Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Analgesics

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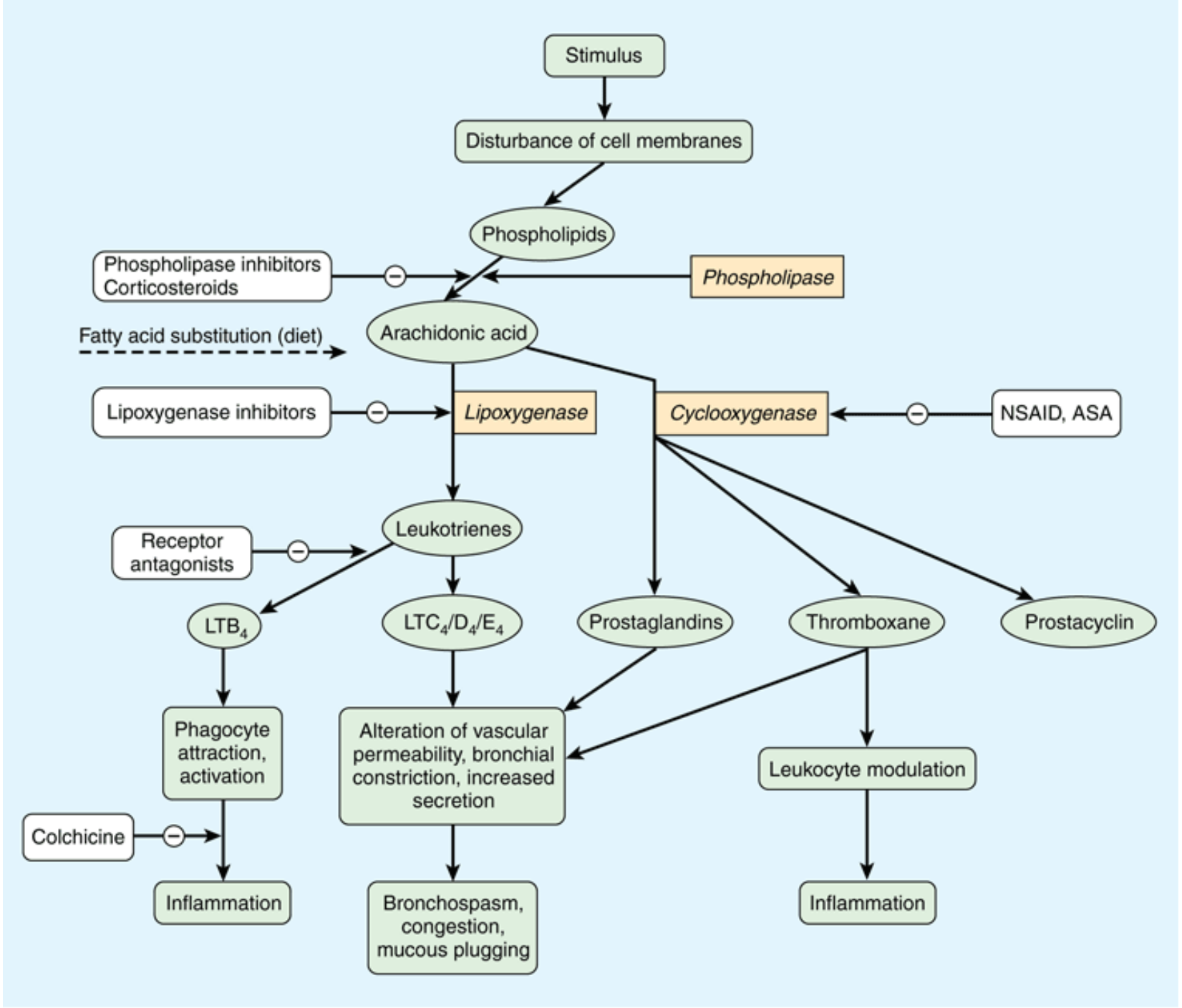
