# MSS

## Pharmacology

LEC no. V2


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# Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Analgesics





Dr. Alia Shatanawi

**In this modified, we'll begin by reviewing a few slides from the previous modified – as the Dr revised some points -**
**Keep it up and let's start, this lec would be easy as it is just about basic info** 💪

# Aspirin

- ✦ It can cause **irreversible** inactivation of COX-1 and COX-.2

- Aspirin is the prototype of **traditional** NSAIDs and was officially approved by the FDA in .1939

**important : for our exam purpose, all NSAIDs in our slides are non-selective (inhibit cox1 and cox2) except this one :**

**celecoxib**

**It is the only cox-2 inhibitor (selective)**

# Mechanism of action

- Aspirin is a weak organic acid that is unique among the NSAIDs in that it **irreversibly** inactivates cyclooxygenase

- The other NSAIDs are all reversible

أهم خاصية تميز الاسبرين عن باقي ال **NSAIDs**

- Aspirin is rapidly deacetylated by esterases in the body producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects .

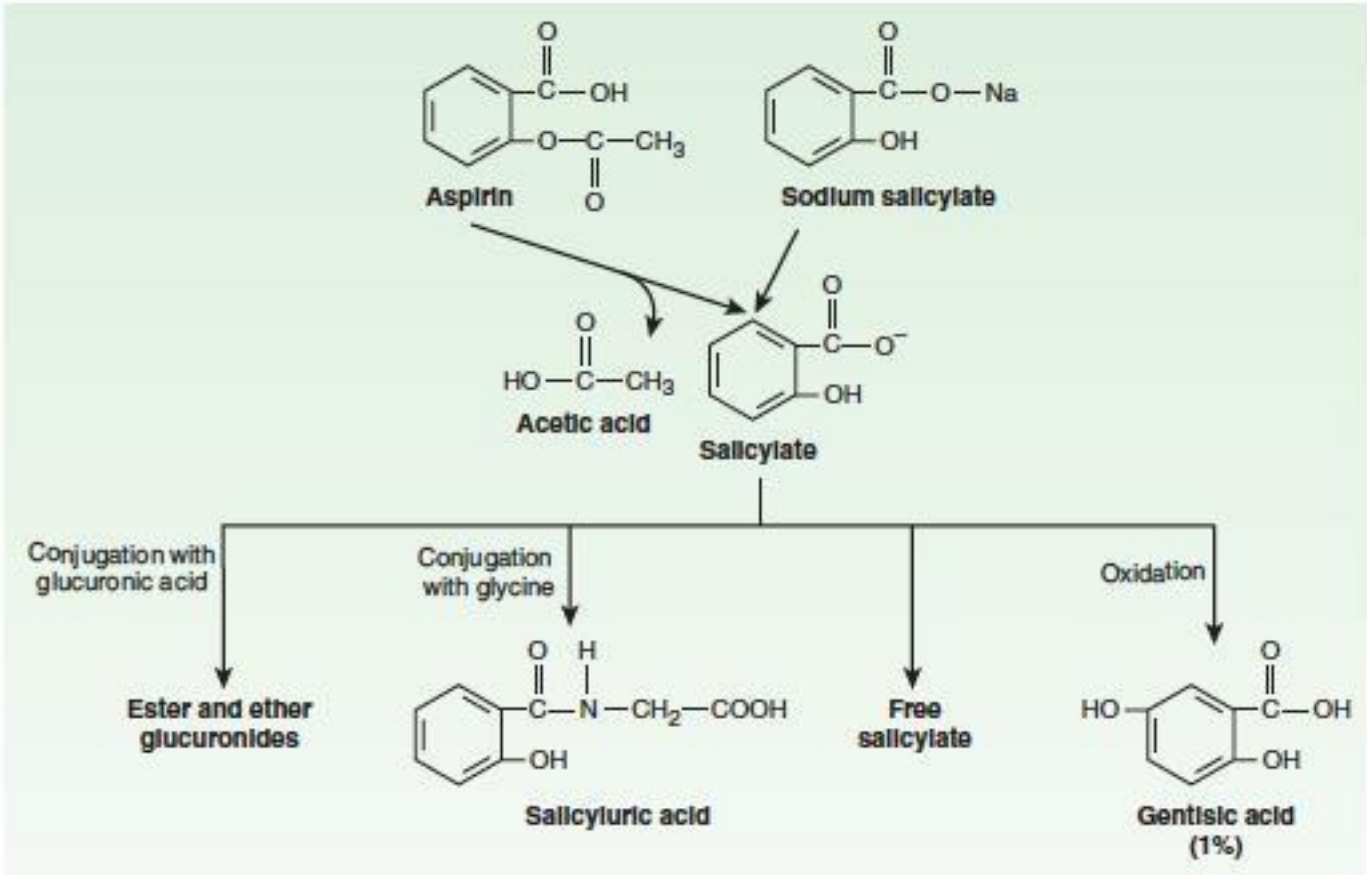



**FIGURE 36–3** Structure and metabolism of the salicylates. (Modified and reproduced, with permission, from Meyers FH, Jawetz E, Goldfien A: *Review of Medical Pharmacology*, 7th ed. McGraw-Hill, 1980.)

## Respiratory actions:

**!الدكتورة ركزت على هذا الموضوع !**

Aspirin can cause bronchoconstriction in some asthmatic patients through increased production of proinflammatory mediators, particularly leukotrienes.

**why asthmatic patients should not take NSAIDs drugs?**
**In our bodies we have a balance between the two pathways ( COX , LOX ) so when I block one of these two pathways ,we are going to increase the activity of the other one.**
**In our case we will have higher activity for " LOX " ( balance shifted toward the LOX pathway ) which is responsible for bronchoconstriction, this make things worse for Asthma patients**
**So again why NSAIDs are not recommended for asthmatic patients? inhibition of COX pathway ——> shift to LOX pathway ——> increased production of leukotienes ——> increased asthmatic manifestations.**

# Clinical Uses

Aspirin decreases the incidence of transient ischemic attacks, unstable angina, coronary artery thrombosis with myocardial infarction, and thrombosis after coronary artery bypass grafting

