Pharmacology
Of Non-steroid anti-inflammatory drugs

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Nonsteroidal anti-inflammatory drugs

- NSAIDs are a class of medications used to treat pain, fever, and other inflammatory processes. This activity describes the indications, mechanism of action, administration, adverse effects, contraindications, monitoring, and important points for providers regarding NSAIDs.
- NSAIDs are a drug class use as antipyretic, anti-inflammatory, and analgesic agents. These effects make NSAIDs useful for treating muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout, migraines, and used as opioid-sparing agents in certain acute trauma cases.

- **Indications for NSAIDS include the following:**
- Inflammatory conditions
- Chronic joint disease
- Musculoskeletal pain
- Headache
- Menstrual pain
- Dental pain
- Postoperative mild to moderate pain
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NSAIDs are typically divided into groups based on their chemical structure and selectivity:

- **Non-selective $COX_{1,2}$ blockers:**
- Salicylates: Acetylsalicylic acid, sodium salicylate, salicylic acid, Methyl salicylate, phenyl salicylate, mesalazine, diflunisal
- Para-aminophenol derivatives: acetaminophen (paracetamol)
- Pyrazolone derivatives: aminopyrine, methamisole (analgin), propiphenazone, Phenylbutazone, oxyphenbutazone
- Phenylpropionic acid derivatives: (profenes) ibuprofen, naproxen, fenbufen,
- Thiaprofen, ketoprofen, phenoprofen.
- Phenylacetic acid derivatives: Diclofenac sodium, Nabumetone, phenclofenac

- Indoleacetic acid derivatives: Indometacin, Tolmetin, Ketorolac, Sulindac
- Phenamic acid derivatives: Mephenamic acid, Fluphenamic acid, Tolphenamic acid,
- Oxycams: Piroxicam, Tenoxicam, Procuazone, Azapropazone
- **COX-2 inhibitors:**
- 1. COX-2 selective inhibitors: Celecoxib, Valdecoxib, Etherecoxib Rofecoxib
- 2. Non-selective COX-2 inhibitors: Nimesulide, Meloxicam, Etodolac
- :

- **III. Drugs of different groups:**
- 1. Gold drugs: crizanol, auranofin, myocrysin
- 2. Bee venom preparations: apizatron, virapin, ungapevin, apifor, apitoxin
- 3. Drugs based on snake venom: vipraxin, nayaxin, viprosal, nizvisal, nazatox
- 4. Various anti-inflammatory agents: dimethyl sulfoxide (dimethoxide), bischofit
- Topical NSAIDs are also available for use in acute tenosynovitis, ankle sprains, and soft tissue injuries

NSAID

Non steroidal anti-inflammatory Drugs

*Classification- KD Tripathi

Non-Selective
COX Inhibitor

Preferential
COX_2 Inhibitor
Nimesulide, Diclofenac, Aceclofenac, Meloxicam, Etodolac

Selective
COX_2 Inhibitor
Celecoxib, Etoricoxib, Parecoxib

Analgesic-Antipyretic with poor Anti-inflammatory Action

Category	Example
Salicylates	Aspirin
Acetic acid derivative	Indomethacin, Nabumetone, Ketorolac,
Pyrazolone derivative	Oxyphenbutazone, Phenylbutazone
Propionic acid derivative	Ketoprofen, Flurbiprofen, Ibuproprofen, Naproxen,
Fenamate	Mephenmic acid
Enolic acid derivative	Piroxicam, Tenoxicam

Example
Paracetamol (Acetaminophen)
Metamizol, Propiphenazone
Nefopam

*Constitutive = Constant Production

Key Point (Solution) - As name Indicate NSAIDs are those agents which are used to get relief from pain, inflammation and fever. And as per the COX pathway we understand that **COX-1** and **COX-2** ultimately form prostaglandin which initiates perception of pain and inflammation. So anyhow if we block or inhibit the synthesis of PG we may reduce pain and inflammation. Although COX-1 is constitutive in nature thus it always get secreted without induction of injury and called as a house keeper so it's better to inhibit COX-2 rather than COX-1