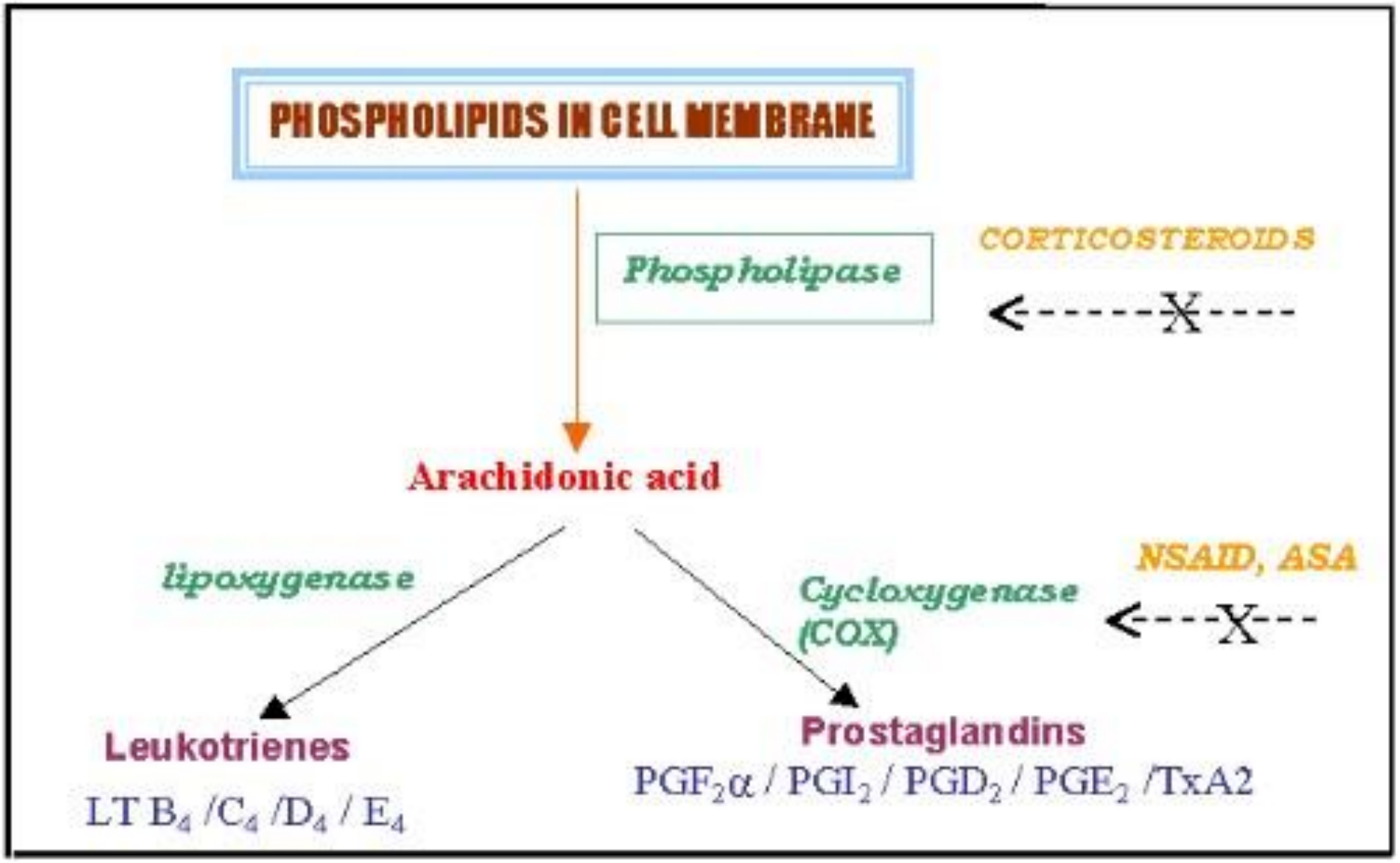
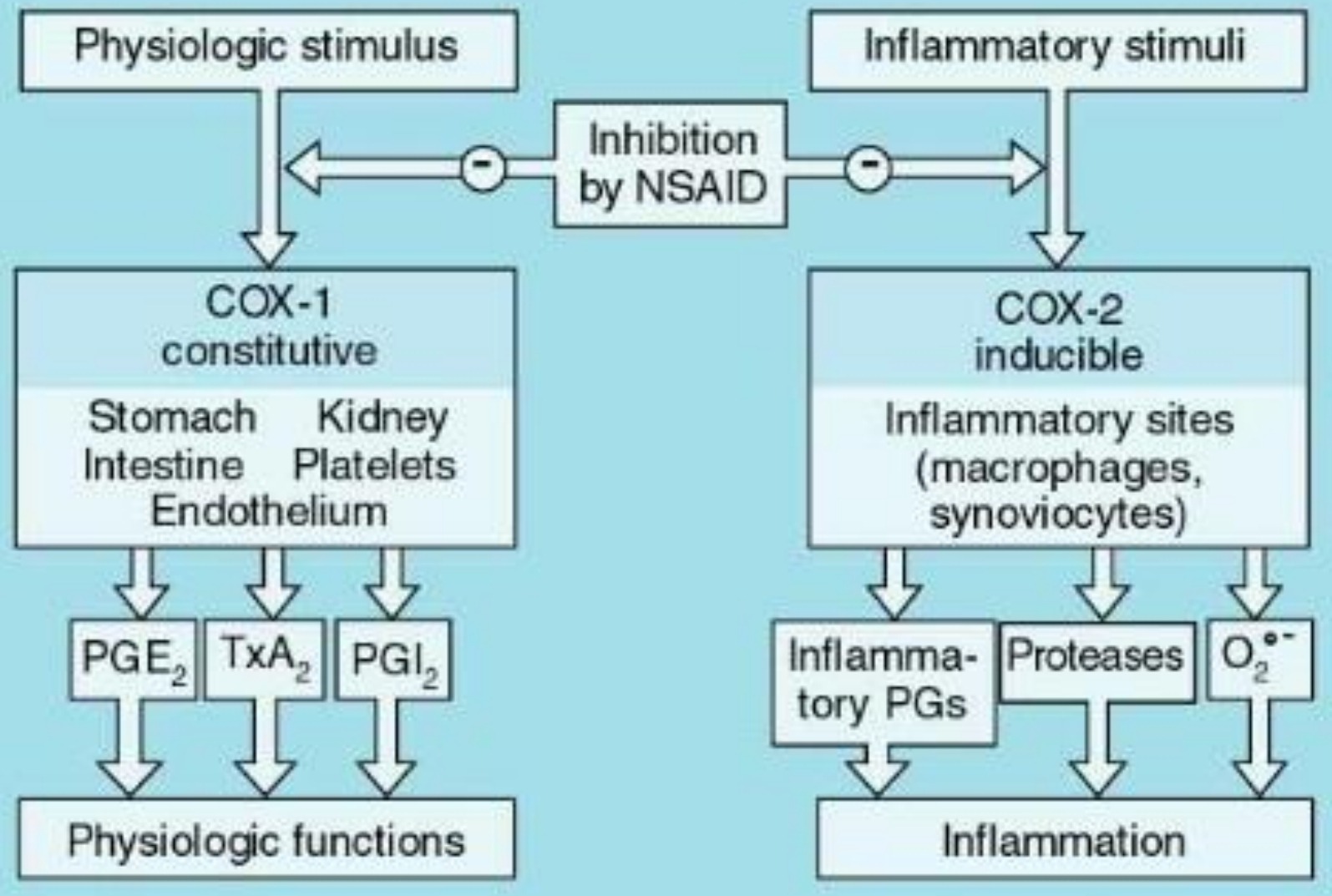
Inflammatory pathways