Epidemiologic studies suggest that long-term use of aspirin at low dosage is associated with a lower incidence of colon cancer, possibly related to its COX-inhibiting effects.

this is a promising usage of the aspirin but it's under studying until now

Aspirin helps prevent blood clots from forming in arteries, which can lead to various cardiovascular issues. By inhibiting the production of thromboxane A2, a molecule that causes platelets to clump together, aspirin reduces the risk of transient ischemic attacks (mini-strokes), unstable angina (chest pain due to heart not getting enough blood), coronary artery thrombosis (clots in the arteries of the heart leading to heart attack), and thrombosis after coronary artery bypass grafting (clots in the arteries after surgery to improve blood flow to the heart). عملية تحويل مسار الشريان التاجي

## Gastrointestinal effects:

**So inhibiting PG synthesis by Aspirin would lead to ulcers**

- **PGE2** stimulate synthesis of protective **mucus** in both the stomach and small intestine.
- In the presence of aspirin, these prostanoids are not formed, resulting in increased gastric acid secretion and diminished mucus protection .
- Agents used for the prevention of gastric and/or duodenal ulcers include proton-pump inhibitors (**PPIs**); esomeprazole, lansoprazole, omeprazol

**the strongest drugs to deal with these ulcers are PPI ( they're given with aspirin ),These PPIs mediate gastric acid secretion , but there are other drugs which we'll take in GI system whithin weeks :)**

**Effect on platelets:**

Aspirin irreversibly inhibits platelet COX so that aspirin's anti platelet effect lasts 8-10 days (the life of the platelet .)
In other tissues, synthesis of new COX replaces the inactivated enzyme so that ordinary doses have a duration of action of 6-12 hours.