Mechanism of action of NSAIDs

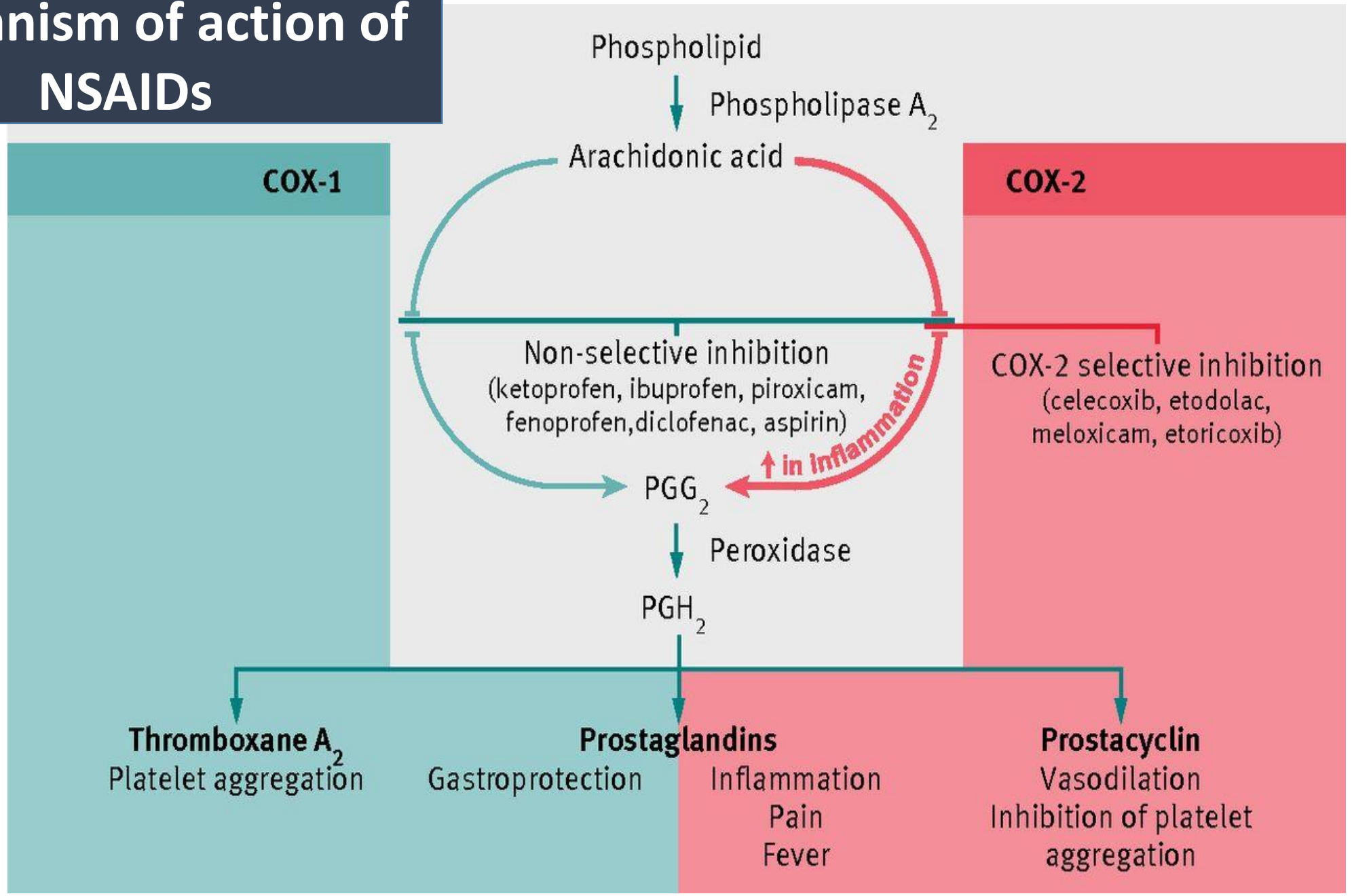