- Cyclooxygenase (COX) pathway of arachidonate metabolism produces prostaglandins
- Effects on blood vessels, on nerve endings, and on cells involved in inflammation.
- The lipoxygenase pathway of arachidonate metabolism yields leukotrienes
- have a powerful chemotactic effect on eosinophils, neutrophils, and macrophages and promote bronchoconstriction and alterations in vascular permeability.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 12th edition:


PHOSPHOLIPIDS IN CELL MEMBRANE
Phospholipase
CORTICOSTEROIDS
Arachidonic acid
lipoxygenase
Cycloxygenase (COX)
NSAID, ASA
Leukotrienes
LT B4 /C4 /D4 / E4
Prostaglandins
PGF2α / PGI2 / PGD2 / PGE2 /TxA2


Physiologic stimulus
Inflammatory stimuli
Inhibition by NSAID
COX-1 constitutive
Stomach Kidney
Intestine Platelets
Endothelium
COX-2 inducible
Inflammatory sites (macrophages, synoviocytes)
PGE2
TxA2
PGI2
Inflamma-tory PGs
Proteases
O2°-
Physiologic functions
Inflammation

Cyclo-oxygenase (COX)

- Exists in the tissue as constitutive isoform (COX-1).
- At site of inflammation, cytokines stimulates the induction of the 2nd isoform (COX-2).
- Inhibition of COX-2 is thought to be due to the anti-inflammatory actions of NSAIDs.
- Inhibition of COX-1 is responsible for their GIT toxicity.

Non -steroidal Anti-Inflammatory Drugs

- Analgesic
- Antipyretic
- Anticoagulant
- Anti-inflammatory (at higher doses)

Comparison of Analgesics

Feature	Narcotic (Opioids)	Nonnarcotic (nonopioid)
Efficacy	Strong	Weak
Prototype	Morphine	Aspirin
Pain Relieved	Any Type	Musculoskeletal
Site of Action	Central	Peripheral and Central
Mechanism	Specific Receptors	PG Synthesis
Danger	Tolerance & Dependence	G.I irritation
Anti-inflammatory	No	Yes
Antipyretic	No	Yes
Antiplatelets	No	Yes

Mechanisms of Action

- Fever → release of endogenous pyrogens (e.g., interleukin-1) released from leucocytes → acts directly on the thermoregulatory centers in hypothalamus → incr body T°.

  - This is assoc with incr in brain PGs (pyrogenic).

  - Aspirin prevents the T° -rising effects of interleukin-1 by preventing the incr in brain PGs.

Adverse effects are generally quite similar for all of the NSAIDs:

1. **Central nervous system:** Headaches, tinnitus, dizziness, and rarely, aseptic meningitis.
2. **Cardiovascular:** Fluid retention, hypertension, edema.
3. **Gastrointestinal:** Abdominal pain, dysplasia, nausea, vomiting, and rarely, ulcers or bleeding.
4. **Hematologic:** Rare thrombocytopenia, neutropenia, or even aplastic anemia.
5. **Hepatic:** Abnormal liver function test results and rare liver failure.
6. **Pulmonary:** Asthma.
7. **Skin:** Rashes, all types, pruritus.
8. **Renal:** Renal insufficiency, renal failure, hyperkalemia, and proteinuria

Cardiovascular

- Platelets: Inhibition of platelet COX-1-derived TxA_2 with the net effect of increasing bleeding time (inhibition of platelet aggregation)
- Endothelial COX-2 derived PGI_2 can inhibit platelet aggregation (inhibition augments aggregation by TxA_2).

Additional Cardiovascular Considerations

- *Blood vessels/smooth muscle*

COX-2 derived PGI_2 can antagonize catecholamine- and angiotensin II-induced vasoconstriction (NSAIDs can elevate bp).

- *Atherosclerosis*

  Inhibition of COX-2 can destabilize atherosclerotic plaques (due to its anti-inflammatory actions)

Renal

- COX-1 and COX-2 – generated PGs (TxA_2, PGF_2 , PGI_2 (glom), PGE_2 (medulla), powerful vasodilators) can both incr and decr Na^+ retention (natriuresis predominates), usually in response to changes in tubular Cl^-, extracellular tonicity or low bp.
- NSAIDs tend to promote Na^+ retention and can therefore increase bp. Can counteract effects of many anti-hypertensives (diuretics, ACE inhibitors and -AR antagonists).
- PGs have minimal impact on normal renal blood flow, but become important in the compromised kidney. Patients (particularly elderly and volume depleted) are at risk of renal ischemia with NSAIDs.

Gastrointestinal

- PGs (generated via COX-1)

  1) inhibit stomach acid secretion,

  2) stimulate mucus and HCO_3^- secretion, vasodilation and therefore,

  3) are cytoprotective for the gastric mucosa.
- Therefore, NSAIDs with COX-1 inhibitory activity will produce opposite effects, leading to:
- Gastric distress, gastric bleeding, sudden acute hemorrhage (*effects are dose-dependent)*

Gestation

PGs (generated from COX-2) are involved in the initiation and progression of labor and delivery. Therefore, inhibition of their production by NSAIDs can prolong gestation.

