral, transdermal, intravenous, intramuscular, or subcutaneous) The choice of route and formulation depends on factors such as the type and severity of pain, the patient's medical condition, and the desired duration of action.

Opioids listed by potency

- **Fentanyl**: is a potent synthetic opioid that is 50-100 times stronger than morphine. It is often used for severe chronic pain and cancer pain.
- **Hydromorphone**: is a semi-synthetic opioid that is 5-7 times more potent than morphine. It is commonly used for moderate to severe chronic pain.
- **Methadone**: is a synthetic opioid that is often used for chronic pain management and opioid addiction treatment. It has a long duration of action and may be less likely to cause respiratory depression compared to other opioids.
- **Oxycodone**: is a semi-synthetic opioid that is 1.5-2 times more potent than morphine. It is commonly used for moderate to severe chronic pain.
- **Morphine**: is a natural opioid that is often used for chronic pain, particularly in cancer patients. It is less potent than some of the other opioids on this list but is still effective for managing moderate to severe pain.

Uses of opioids

- Manage **acute and chronic pain**, including postoperative pain, cancer pain, and pain associated with injuries or medical conditions.
- Opioids are also used in **palliative care** and **end-of-life care** to alleviate suffering and improve quality of life.
- Opioids can produce a range of effects beyond pain relief, including cough suppression, sedation, and mood elevation. This is due to the activation of opioid receptors in different areas of the brain and spinal cord.
- Other medical conditions (severe diarrhea or cough, where their ability to slow down gut motility or suppress cough reflex can be beneficial)
- Potential for abuse, dependence, and addiction due to their pleasurable effects and reinforcing properties.

Addiction and abuse

- High potential because of the way they affect the brain's reward system.
- Opioids **bind receptors** —> activate the release of **dopamine (**neurotransmitter associated with **pleasure, reward, and motivation)**—>can produce feelings of **euphoria, relaxation, and pain relief**.
- Repeated use —> brain can **adapt to the presence** of the drug and **begin to rely on it to produce dopamine**—> changes in the **brain's reward system**, where other activities or substances that once produced pleasure or reward are no longer as effective —> **Tolerance**, where higher doses of the drug are needed to achieve the same effect.
- Brain become **more sensitive to the effects of opioids**, which can lead to **withdrawal symptoms when the drug is not present**. (Anxiety, agitation, nausea, and muscle aches) *—>The fear of withdrawal symptoms can contribute to continued opioid use*

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Factors that can increase the risk of opioid abuse

- A personal or family history of substance abuse or addiction
- Mental health disorders, such as depression or anxiety
- Chronic pain conditions
- Social or environmental factors, such as a history of trauma or social isolation
- Using opioids in ways other than prescribed, such as crushing or snorting pills or injecting the drugs

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Antidepressants

- Chronic pain is a complex and challenging condition that affects millions of people worldwide.
- Antidepressant medications, such as tricyclic antidepressants (TCAs), have been found to be effective in treating chronic pain in some cases.
- TCAs were originally developed as antidepressants, but they have since been found to have analgesic properties.

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Antidepressants

- TCAs work by **blocking the reuptake serotonin and norepinephrine**
- Regulation of **mood, sleep, and pain perception.** Increasing levels TCAs can reduce pain signals and improve mood. TCAs block pain receptors in the brain, reducing pain signals.
- *The mechanism not fully understood (*involve the modulation of the pain processing pathways in the brain and spinal cord)
- TCAs affect the release of neurotransmitters LIKE **substance P**, which is involved in the transmission of pain signals.
- Several weeks to **start working**, and their effectiveness may vary depending on the type and severity of the pain.

Antidepressants

Benefits and side effects of TCAs for chronic pain

- TCAs have been found to be effective in treating several types of chronic pain, including neuropathic pain, migraine headaches, and fibromyalgia.
- However, TCAs can have significant side effects, such as dry mouth, blurred vision, constipation, urinary retention, and dizziness.
- TCAs can also interact with other medications, such as blood thinners and antihistamines, which can increase the risk of adverse effects.

Anticonvulsants

Introduction

- Anticonvulsants are a class of medications used to treat seizures.
- Certain anticonvulsants (gabapentin and pregabalin) have been found to be effective in treating chronic pain.
- Anticonvulsants work **by blocking voltage-gated calcium channels** in the brain and nervous system, which can help to reduce pain signals.

Anticonvulsants

Gabapentin

- Gabapentin has been found to be effective in treating various types of chronic pain, such as **neuropathic pain and fibromyalgia.**
- Gabapentin works by **blocking calcium channels** in the brain and nervous system, **reducing the release of pain neurotransmitters**.
- **Side effects** of gabapentin include dizziness, fatigue, and drowsiness.
- Can be **addictive**, and withdrawal symptoms can occur when the medication is discontinued.

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Anticonvulsants

Pregabalin

- Effective in treating various types of chronic pain, such as **neuropathic pain and postherpetic neuralgia.**
- Works by **binding to alpha-2-delta subunits of voltage-gated calcium channels** reducing the release of pain neurotransmitters.
- **Side effects** of pregabalin include dizziness, drowsiness, and weight gain.
- Can be **addictive**, and withdrawal symptoms can occur when the medication is discontinued.

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Anticonvulsants

Considerations and Contraindications

- Gabapentin and pregabalin can be effective in chronic pain, but they may **not be suitable for everyone**.
- History of **kidney or liver disease** may not tolerate anticonvulsants,
- With caution in **elderly patients**, as they may be more sensitive to side effects.
- Patients should be monitored closely for side effects and signs of addiction or dependence when taking anticonvulsants for chronic pain.

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Topic Medications

Introduction

- Applied directly to the **skin over painful areas** to provide localized pain relief.
- They can include **creams, gels, patches, and sprays** containing various ingredients, such as ***lidocaine, capsaicin, or nonsteroidal anti-inflammatory drugs (NSAIDs).***
- Topical medications are often used for **musculoskeletal pain, such as arthritis, and neuropathic pain, such as diabetic neuropathy**



Topic Medications

Lidocaine

- Local anesthetic that **blocks nerve signals** in the area where it is applied.
- It can be used topically as a **cream or gel** to provide pain relief for conditions such as **shingles, post-herpetic neuralgia, and diabetic neuropathy**.
- Lidocaine can also be administered as a **patch**, which can provide continuous pain relief for up to 12 hours.



Topic Medications

Capsaicin

- Capsaicin derived from **chili peppers** works by **reducing the amount of a neurotransmitter called substance P**.
- Available as creams, gels, and patches, and is commonly used for **neuropathic pain.**
- Capsaicin can cause a burning sensation when first applied, but this typically subsides after a few days of use. It may take several weeks of regular use to see the full pain-relieving effects.