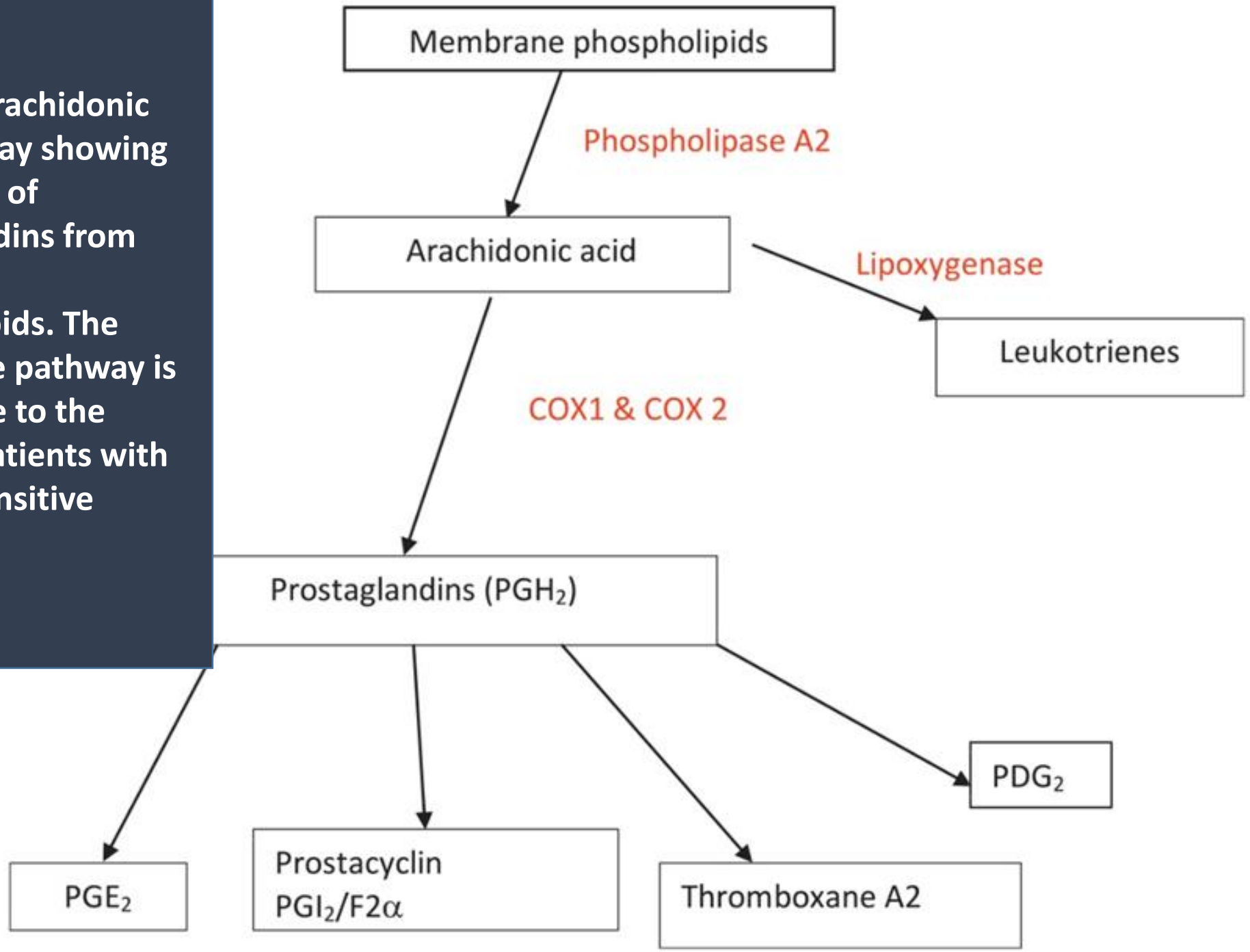