Respiratory system

High doses (salicylates) cause partial uncoupling of oxidative phosphorylation with increased CO_2 production (COX-independent effects). Increase in plasma CO_2 → hyperventilation. Even higher doses cause depression of respiration.

Other uses of NSAIDs (mechanisms less understood) -
Decreased risk of fatal colon carcinoma

The Salicylates - Aspirin

- Duration of action ~ 4 hr.
- Orally taken.
- Weak acid (pK_a ~ 3.5); so, non-ionized in stomach → easily absorbed.
- Hydrolyzed by esterases in tissues and blood to salicylate (active) and acetic acid.
- Most salicylate is converted in liver to water soluble conjugates that are rapidly excreted by kidneys.

Aspirin

- Aspirin (acetylsalicylic acid) covalently modifies and, irreversibly inhibits platelet COX. The enzyme is inhibited for the lifetime of the platelet (~8 -11 days). Effect achieved at very low dose.

Aspirin - Therapeutic Uses

- Antipyretic, analgesic
- Anti-inflammatory: rheumatic fever, rheumatoid arthritis (joint dis), other rheumatological diseases. High dose needed (5-8 g/day).
- But many pts cannot tolerate these doses (GIT); so, proprionic acid derivatives, ibuprofen, naproxen tried first.
- Prophylaxis of diseases due to platelet aggregation (CAD, post-op DVT)

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.

Acetaminophen = Paracetamol

- **Less plasma protein bound**
- **Weak PG synthesis inhibitor**
- **CNS actions.**

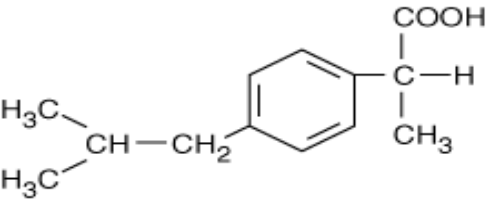
Acetaminophen = Paracetamol

- **<u>Not:</u>**
  - **antiinflammatory**
  - **Platelets inhibitor**
  - **Ulcerogenic**
  - **Teratogenic**

Acetaminophen = Paracetamol

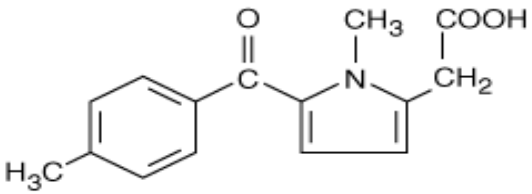
- **Toxicity**
  - **Severe hepatotoxicity with high doses**
  - **N- acetylcysteine is the antidote when given in the first 24hours.**
  - **-acetyl-p-benzoquinone**

