NSAIDs

Non-Steroidal Anti-Inflammatory Drugs

Pharmacology | FINAL 4 — Comprehensive Summary

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1. Pain & Analgesics — Overview

1.1 Pain

- Universal, complex, subjective experience; #1 reason patients seek medication.
- Serves as a warning signal related to tissue damage — alerts the body to infection or injury.
- Can be acute or chronic; driven by neurochemical processes in either the peripheral or central nervous system.

1.2 Analgesics (Definition)

- Drugs that relieve pain selectively without blocking nerve conduction, altering sensory perception, or affecting consciousness.
- Derived from Greek: an- (without) + -algia (pain).
- Distinguished from anesthesia: analgesia preserves consciousness; anesthesia causes total loss of sensation.

1.3 Classification of Analgesics

Feature	Narcotics (Opioids)	Non-Narcotics (NSAIDs / Paracetamol)
Site of Action	Central NS only	Mainly peripheral NS (some CNS)
Mechanism	Bind opioid receptors in CNS	Inhibit prostaglandin synthesis (COX)
Efficacy	Strong — any type of pain	Weaker — mainly musculoskeletal
Prototype	Morphine	Aspirin
Uses	Analgesic only	Analgesic + Anti-inflammatory + Antipyretic + Antiplatelet
Risk	Tolerance & dependence	GI irritation
Anti-inflammatory?	No	Yes
Antipyretic?	No	Yes
Antiplatelet?	No	Yes (especially aspirin)

Key Point: Paracetamol (acetaminophen) is classified separately: it inhibits PG synthesis like NSAIDs but acts mainly in the CNS, lacks significant peripheral anti-inflammatory activity, and has a distinct safety/toxicity profile.

2. NSAIDs — Mechanism of Action

2.1 Definition

- A chemically diverse group sharing three core activities: analgesic, antipyretic, anti-inflammatory.
- Common mechanism: inhibition of cyclooxygenase (COX) enzymes, which catalyze the first step in prostanoid biosynthesis from arachidonic acid.
- Result: decreased prostaglandin synthesis → both therapeutic and unwanted effects.

2.2 Arachidonic Acid Cascade

Stimulus (injury/infection) → Cell membrane disturbance → **Phospholipase A2** acts on phospholipids → releases **Arachidonic Acid**, which then splits into two pathways:

- **COX Pathway:** Arachidonic acid → Prostaglandins (PGs), Thromboxane A2 (TXA2), Prostacyclin (PGI2). These prostanoids cause vascular changes, pain sensitization, fever, and inflammation.
- **Lipoxygenase (LOX) Pathway:** Arachidonic acid → Leukotrienes. LTB4 attracts/activates phagocytes (inflammation); LTC4/D4/E4 cause bronchospasm, vascular permeability changes, increased secretion.

2.3 Drugs Targeting the Cascade

- **Corticosteroids:** Block Phospholipase A2 → shut down entire cascade upstream.
- **NSAIDs & Aspirin:** Block COX → reduce PGs, TXA2, PGI2.
- **Lipoxygenase Inhibitors:** Block LOX enzyme directly.
- **Leukotriene Receptor Antagonists:** Block effects of leukotrienes (e.g., montelukast — not in this lecture).

2.4 COX Isoforms: COX-1 vs COX-2

Feature	COX-1	COX-2
Expression	Constitutive (always present)	Inducible (absent normally; induced by inflammation)
Location	Stomach, intestine, kidney, platelets, endothelium	Inflammatory sites: macrophages, synoviocytes
Products	PGE2, TXA2, PGI2	Inflammatory PGs, proteases, superoxide radicals ($O_2^{\bullet -}$)

Feature	COX-1	COX-2
Function	Normal physiology (GI protection, platelet aggregation, renal blood flow)	Promotes inflammation, pain, fever
NSAID inhibition consequence	GI irritation, renal effects, antiplatelet effects (unwanted)	Reduced pain and inflammation (desired)

Key Point: The NSAIDs Dilemma: Non-selective NSAIDs block both COX-1 and COX-2. Blocking COX-2 gives therapeutic benefit, but blocking COX-1 removes its cytoprotective functions, causing GI irritation, renal effects, and prolonged bleeding time.