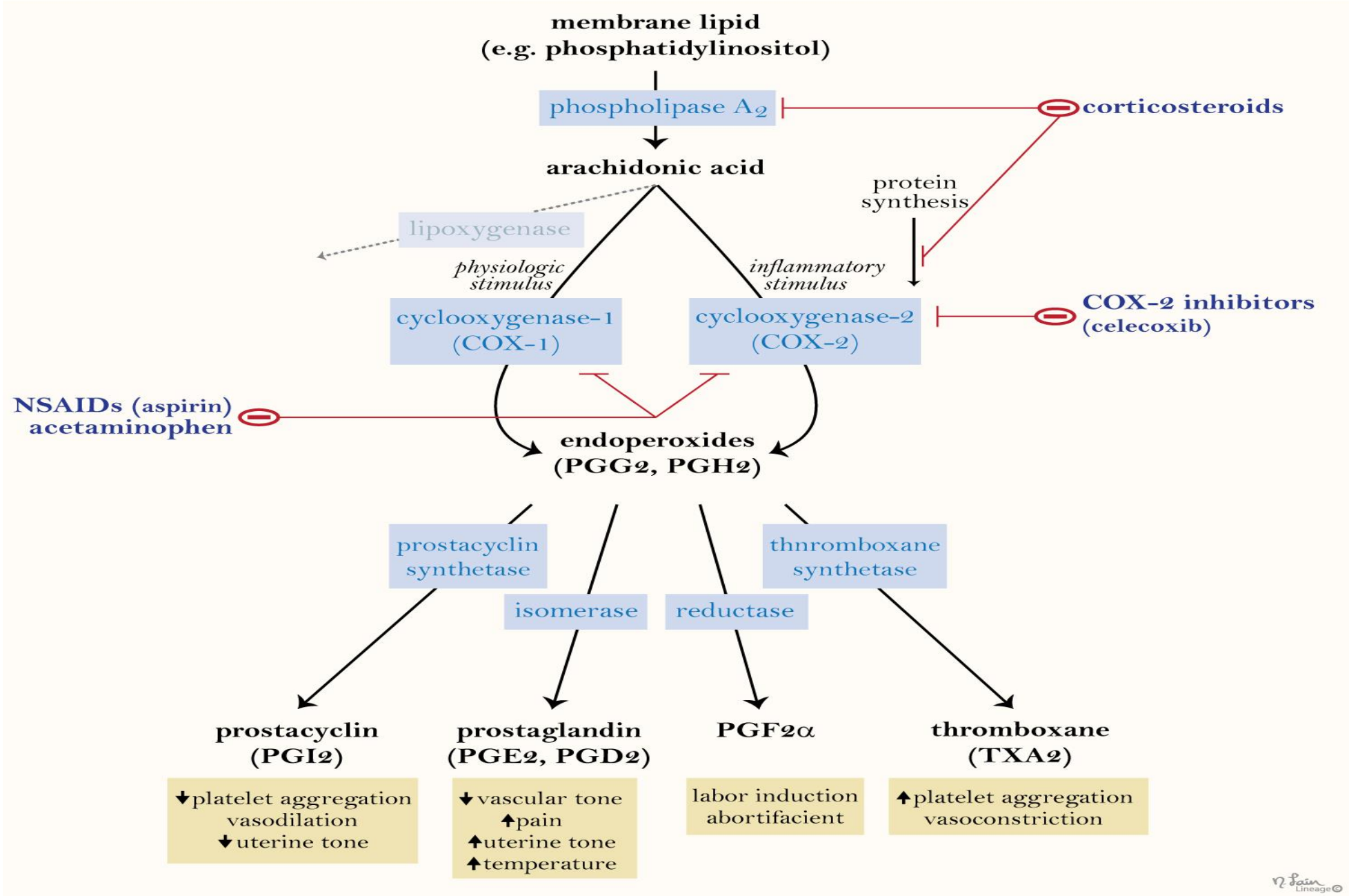