**Aspirin irreversibly inhibits the enzyme cyclooxygenase in platelets, preventing them from producing thromboxane (TX), -a molecule essential for platelet aggregation-, and because platelets cannot synthesize new proteins to replace the inhibited enzyme (due to their lack of nuclei), this effect lasts for about 8 – 10 days until the body produce new ones**

**when the doctor asks about the mechanism of action, you should mention what receptors or enzymes this drug inhibits or activates. For example here it targets PG**

## Actions on the kidney:

**Detailed Explanation in the next slide, gently check it : ) ♥**

- Cyclooxygenase inhibitors prevent the synthesis of PGE2 and PGI2 that are responsible for maintaining **renal blood flow.**

- Decreased synthesis of prostaglandins can result in **retention of sodium and water** and may cause **edema** and **hyperkalemia** in some patients.

**PG = vasodilation**
**NSAIDs ( inhibition of PG ) =vasoconstriction**
**So we can conclude that there is contraindication between hypertensive drugs and NSAIDs**

## Just for clarification

***Impact on Renal Blood Flow**: PG helps dilate blood vessels in the kidneys, which supply it with adequate blood flow. When inhibiting COX enzymes, NSAIDs reduce the synthesis of these prostaglandins, potentially leading to decreased renal blood flow.

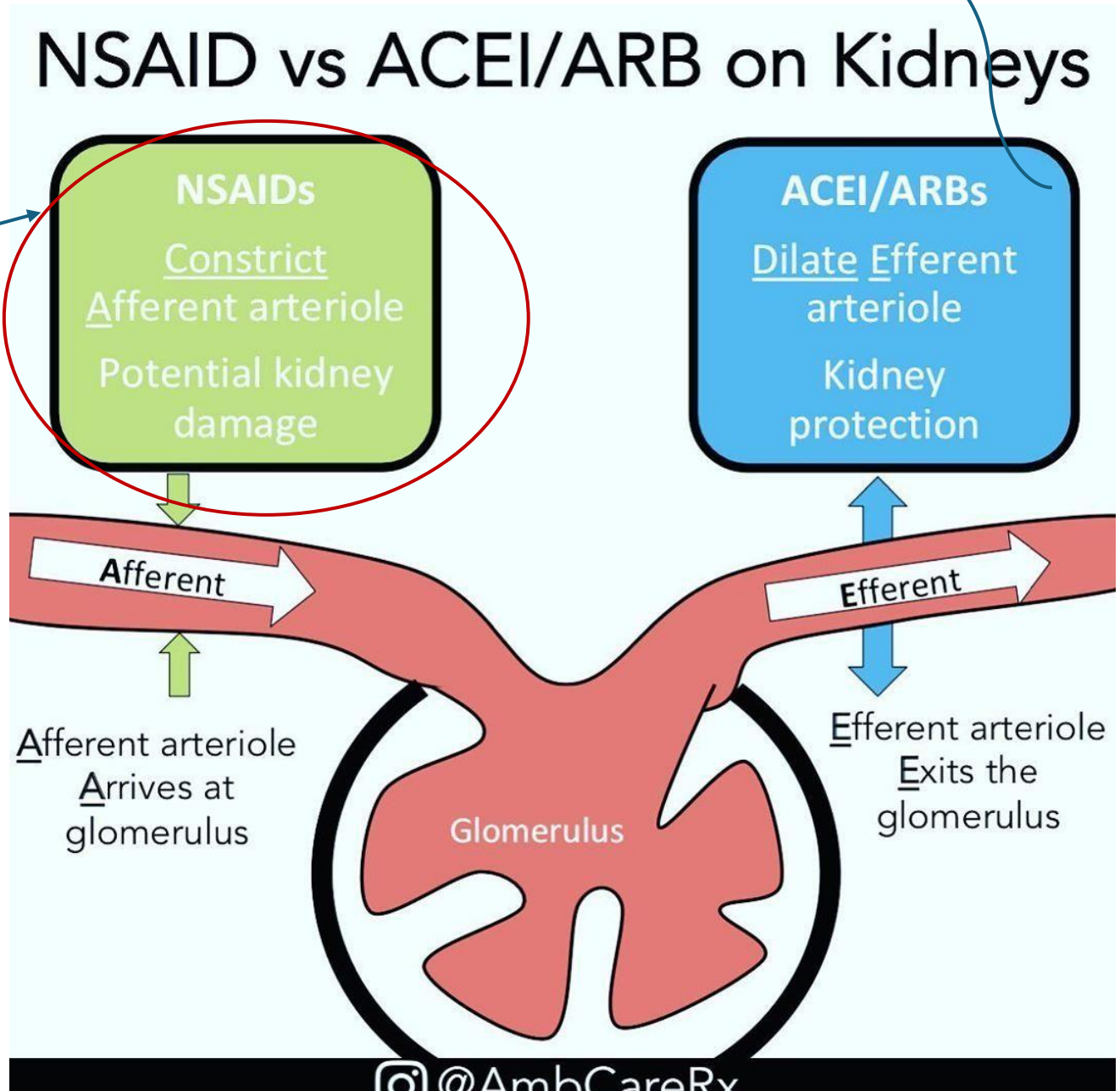
***Sodium and Water Retention**: The kidneys are also involved in regulating the body's balance of sodium and water. Prostaglandins like PGE2 facilitate the excretion of sodium and water. When NSAIDs reduce prostaglandin synthesis, this can lead to the kidneys retaining more sodium and water, contributing to an increase in blood volume. This increased volume can raise blood pressure and result in edema (the accumulation of fluid in the body's tissues). احتباس سوائل

