Pharmacological Actions:

Analgesic action: effective against dull throbbing pain of inflammation

- Peripheral effect: NSAIDs block the synthesis of prostanoids (PGE_2 & PGI_2) which sensitize pain receptors to activators
- Central effect: equi-analgesic effects when administered intrathecally & systemically

Antipyretic action: NSAIDs inhibit the production of PGE_2 resulting in an antipyretic effect by changing the hypothalamic temperature set-point back to normal

Uricosuric effect: NSAIDs inhibit urate crystal phagocytosis & prostaglandin production by inhibit COX enzymes

Anti-inflammatory action: NSAIDs block the production of prostanoids by inhibiting COX enzymes
→ COX2 is major source of pro-inflammatory prostanoids

PGE_2 & PGI_2 involved in inflammation

- Increase local blood flow
- Increase vascular permeability
- Increase leukocyte infiltration

NSAIDs:

- Organic acids
- Well-absorbed orally
- Highly protein bound
- Excreted by glomerular filtration or tubular secretion

COX non-selective (Naproxen)

- Risk of GI ulceration
- Inhibit platelet aggregation

COX-2 selective (Celexocib)

- Designed to limit GI ulceration (protection mediated by COX1)
- CV events (no significant platelet aggregation inhibition)

ASA: irreversibly blocks COX enzymes by acetylation

- Low doses preferentially block COX-1 enzymes in platelets → blocks thromboxane A_2 production → decreased platelet aggregation & vasodilation
- Duration of effect related to platelet lifetime (7 days)

Side Effects:

GI: NVD, abd pain, dyspepsia, GI ulceration & bleeding

GI ulcer risk factors:

- History of ulcer complications
- Multiple, high-dose or long-acting NSAIDs
- Concomitant anticoagulants
- Age ≥ 60 (further increased if ≥ 70)
- Heart disease

→ Risk highest with: piroxicam, ketorolac, SR form
→ Risk lowest with ibuprofen; celecoxib (<6 mo use)

CV: thrombosis, myocardial infarction, stroke

→ Risk thought to be higher with COX-2 selective NSAIDS

Hematology: bruising, bleeding

CNS: HA, dizziness, vertigo

Renal: salt & water retention; edema; worsening of renal function; hyperkalemia

Nephrotoxicity:

TRIPLE WHAMMY: ACEI/ARB + diuretic + NSAID
→ Diuretic reduces blood volume
→ ACEI/ARB prevents efferent arteriolar vasoconstriction
→ NSAID prevents prostaglandin-mediated afferent arteriolar vasodilation

= reduced renal perfusion & renal dysfunction

[Risk factors: pre-existing renal dysfunction, elderly, heart failure]

	Low GI ulcer risk	Mod GI ulcer risk	High GI ulcer risk
Low CV risk	Ibuprofen	Celecoxib NSAID + PPI/ misoprostol	Avoid NSAIDs Celecoxib + PPI/ misoprostol
High CV risk	Naproxen	Naproxen + PPI / misoprostol	Avoid NSAIDs

Contraindications

- Hypersensitivity (potential cross-sensitivity)
- Caution/avoid in:
  - History of GI ulceration
  - Blood dyscrasias, coagulation defects, on anticoagulants
  - Congestive heart failure
  - Low circulatory volume (risk of renal toxicity)

ASA toxicity and treatment

- Salicylism: vomiting, tinnitus, decreased hearing, vertigo
  → Reversible with dose decrease
- Acute ingestion of > 200 mg/kg → toxic
  - Hyperpnea (direct effect on medulla)
    →respiratory alkalosis
  - Followed by salicylate accumulation
    → metabolic acidosis
  - Respiratory depression, cardiotoxicty, seizures

→ Supportive care, activated charcoal, gastric lavage

Drug interactions

- Some NSAIDs metabolized by Phase I, then Phase II enzymes; others by direct glucoronidation (Phase II)
- Renal excretion for final elimination
- Highly protein bound → potential to displace other drugs from plasma membranes

Methotrexate	Decreases renal clearance of MTX, increasing MTX levels; minimal with COX2 selective
Warfarin	Increased bleed risk
Penicillins	Levels of both decreased because of plasma protein competition
SSRIs, SNRIs	Increased risk of upper GI bleed; inhibit serotonin uptake by platelets necessary for platelet aggregation
Corticosteroids	Increased GI irritation; decreased healing; ulcer risk
Digoxin	Increase digoxin levels
Lithium	Increased lithium levels due to decreased excretion
ACEIs, diuretics	Triple whammy → nephrotoxicity

Acetaminophen: analgesic and antipyretic activity (no anti-inflammatory activity); NOTE: NOT AN NSAID

Potential mechanisms of action:

1. APAP reduces COX → inactive form (peroxide-dependent) → blocks PG synthesis
2. APAP may inhibit COX-3 (weakly produces PGs)
3. APAP involved in activation of descending endogenous opioid pathways & self-synergistic interaction b/w spinal and supraspinal sites
4. APAP may be involved in endogenous serotonergic descending pain inhibitory pathway (originates in PAG in midbrain)
5. A metabolite of APAP blocks cellular uptake of endocannabinoid, indirectly activating CB1 receptors
   a. Endocannabinoids inhibit nociception
   b. Via CB1R, lowers body temperature
6. APAP metabolite activates TRPV1 (antinociception)

Drug interactions:
Warfarin: enhanced coagulation

SEs (rare): rash, neutropenia, thrombocytopenia

Metabolism: glucuronidation & sulfation in liver

→ If exceeds therapeutic doses, glucurodination & sulfation pathways are saturated & CY2E1/3A4 (glutathione conjugation) becomes more important
  - MAX DOSE: 3-4 g/24 h

→ If there is not enough glutathione for CYP450 pathway, conjugation cannot occur → toxic metabolite

→ Chronic alcoholics at higher risk
  - Ethanol induces CYP2E1
  - Often malnourished, so glutathione levels

APAP toxicity: acute ingestion of 150-200 mg/kg for children or 7g total for adults toxic

- Initially: asymptomatic or mild GI upset
- After 24-36h: evidence of hepatotoxicity
- Severe: fulminant liver failure, death

→ >150-200 mg/L 4h after = risk for hepatotoxicity

→ Staggered overdoses associated w/ multi-organ injury & need for liver transplantation

→ Txt: acetylcysteine (glutathione substitute)