Figure 1. Arachidonic acid pathway showing production of prostaglandins from membrane phospholipids. The leukotriene pathway is responsible to the group of patients with NSAIDs–sensitive asthma.



Cyclooxygenase Inhibitors



Prostaglandin Subtype	Function
PGE_2	Sensitise nerve endings to bradykinin, increase body temperature, vasodilation, gastroprotection
$PGF2_\alpha$	Bronchoconstriction, uterine contractions
PGD_2	Bronchoconstriction
PGI_2 (prostacyclin)	Vasodilatation (vasoconstriction in pulmonary epithelium), decreased platelet aggregation, gastroprotection
TXA_2	Platelet aggregation, vasoconstriction

A wide variety of NSAIDs are available with different degrees of inhibition of COX-1 and COX-2. Their degree of each isoenzyme inhibition determines their side-effect profile.

Pharmacokinetic properties

- ✓The majority of NSAIDS are administered **orally**
- ✓They are weak organic acids and are therefore absorbed rapidly in the stomach and small intestine.
- ✓The stomach has a lower pH than the small intestine and therefore, more drug is in the more absorbable unionised form
- ✓NSAIDs have a high bioavailability due to limited first-pass hepatic metabolism.
- ✓They are highly protein-bound molecules and as a result can displace other protein-bound medications leading to increased free drug concentrations and increased risk of adverse events (eg, displacement of warfarin from albumin leading to an increased risk of bleeding).
- ✓Bioconversion is mostly hepatic with metabolites excreted in the urine.

- **Adverse effects of NSAIDs**
- NSAIDs have well-known adverse effects affecting the gastric mucosa, renal system, cardiovascular system, hepatic system, and hematologic system.
- **Gastric adverse effects** ,.
- **Renal adverse effects** ,
- **Cardiovascular adverse effects** can also be increased with NSAID use; these include MI, thromboembolic events, and atrial fibrillation. Diclofenac seems to be the NSAID with the highest reported increase in adverse cardiovascular events.
- **Respiratory adverse effects**
- **Hepatic adverse effects**
- **Hematologic adverse effects** ,
- **Bone Healing** ,

Acetilsalicylic acid

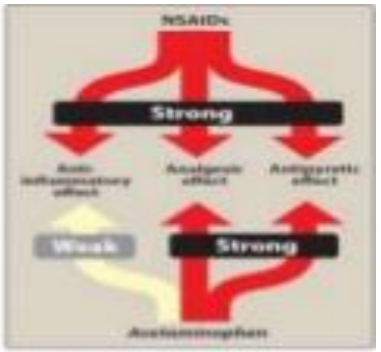
Pharmacological effects:

- Antiinflammatory (high dose)
- Analgetic (moderate dose)
- Antipyretic (moderate dose)
- Antiplatelet (low dose)

Side effects:

- Gastrointestinal irritation
- Salicylism: tinnitus, vertigo, J.. hearing- often first signs of toxicity
- Bronchoconstriction
- Reye syndrome: encephalopathy
- hemorrhage
- Chronic use: associated with renal dysfunction
- Drug interactions: ethanol (i gastrointestinal bleeding) and warfarin (i effects), and uricosurics (J.. effects)

Paracetamol



- **Mechanism of Action**
  - The drug is **only a weak COX-1 and COX-2 inhibitor** in peripheral tissues, which accounts for its **lack of anti-inflammatory effect.**
  - Evidence suggests that acetaminophen may inhibit a third enzyme, COX-3, in the CNS.
- **Uses**
  - **As antipyretic**
  - **As analgesic:** To relieve headache, toothache, dysmenorrhoea, etc.
  - It is the preferred analgesic and antipyretic in patients with peptic ulcer, bronchial asthma and children.

Acetaminophen - COX-III inhibitor (CNS)

- **Mechanisms**

- No inhibition of COX in peripheral tissues and lacks significant antiinflammatory

Effects

Equivalent analgesic and antipyretic activity to ASA due to inhibition of cyclooxygenases

