Pharmacological Actions:

**Analgesic action:** effective against dull throbbing pain of inflammation
- Peripheral effect: NSAIDs block the synthesis of prostanoids (PGE₂ & PGI₂) which sensitize pain receptors to activators
- Central effect: equipanelgesic effects when administered intrathecally & systemically

**Antipyretic action:** NSAIDs inhibit the production of PGE₂ resulting in an antipyretic effect by changing the hypothalamic temperature set-point back to normal

**Anti-inflammatory action:** NSAIDs block the production of prostanoids by inhibiting COX enzymes
- COX₂ is major source of pro-inflammatory prostanoids
- PGE₂ & PGI₂ involved in inflammation
- Increase local blood flow
- Increase vascular permeability
- Increase leukocyte infiltration

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

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 (Celecoxib)
- 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 A₂ 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]

<table>
<thead>
<tr>
<th>Low GI ulcer risk</th>
<th>Mod GI ulcer risk</th>
<th>High GI ulcer risk</th>
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**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, cardiotoxicity, seizures → Supportive care, activated charcoal, gastric lavage

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

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

**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, glucuridnation & 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)