***Hyperkalemia**: Similarly, prostaglandins affect the excretion of potassium. With decreased prostaglandin production, the kidneys may excrete less potassium, leading to hyperkalemia. High potassium levels can disrupt normal heart rhythms and increase a risk to cardiovascular diseases.

يعني باختصار المبدأ هو أن البروستاغلاندين بالوضع الطبيعي بأثر ع الكلى بحيث انه : يوسع الاوعية الدموية الواصلة للكلى ، ويزيد التخلص من الأملاح .. هاي الأدوية بتعكس الـ وظائف يلي ذكرناها ف ينتج عن ذلك الاعراض المذكورة فوق

we'll take This part ( in blue )next years, don't worry about it now

**NSAIDs inhibit the cyclooxygenase enzymes (COX-1 and COX-2), which are necessary for the synthesis of prostaglandins. With reduced prostaglandin levels, the kidneys may receive less blood flow. The decrease in prostaglandin-mediated dilation of afferent arterioles can lead the kidneys to respond as if there were an overall reduction in blood pressure, triggering mechanisms to retain sodium and water to increase blood volume and pressure. This retention can contribute to edema (swelling from fluid buildup in the body) and increase blood pressure, potentially worsening or leading to hypertension.**



# Common Adverse Effects

**explanation in the next slide, take a breath and stay tuned!** 

- Platelet Dysfunction
- Gastritis and peptic ulceration with bleeding (inhibition of PG + other effects)
- Acute Renal Failure in susceptible
- Sodium+ water retention and edema
- Analgesic nephropathy
- Prolongation of gestation and inhibition of labor.
- GIT bleeding and perforation

**1. Platelet Dysfunction:** NSAIDs inhibit COX-1, affecting thromboxane A2 production, which is necessary for platelet aggregation. This can lead to impaired clot formation, increasing bleeding time ( But in low doses this is helpful for people with thromboembolic diseases .. in thrombosis, the clot forms and stays in place,. In embolism, the clot travels through the bloodstream )

**2. Gastritis and Peptic Ulceration with Bleeding:** By inhibiting COX-1, NSAIDs reduce the production of protective gastric prostaglandins. This decreases the stomach's mucosal defenses against acids, leading to gastritis, ulcers, and potentially bleeding.

**3. Acute Renal Failure in Susceptible Individuals:** NSAIDs can reduce kidney function in individuals with pre-existing kidney conditions, heart failure, or dehydration, due to decreased prostaglandin-mediated renal blood flow.

**4. Sodium and Water Retention and Edema:** The reduction in prostaglandin synthesis can lead to decreased renal blood flow and sodium excretion, causing fluid retention and edema.