- **Comparisons with ASA:**

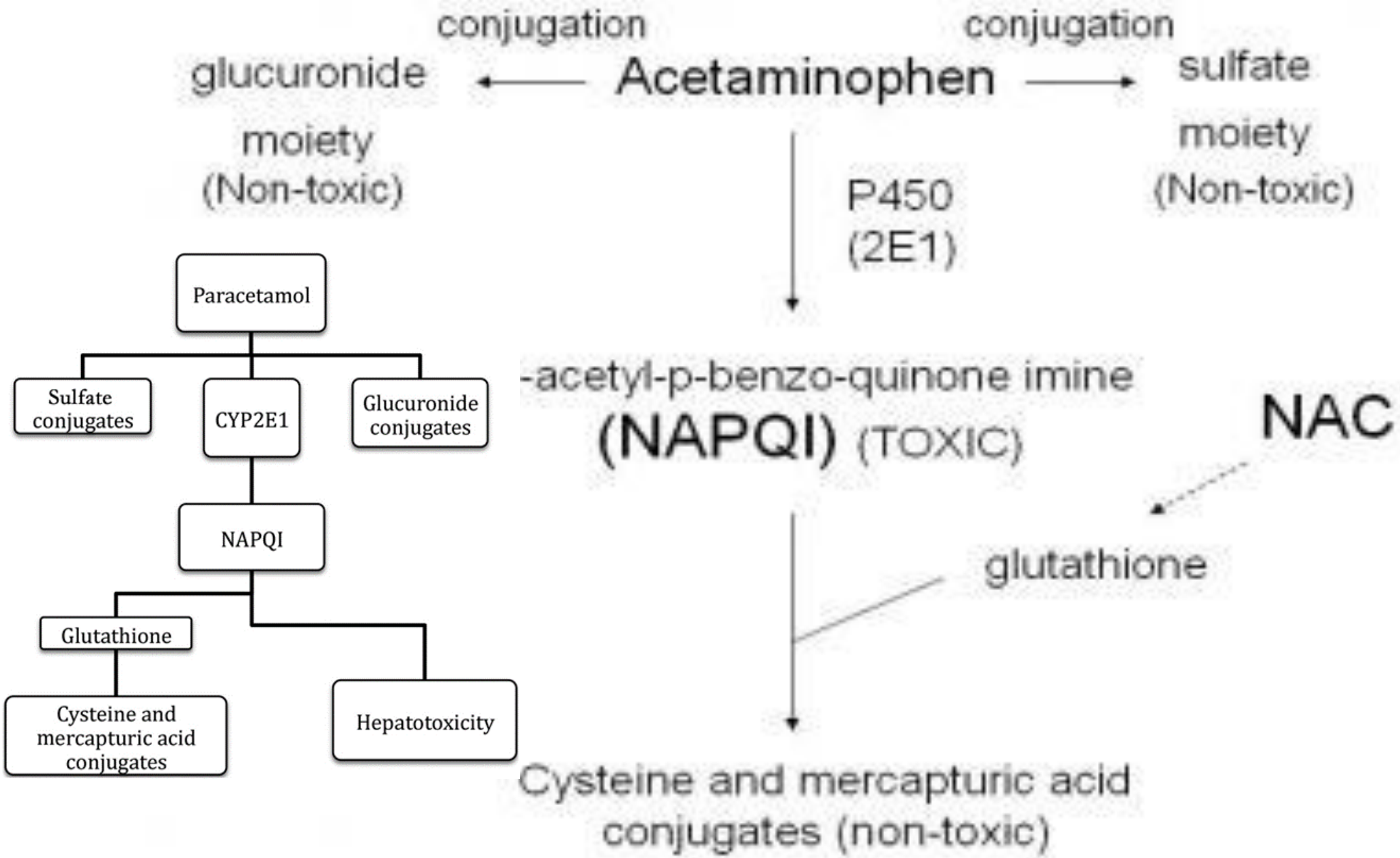
No antiplatelet action

Not implicated in Reye syndrome

- No effects on uric acid

Not bronchospastic (safe in NSAID hypersensitivity and asthmatics)

- Gastrointestinal distress is minimal at low to moderate doses


conjugation
conjugation
glucuronide
Acetaminophen
sulfate
moiety
(Non-toxic)
moiety
(Non-toxic)
P450
(2E1)
Paracetamol
Sulfate conjugates
CYP2E1
Glucuronide conjugates
-acetyl-p-benzo-quinone imine
(NAPQI) (TOXIC)
NAC
NAPQI
glutathione
Glutathione
Cysteine and mercapturic acid conjugates
Hepatotoxicity
Cysteine and mercapturic acid
conjugates (non-toxic)