3. NSAIDs — Shared Pharmacological Effects

3.1 Anti-Inflammatory Effect

- **Vasodilator PG reduction:** Decreasing PGE2 and PGI2 → less vasodilation and vascular permeability → less edema.
- **Adhesion molecule inhibition:** Reduces WBC adhesion to vessel walls → fewer inflammatory cells reaching the site.
- **Reduced cellular accumulation:** Less immune cell infiltration at inflamed tissue.

3.2 Analgesic Effect

- **PGE2 sensitizes nociceptors:** PGE2 makes pain nerve endings hyperresponsive to bradykinin and histamine. Blocking PG synthesis desensitizes nociceptors.
- **Headache relief:** PGs cause vasodilation of cerebral vessels → throbbing headache. NSAIDs block this.
- Best for: mild-to-moderate musculoskeletal pain (headache, arthralgia, myalgia).
- Not adequate for: severe pain or visceral pain (use opioids instead).

3.3 Antipyretic Effect

- **Mechanism:** Fever occurs when PGE2 raises the set-point of the anterior hypothalamic thermoregulatory center. NSAIDs block PGE2 synthesis → set-point resets to 37°C.
- **Heat dissipation:** At higher doses, promotes peripheral vasodilation and sweating to dissipate accumulated heat.
- **Safety feature:** No effect on normal body temperature — only works when PGE2 is elevating the set-point.

4. Aspirin (Acetylsalicylic Acid) — Prototype NSAID

4.1 Key Features

- **Unique property:** IRREVERSIBLE inhibitor of COX-1 and COX-2 (via acetylation). All other NSAIDs are reversible.
- **Origin:** Derived from acetylsalicylic acid found in willow bark; used since ancient times. FDA approval 1939.
- **Prototype status:** All new NSAIDs are compared to aspirin for potency.

4.2 Mechanism of Action

- Aspirin (weak organic acid) irreversibly acetylates the active site of COX.
- Rapidly deacetylated by esterases in the body → produces salicylate, the active moiety.
- Salicylate provides: antipyretic + anti-inflammatory + analgesic effects.
- Prolonged duration: body must synthesize new COX enzymes to restore function.

4.3 Specific Mechanisms per Effect

- **Antipyretic/Anti-inflammatory:** Blocks PG synthesis at thermoregulatory centers (hypothalamus) and peripheral target sites.
- **Analgesic:** Decreases PGE2 → prevents sensitization of pain receptors to bradykinin/histamine. May also depress pain stimuli at subcortical sites.

4.4 Respiratory Actions (Dose-Dependent)

Dose Level	Effect	Mechanism
Therapeutic	Increased alveolar ventilation (↑ breathing rate)	Uncouples oxidative phosphorylation → ↑ CO_2 → stimulates breathing
High (moderate toxicity)	Hyperventilation → Respiratory Alkalosis	Direct stimulation of medullary respiratory center → rapid CO_2 loss → ↑ pH
Toxic	Central respiratory paralysis → Acidosis	Respiratory center depression → CO_2 buildup → severe metabolic acidosis

4.5 Gastrointestinal Effects

- PGE2 normally stimulates gastroprotective mucus secretion and reduces acid. Aspirin blocks this.
- Result: increased gastric acid secretion + diminished mucus protection → risk of ulceration.
- Direct mechanism: at stomach pH (low/acidic), aspirin is uncharged and fat-soluble → enters mucosal cells → becomes charged inside (normal pH) → trapped → direct cell damage/necrosis.
- **Prevention:** Co-prescribe PPIs (esomeprazole, lansoprazole, omeprazole) for patients on long-term aspirin.

4.6 Effect on Platelets

- TXA2 (from COX-1) normally enhances platelet aggregation.
- Low-dose aspirin (81 mg/day) irreversibly inhibits TXA2 production via COX acetylation.

- Platelets lack nuclei → cannot synthesize new COX → antiplatelet effect lasts the platelet lifetime (~7 days).
- Clinical result: prolonged bleeding time.
- **Use:** Prophylaxis for TIAs, stroke, acute MI. Reduced mortality in acute MI.

4.7 Renal Effects

- PGE2 and PGI2 maintain renal blood flow by keeping afferent arterioles dilated.
- NSAIDs/aspirin block these → sodium and water retention → edema and hyperkalemia.
- Interstitial nephritis can occur (less common with low-dose aspirin).
- Avoid in patients with creatinine clearance < 10 mL/min.