**5. Analgesic Nephropathy**(kidney injury) **:** Long-term or excessive use of NSAIDs can lead to chronic kidney disease or worsen existing kidney function, a condition known as analgesic nephropathy.

**6. Prolongation of Gestation and Inhibition of Labor:** Prostaglandins play a role in labor initiation. NSAIDs can delay or prolong labor by inhibiting prostaglandin synthesis. ( PG make constriction for muscles of uterus ) more explanation of this point in the next slide.

**7. GIT Bleeding and Perforation:** Similar to gastritis and peptic ulceration, the inhibition of gastric mucosal protection can lead to gastrointestinal bleeding and, in severe cases, perforation of the ulcer, creating a life-threatening condition.

Some drugs that are used in treating gastric acidity are PG analogs. (make sense because PG increase mucus formation and decrease acidity.
So, are PG analogs the best drugs to treat gastric acidity? No! Proton pump inhibitors are the best, as we previously stated.

**6. Prolongation of Gestation and Inhibition of Labor:**

We said that PG cause constriction of uterus muscles, so PG analogs could be used as **facilitator for childbirth.**

We can use PG analogs in cases of abortion اجهاض.

Medical use is to facilitate birthing process. في حالات تعسر الولادة ممكن نعطي هاي الادوية برضه

So, if we use NASIDs (PG inhibitors) that will cause **Prolongation of Gestation and Inhibition of Labor.**

المرأة الحامل لازم تقريبا تبطل تاخذ هاي الأدوية في الثلث الأخير من الحمل

Misoprostol is used to treat gastric acidity (not frequently nowadays because there are better drugs) it also affects the muscles of the uterus since it is PG analog.
Oxytocin is the frug that is used to facilitate birthing.

# Adverse effects

**Gastrointestinal** :

- The most common GI effects of the salicylates are **epigastric distress**, nausea, and vomiting.
- Microscopic **GI bleeding** is almost universal in patients treated with salicylates .
- At stomach pH, aspirin is uncharged; consequently, it readily crosses into mucosal cells, where it ionizes (becomes negatively charged) and becomes trapped, thus potentially causing **direct damage to the cells.**

**I have to ask the patient if he has allergy to aspirin or no in order to avoid risks such as anaphylactic which could be fatal.**

**Hypersensitivity: Approximately 15 percent of patients taking aspirin experience hypersensitivity reactions.**

- Symptoms of true allergy include urticaria, bronchoconstriction, or angioedema. Fatal anaphylactic shock is rare.

**Reye's syndrome:**

- **Aspirin** and **other salicylates** given during viral infections has been associated with an increased incidence of Reye's syndrome, which is an often fatal, fulminating hepatitis with cerebral edema.

**Like bismuth subsalicylate (we will talk about it in GI system) that is used for gastric acidity,....**
**But for now just know that its structure contain salicylates, so we have to be careful when giving this drug.**

- This is especially encountered in children, who therefore should be given **acetaminophen** instead of **aspirin**

# Reye's syndrome

- Reye's syndrome is a potentially **fatal disease** that has numerous detrimental effects to many organs, especially the **brain and liver**, as well as causing a lower than usual level of blood sugar (**hypoglycemia**) The classic features are a **rash, vomiting, and liver damage**. The exact cause is **unknown** and, while it has been **associated with aspirin consumption by children with viral illness**, it also occurs **in the absence of aspirin use.**

**فإذا اجاك طفل مريض وحلقه ملتهب ولسا مش متأكد اذا هو فيروسي او بكتيري ما بعطيه اسبرين**
**aspirin is contraindicated in children who are below the age of six years who have viral infection or susceptible to have viral infection because these patients more susceptible to have Reye's syndrome**
**It can occur in the absence of aspirin, but aspirin increase the chance**

# Drug interactions :

- Salicylate is 90 to 95 percent protein bound and can be displaced from its protein-binding sites, resulting in increased concentration of free salicylate

**Protein binding mostly happens in the blood, particularly during the distribution phase of how drugs move through the body.**

- alternatively, aspirin could displace other highly protein- bound drugs, such as **warfarin**, **phenytoin**ادوية صرع, or **valproic** acidادوية صرع, resulting in higher free concentrations of the other agent .