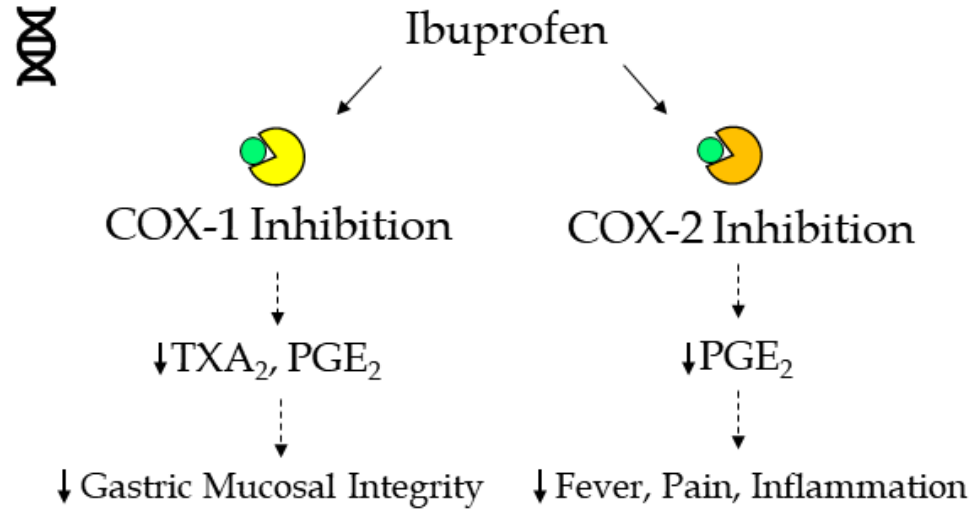
Other NSAIDs

- Reversible inhibitors of COX 1 and COX 2, with analgesic, antipyretic, and antiinflammatory actions, include:
- metamizol
- Ibuprofen Naproxen
- diclofenac
- Indomethacin
- Ketorolac
- Sulindac Nabumeton

Ibuprofen (Motrin®, Caldolor®, Advil®)

Non-Selective COX Inhibitor

- **Arthritis**
  - Osteoarthritis: 300-800 mg PO TID-QID, lowest effective dose, shortest possible duration
  - Rheumatoid Arthritis: 300-800 mg PO TID-QID
- **Dysmenorrhea**
  - 400 mg PO Q4-6h PRN
- **Inflammation**
  - Fever: 200-400 mg PO Q4-6h PRN
  - Acute Gout: *Off-label*: 600 mg PO QID, or 800 mg PO TID
  - SLE: *Off-label*: PO PRN, <3000 mg/day
- **Pain**
  - Mild-Moderate: 400 mg PO Q4-6h PRN



GI Ulcer/Perforation
Thromboembolism
Hypertension
Bronchospasm
Hepato-/Nephrotoxicity
Hematological Cytopenias
SJS/TEN

Hypersensitivity
NSAID Asthma/Urticaria
Pregnant > 30w
CABG Perioperative

Hepatic Metabolism
CYP2C9 Substrate

½-Life: 1.8-2h
Renal Excretion

Pregnancy Category B (<26w)

$0.13/800 mg tablet (Generic)

COX 2 Inhibitors:

Selective: Celecoxib

- Compared with conventional NSAIDs, it is no more effective as an antiinflamrnatory agent.
- Primary differences are:

- Less gastrointestinal toxicity
- Less antiplatelet action

- However, it may possibly exert prothombotic effects via inhibition of endothelial cell function (MI and strokes) .
- Cross-hypersensitivity between celecoxib and sulfonamides

COX 2 Inhibitors: Compared with conventional NSAIDs, it is no more effective as an antiinflamrnatory agent.

Primary differences are:

- Less gastrointestinal toxicity
- Less antiplatelet action

- Semi-selective:

Meloxicam

Nimesulid

Etodolac

- Selective:

Celecoxib - it may possibly exert prothombotic effects via inhibition of endothelial cell function (MI and strokes)

Rofecoxib

Etericoxib

Valdecoxib