4.8 Toxicity of Salicylates (Summary)

Toxic Mechanism	Clinical Result
Respiratory center stimulation	Hyperpnea (fast breathing) → less CO2 → Respiratory Alkalosis
Uncoupling of oxidative phosphorylation	↑ O2 use, ↑ glucose demand, ↑ heat production (Hyperthermia)
Krebs cycle inhibition	↓ glucose availability, ↑ organic acids → Metabolic Acidosis
Altered lipid/amino acid metabolism	Further enhances Metabolic Acidosis
Fluid & electrolyte loss	Dehydration, Na+ depletion, K+ depletion, ↓ buffer capacity (via hyperventilation, sweating, renal losses)

4.9 Pharmacokinetics

- **Absorption:** Oral (passive absorption from stomach and small intestine) or rectal suppository (slow, unreliable, but useful for vomiting children).
- **Distribution:** Highly protein-bound (90-95%, mainly albumin).
- **Metabolism:** Hepatic; salicylate converted to water-soluble conjugates.
- **Excretion:** Renal. Monitor hepatic and renal function with long-term use.

4.10 Dosage Guide

Indication	Dose
Antiplatelet (MI prophylaxis)	81 mg/day (low dose; < 325 mg/day)
Stroke prophylaxis	50–325 mg/day
Analgesia only	2 × 325 mg tablets, 4×/day (~2.6 g/day)
Analgesia + Anti-inflammation (RA, OA)	Initial 3 g/day (12–20 tablets/day)

4.11 Adverse Effects & Contraindications

- **Hypersensitivity (~15%):** Urticaria, bronchoconstriction, angioedema. Rare fatal anaphylaxis.
- **Reye's Syndrome:** Fatal fulminating hepatitis + cerebral edema in children/teens (<15 y) with viral illness (chickenpox/flu). AVOID aspirin; use acetaminophen instead.
- **Asthma exacerbation:** COX inhibition → more arachidonic acid shunted to LOX pathway → more leukotrienes → bronchospasm, edema, ↑ mucus.
- **Pregnancy:** Category C (1st & 2nd trimester), Category D (3rd trimester). Excreted in breast milk — avoid while breastfeeding.
- **Drug interactions:** Displaces warfarin, phenytoin, valproic acid from albumin → raises free drug levels. Ketorolac + aspirin = contraindicated (↑ GI bleeding).

5. Classification of NSAIDs

5.1 Overview

Class	Drugs	Key Feature
Salicylates	Aspirin	Irreversible COX inhibitor; prototype
Propionic acid derivatives	Ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Flurbiprofen	Reversible; less GI toxicity than aspirin
Acetic acid derivatives	Indomethacin, Sulindac, Etodolac	Reversible; indomethacin is very potent but toxic
Oxicam derivatives	Piroxicam, Meloxicam	Long t½ → once daily; meloxicam COX-2 preferential
Fenamates	Mefenamic acid	No advantage over others; risk of diarrhea, hemolytic anemia
Heteroaryl acetic acids	Diclofenac, Tolmetin, Ketorolac	Diclofenac accumulates in synovial fluid; potent
Selective COX-2 inhibitors	Celecoxib (Rofecoxib — withdrawn)	↓ GI side effects; ↑ thrombotic risk

5.2 Propionic Acid Derivatives (Ibuprofen, Naproxen, etc.)

- All: anti-inflammatory + analgesic + antipyretic. Reversible COX inhibitors.
- Well absorbed orally; highly albumin-bound. Hepatic metabolism, renal excretion.
- GI effects less intense than aspirin.
- CNS side effects: headache, tinnitus, dizziness.
- **Ibuprofen:** Max 3200 mg/day; take with food/water to reduce GI effects.
- **Asthma:** Contraindicated or use with caution — same LOX pathway shunting mechanism as aspirin.
- **Pregnancy:** Category C (1st/2nd trimester), Category D (3rd trimester). ↑ risk of CV thrombotic events, MI, stroke.

- **Sulindac special note:** Associated with acute pancreatitis. Topical DMSO combination → severe neuropathies.