**توضيح لهاي النقطة:**
**لما انا أوصف لشخص دوا واحكيله كم مقدار الجرعة وعددها بكون حاسب حسابي انه راح يصير ارتباط بالبروتين وزي ما اخذنا انه ال free form هو الي بعطيني ال effect, هسا اذا كان شخص ياخذ دوا زي warfarin الي هو مميع اقوى بكثير من ال aspirin هذا الدوا برتبط برضه بالبروتين ففي حال اخذ المريض دوا زي aspirin وهو اصلا باخذ warfarin راح يفك جزء من ال warfarin عن البروتينات عشان يرتبط ال aspirin لانه زي ما حكينا ال aspirin برتبط بنسبة عالية بالبروتين (فراح يزيد تركيز ال warfarin بالدم ,وبما انه مميع قوي فممكن رضة تعمل internal or external bleeding فعشان هيك في ادوية لازم ما اخذها مع ادوية ثانية.**

- Concomitant use of **ketorolac** and aspirin is contraindicated because of increased risk of GI bleeding and platelet aggregation inhibition .

# Toxicity :

**The mild form is called salicylism happens in patients with little allergy to aspirin**
**major form is called toxicity**

- nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears .)

Aspirin has a direct effect on the respiratory center in the brain leading to hyperventilation. The body responds to **hyperventilation (زيادة التنفس)** by having the kidneys produce more bicarbonate and excrete more potassium which leads to an elevated anion gap metabolic acidosis. **More details in the next slide.**

## Treatment:

In serious cases, mandatory measures include the intravenous administration of **fluid**, **dialysis of the kidney كلى غسيل,** correction of **acid-base** and electrolyte balances.

**In cases of aspirin poisoning, activated charcoal, acting as a scavenger, can help eliminate aspirin from the gastrointestinal tract if it hasn't been absorbed, reducing the risk of toxicity.**
**scavenging refers to the process by which a substance binds to or absorbs other molecules.**

# Toxic effects of aspirin on respiratory center

- (1) stimulation of the respiratory center of the brain, leading to hyperpnea and respiratory **alkalosis (because of the loss of CO2)**
- (2) uncoupling of oxidative phosphorylation, leading to increased oxygen utilization and glucose demand, increased oxygen utilization and glucose demand, increased gluconeogenesis, and increased heat production
- (3) inhibition of Krebs cycle enzymes, leading to decreased glucose availability and increased organic acids
- (4) alterations in lipid metabolism and amino acid metabolism, enhancing metabolic acidosis. **In case of uncoupling of oxidative phosphorylation, that will lead to relying on anaerobic respiration which in turn will increase the concentration of lactic acid leading to lactic acidosis. This step shows you why I would have acidosis**
- (5) increased fluid and electrolyte losses, leading to dehydration, sodium depletion, potassium depletion, and loss of buffer capacity. **we said that chronic use of NSAIDs will lead to electrolyte retention. But in toxicity, kidney will try to fix acidosis by increasing fluid and electrolyte loss, so patients will have dehydration**
  **it could cause certain condition related to heart like Arrhythmias.**

**So we will have alkalosis at first then acidosis.**

**When taking high doses, This effect can happen due to changes in the kidney's compensatory mechanisms attempting to correct disturbances in salts and water balance.**