Propionic acid derivative



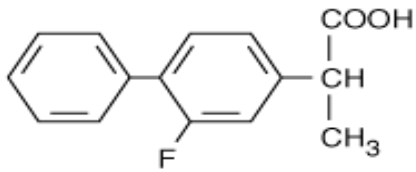
Ibuprofen

Pyrrolealkanoic acid derivative



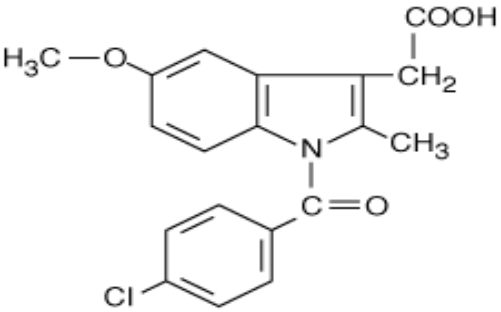
Tolmetin

Phenylalkanoic acid derivative



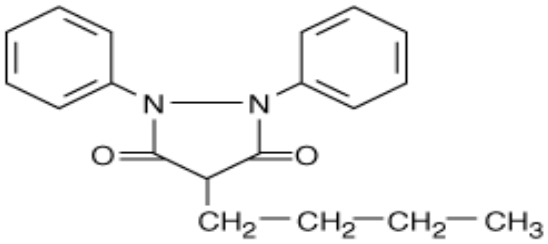
Flurbiprofen

Indole derivative



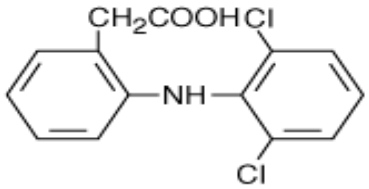
Indomethacin

Pyrazolone derivative



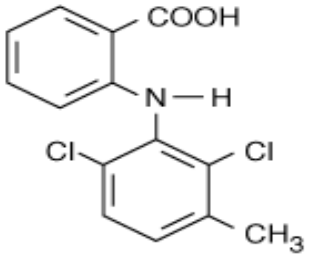
Phenylbutazone

Phenylacetic acid derivative



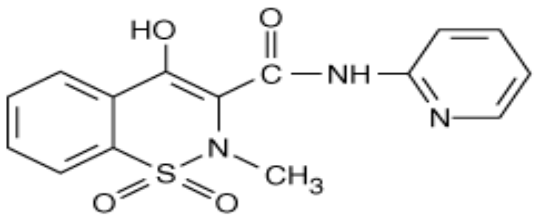
Diclofenac

Fenamate



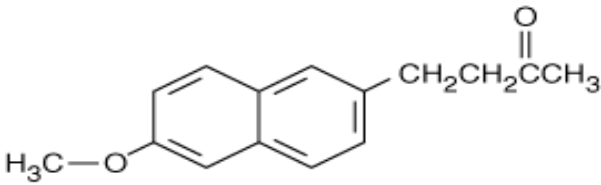
Meclofenamic acid

Oxicam



Piroxicam

Naphthylacetic acid prodrug



Nabumetone

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Acetic Acid Derivatives

- **Diclofenac:**
  - **Potent, widely used.**
  - **Available for oral, local(ophthalmic, topical gel), mouth wash, rectal and parenteral administration(for renal colic).**

Propionic Acid Derivatives

- **Ibuprofen**
- **Ketoprofen**
- **Naproxin**

Older Analgesics

- **Indomethacin**
  - **Pancytopenia**
- **Phenylbutazone**
  - **Aplastic Anemia**
- **Mefenamic Acid**

Cyclooxygenase II Inhibitors

- **Meloxicam**
- **Rofecoxib**
- **Celocoxib**

Cyclooxygenase II Inhibitors

- **Do not affect platelet function.**
- **May increase the incidence of edema and hypertension.**
- **Less gastroirritant (half of COX2-non selective drugs).**
- **Higher incidence of cardiovascular thrombotic events.**

TABLE II—SUMMARY OF CLINICALLY SIGNIFICANT NSAID DRUG INTERACTIONS

DRUG	MECHANISM	EFFECT
Anticoagulants	Displacement/ additive effect	Increased anticoagulant activity via displacement. Also, some NSAIDS affect platelet function.
Lithium	NSAIDS inhibit renal elimination of lithium	Elevated serum lithium levels
Antihypertensives	NSAIDS may cause fluid retention and edema	Decreased antihypertensive effects

Other NSAIDs

- Phenylbutazone: additional uricosuric effect. Aplastic anemia.
- Indomethacin: Common adverse rxns: gastric bleeding, ulceration, CNS most common: hallucinations, depression, seizures, headaches, dizziness.
- Proprionic acids: better tolerated. Differ in pharmacokinetics; ibuprofen, fenbufen, naproxen widely used for inflammatory joint disease and few side-effects.
- Acetaminophen: differs in effects and adverse rxn from rest. Main toxicity: hepatitis due to toxic intermediate which depletes glutathione. Treat with N-acetylcysteine.