5.3 Acetic Acid Derivatives — Indomethacin

- Reversible COX inhibitor. Very potent anti-inflammatory.
- Uses: acute gouty arthritis, ankylosing spondylitis, RA, OA, bursitis, tendinitis.
- Toxicity limits use — most CNS side effects of any NSAID:
  - Severe headache (25-50%), vertigo, confusion, psychological disturbances.
  - GI symptoms more frequent than other NSAIDs.
  - Hematological: leukopenia, hemolytic anemia, aplastic anemia, purpura, thrombocytopenia, agranulocytosis.
  - Ocular effects: blurred vision, corneal deposits.
  - Hepatitis, jaundice, pancreatitis, hypersensitivity reactions.
- Sulindac: similar but less severe adverse effects than indomethacin.

5.4 Oxicam Derivatives — Meloxicam & Piroxicam

- Uses: RA, ankylosing spondylitis, osteoarthritis.
- Long half-lives → once-daily dosing. Excreted renally.
- **Meloxicam:** Preferentially inhibits COX-2 over COX-1 → less GI irritation at low-moderate doses compared to piroxicam and non-selective NSAIDs.

5.5 Fenamates — Mefenamic Acid

- Same mechanism and effects as other NSAIDs — no advantages.
- Notable side effects: severe diarrhea, bowel inflammation, hemolytic anemia.

5.6 Heteroaryl Acetic Acids — Diclofenac

- Most commonly used: Diclofenac sodium and diclofenac potassium.
- Approved for long-term RA and OA treatment.
- **Potency:** More potent than indomethacin or naproxen.
- **Key feature:** Accumulates in synovial fluid → ideal for joint inflammatory conditions.
- Available in ophthalmic preparation as well.
- Metabolism: hepatic. Excretion: urine.
- **Diclofenac K (potassium):** Prompt release, quicker onset.
- **Diclofenac Na (sodium):** Delayed release. PO 50 mg after food; IM injection 75 mg.
- Pregnancy: Category C.
- **Contraindications:** Asthma; history of peptic ulcer. Side effects include hypersensitivity.

5.7 Selective COX-2 Inhibitors — Celecoxib

- Developed to avoid GI side effects of non-selective COX inhibition.
- More selective for COX-2 than COX-1 → reduced GI irritation.

- Currently available: Celecoxib (Celebrex). Rofecoxib withdrawn due to thromboembolic deaths.
- **Risk:** Imbalance between TXA2 (not blocked — COX-1 still active) and PGI2 (blocked) → net pro-thrombotic state → ↑ risk of MI and stroke.
- Carries a BLACK BOX WARNING — use only under physician supervision, especially in patients prone to thromboembolic events.
- May increase edema and hypertension.
- Indicated for RA, OA, and other chronic inflammatory conditions.

6. Acetaminophen (Paracetamol) — Distinct Group

6.1 Mechanism

- Inhibits prostaglandin synthesis primarily in the CNS (central COX inhibition).
- Minimal effect on peripheral cyclooxygenase → weak anti-inflammatory activity.
- Does NOT affect platelet function or increase bleeding time.

6.2 Pharmacological Effects

- **Analgesic:** Centrally mediated PG inhibition reduces pain perception.
- **Antipyretic:** Resets hypothalamic set-point via central PGE2 blockade.
- **Anti-inflammatory:** Weak — not suitable for inflammatory conditions like RA.
- **Antiplatelet:** None — safe in patients with bleeding risk.

6.3 Therapeutic Uses

- Substitute for aspirin's analgesic/antipyretic effects when:
  - GI complaints make aspirin intolerable.
  - Prolonged bleeding time is undesirable.
  - Anti-inflammatory action is not needed.
- **Drug of choice:** Children and teenagers with viral infections or chickenpox (instead of aspirin to avoid Reye's syndrome).

6.4 Pharmacokinetics

- Rapidly absorbed from GI tract. Significant first-pass metabolism in intestinal luminal cells and hepatocytes.
- Normal metabolism: conjugation in the liver → inactive metabolites → excreted in urine.
- Minor pathway: hydroxylation → N-acetylbenzoiminoquinone (NAPQI) — a highly reactive, hepatotoxic metabolite.
- At normal doses: NAPQI reacts with glutathione (sulfhydryl group) → non-toxic conjugate. Excreted in urine.

6.5 Dosage

- Standard adult dose: 500 mg per tablet, 1-2 tablets every 6 hours.