الجدول هذا مراجعة لكل الي حكيناه فنعم مطلوب بس فش اشي جديد فيه ,يعني كمراجعة جيد

# Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

| Drugs | Mechanism of action | Side effect | Other notes |
|---|---|---|---|
| **Salicylate**<br>• *Aspirin* | • Irreversibly inhibits Cyclooxygenase 1 (COX-1) and COX-2<br>• Inhibition of COX-2 suppresses prostanoid synthesis providing analgesic, anti-pyretic and anti-inflammatory effects<br>• Aspirin is weakly selective to COX-1 | • **Gastrointestinal:** Inhibition of COX-1 causes dyspepsia and if severe gastric bleeding and ulceration<br>• **Rashes:** Morbiliform rash, urticaria, toxic epidermal necrolysis (TEN)<br>• **Acute renal failure**<br>• **Increase blood pressure**<br>• **Reduce effect of anti-hypertensives** (except CCB)<br>• Salicylate poisoning in aspirin overdose (hyperventilation, tinnitus, deafness, vasodilatation) | • Contraindicated in active peptic ulceration, bleeding disorders, children under 16 years (risk of Reye's syndrome), severe cardiac failure |
| **Propionate**<br>• *Ibuprofen*<br>• *Naproxen* | • Competitive inhibitors of COX-1 and COX-2<br>• Both ibuprofen and naproxen are weakly selective to COX-1 | | • Contraindicated in GI bleed, ulceration, heart failure |
| **Coxibs**<br>• *Celecoxib*<br>• *Etoricoxib* | • Competitive inhibitor of COX-2 only at therapeutic dose | • Similar to other NSAIDs<br>• Less gastrointestinal side-effects | • Contraindicated in active GI bleed, ulceration, cerebrovascular disease, inflammatory bowel disease, ischemic heart disease, heart failure, peripheral arterial disease<br>• Monitor blood pressure |
| **Paracetamol** | • Exact mechanism unknown but has ability to inhibit COX pathways<br>• Good analgesic and anti-pyretic but poor anti-inflammatory effects | • Paracetamol overdose can cause liver damage<br>• Presents with nausea and vomiting, associated with right subcostal pain and tenderness | **No anti-inflammatory effect**<br>**Works centrally not peripherally**<br>**Can cause hepatotoxic only when taking over dose.** |

# 🚨 Test Bank ( Additional questions about this lec )

- Q: How does aspirin uniquely affect cyclooxygenase (COX) enzymes compared to other NSAIDs?
- A) It selectively inhibits COX-2 over COX-1.
- B) It reversibly inhibits both COX-1 and COX-2 enzymes.
- C) It irreversibly inactivates both COX-1 and COX-2 enzymes.
- D) It does not affect COX enzymes but targets a different inflammatory pathway.

- Answer : C
- Q: Why are NSAIDs not recommended for patients with asthma?
- A) They decrease mucus production in the airways.
- B) They cause a shift towards increased LOX pathway activity, leading to bronchoconstriction.
- C) They directly stimulate the respiratory center causing hyperventilation.
- D) They increase COX-2 expression in the lungs.

- Answer : B

- **Q: Which of the following best describes the benefit of aspirin in cardiovascular disease prevention?**
  - **A) It prevents the formation of blood clots by inhibiting the production of thromboxane A2.**
  - **B) It enhances the production of protective mucus in the cardiovascular system.**
  - **C) It selectively inhibits COX-2 to reduce inflammation in the heart.**
  - **D) It increases renal blood flow to improve heart function.**

- **Answer: A**

- **Q: What mechanism leads to the gastrointestinal side effects of aspirin?**
  - **A) Increased production of protective gastric prostaglandins.**
  - **B) Direct stimulation of the gastrointestinal tract's smooth muscles.**
  - **C) Inhibition of PG synthesis, leading to reduced mucus protection and increased acid secretion.**
  - **D) Enhanced renal excretion of gastric acids.**

- **Answer: C**
- **Q: What is a rare but serious complication of prolonged large-dose therapy of acetaminophen?**
  - **A) Bronchoconstriction and asthma exacerbation.**
  - **B) Reye's syndrome in viral infections.**
  - **C) Hepatic necrosis and renal tubular necrosis.**
  - **D) Prolongation of gestation and inhibition of labor.**
- **Answer: C**

- V 2 " The ONLY selective drug is **celecoxib "**

**V2**

**important : for our exam purpose, all NSAIDs in our slides are non-selective (inhibit cox1 and cox2) except this one :**

**celecoxib**

**It is the only cox-2 inhibitor (selective)**