Drugs for RA

- Nonsteroidal anti-inflammatory drugs (NSAIDs)

- Disease-modifying anti-rheumatic drugs (DMARDs)
- Synthetic
- Biologic

- Glucocorticoids

DMARDs

Disease Modifying Anti-Rheumatic Drugs

- Reduce swelling & inflammation
- Improve pain
- Improve function
- Have been shown to reduce radiographic progression (erosions)

Synthetic DMARDs

- Methotrexate
- Sulphasalazine
- Chloroquine
- Hydroxychloroquine
- Leflunomide

Methotrexate (MTX)

- Dihydrofolate reductase inhibitor
- ↓ thymidine & purine nucleotide synthesis
- “Gold standard” for DMARD therapy

- 7.5 – 30 mg weekly

- Absorption variable
- Elimination mainly renal

MTX adverse effects

- Hepatotoxicity
- Bone marrow suppression
- Dyspepsia, oral ulcers
- Pneumonitis
- Teratogenicity

- Folic acid reduces GI & BM effects
- Monitoring
- FBC, ALT, Creatinine

Sulphasalazine

- Sulphapyridine + 5-aminosalicylic acid

- Remove toxic free radicals
- Remission in 3-6 month

- Elimination hepatic

- Dyspepsia, rashes, BM suppression

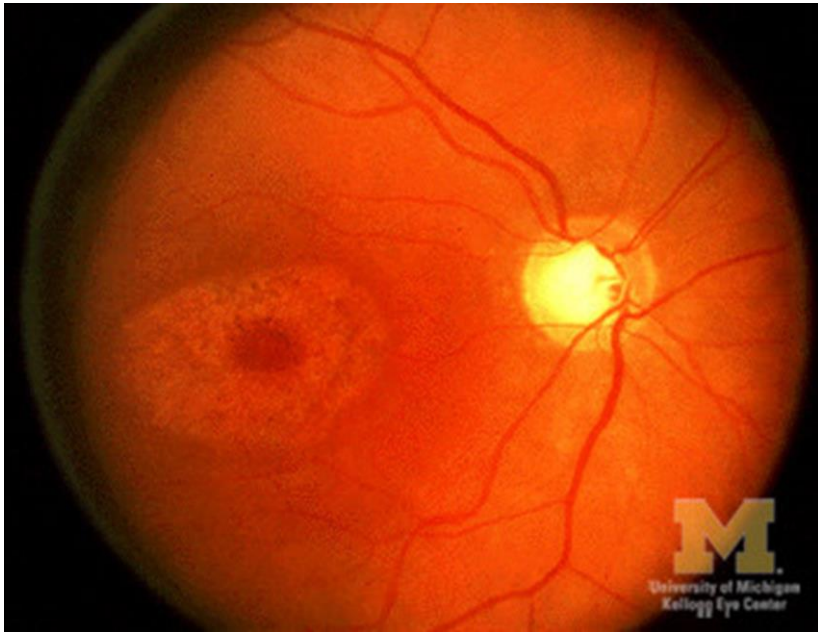
Chloroquine, Hydroxychloroquine

- Mechanism unknown
- Interference with antigen processing ?
- Anti- inflammatory and immunomodulatory

- For mild disease
- Take a month to see the effect

Side effects

- Irreversible Retinal toxicity, corneal deposits
- Ophthalmologic evaluation every 6 months



Leflunomide

- Competitive inhibitor of dihydroorotate dehydrogenase (rate-limiting enzyme in de novo synthesis of pyrimidines)

- Reduce lymphocyte proliferation

Leflunomide

- Oral
- T ½ - 4 – 28 days Elimination hepatic

- Action in one month
- Avoid pregnancy for 2 years

Side effects

- Hepatotoxicity
- BM suppression
- Diarrhoea
- rashes

Combination therapy (using 2 to 3) DMARDs at a time works better than using a single DMARD

Common DMARD Combinations

- Triple Therapy
- Methotrexate, Sulfasalazine, Hydroxychloroquine

- Double Therapy
- Methotrexate & Leflunomide
- Methotrexate & Sulfasalazine
- Methotrexate & Hydroxychloroquine

BIOLOGIC THERAPY

- Complex protein molecules
- Created using molecular biology methods
- Produced in prokaryotic or eukaryotic cell cultures

BIOLOGIC THERAPY

Monoclonal Antibodies to TNF

- Infliximab
- Adalimumab

Soluble Receptor Decoy for TNF

- Etanercept

Receptor Antagonist to IL-1

- Anakinra

Monoclonal Antibody to CD-20

- Rituximab