- Maximum safe dose: 4 g/day (8 tablets of 500 mg). DO NOT exceed.
- Chronic/excessive use saturates glutathione stores → NAPQI accumulates → hepatotoxicity.

6.6 Adverse Effects & Toxicity

Situation	Effect
Normal therapeutic dose	Virtually free of significant adverse effects
Prolonged large-dose	Rare renal tubular necrosis, hypoglycemic coma
Overdose / large doses	Hepatic necrosis (potentially fatal), renal tubular necrosis
Antidote	Acetylcysteine — scavenges toxic free radicals (NAPQI). Effective within 8-12 hours of overdose

Key Point: After 8-12 hours post-overdose, signs of liver necrosis begin appearing. Periodic monitoring of liver enzymes is recommended for patients on high-dose long-term acetaminophen therapy.

7. Master Comparison Table — All NSAIDs

Drug/Class	COX Inhibition	Key Use	Standout Feature	Main Concern
Aspirin	Irreversible, non-selective	Analgesic, anti-inflammatory, antiplatelet	Only irreversible NSAID; antiplatelet lasts platelet lifetime (7d)	GI ulceration, Reye's syndrome in children
Ibuprofen	Reversible, non-selective	Pain, fever, inflammation	Common OTC; max 3200 mg/day	GI effects; avoid in asthma
Naproxen	Reversible, non-selective	Arthritis, pain, dysmenorrhea	Longer half-life than ibuprofen	CV thrombotic risk
Indomethacin	Reversible, non-selective	Acute gout, ankylosing spondylitis	Very potent	Most CNS side effects; hematological toxicity
Diclofenac	Reversible, non-selective	RA, OA, joint conditions	Accumulates in synovial fluid; more potent than indomethacin	Hepatotoxicity; contraindicated in asthma/PUD
Meloxicam	Reversible, COX-2 preferential	RA, OA, ankylosing spondylitis	Once daily; less GI irritation	Still carries CV risk
Celecoxib	Selective COX-2 inhibitor	RA, OA (chronic use)	Least GI side effects	Highest thrombotic risk; black box warning

Drug/Class	COX Inhibition	Key Use	Standout Feature	Main Concern
Acetaminophen	Central COX inhibitor	Fever, mild-moderate pain	Drug of choice in children; no GI/platelet effects	Hepatotoxicity in overdose; antidote = acetylcysteine

8. High-Yield Points for Exam

Must-Know Facts

- **Aspirin:** Only IRREVERSIBLE COX inhibitor → antiplatelet lasts 7 days (platelet lifespan).
- **Aspirin + children + viral illness:** → Reye's syndrome (hepatitis + cerebral edema). Use acetaminophen instead.
- **NSAIDs + asthma:** → ↑ leukotrienes via LOX shunting → bronchospasm. Contraindicated.
- **Celecoxib:** Selective COX-2 inhibitor. Less GI toxicity but MORE thrombotic risk. Black box warning.
- **Rofecoxib:** Selective COX-2 inhibitor — WITHDRAWN from market due to thromboembolic deaths.
- **Acetaminophen overdose antidote:** Acetylcysteine (within 8-12 hours). Toxicity = NAPQI metabolite accumulation.
- **Acetaminophen max dose:** 4 g/day. Hepatotoxic in overdose. Minimal anti-inflammatory activity.
- **Diclofenac:** Accumulates in synovial fluid → best for joint inflammation.
- **Indomethacin:** Most CNS side effects (headache 25-50%, vertigo, confusion). Use limited to gout and AS.
- **COX-1 inhibition side effects:** GI irritation, bleeding, renal retention, antiplatelet effect.
- **COX-2 inhibition benefits:** Anti-inflammatory, analgesic, antipyretic (without GI side effects).
- **Aspirin + warfarin/phenytoin/valproic acid:** Protein displacement interaction → raised free drug levels.
- **Aspirin + ketorolac:** CONTRAINDICATED — increased GI bleeding + platelet inhibition.
- **Salicylate toxicity acid-base:** Starts as respiratory alkalosis (hyperventilation), then mixed/metabolic acidosis (Krebs cycle inhibition + lactic acid accumulation).
- **Aspirin dose principle:** Low dose (81 mg) = antiplatelet. High dose (≥325 mg) = analgesic/anti-inflammatory.

Good luck on your exam! — Pharmacology Final 4