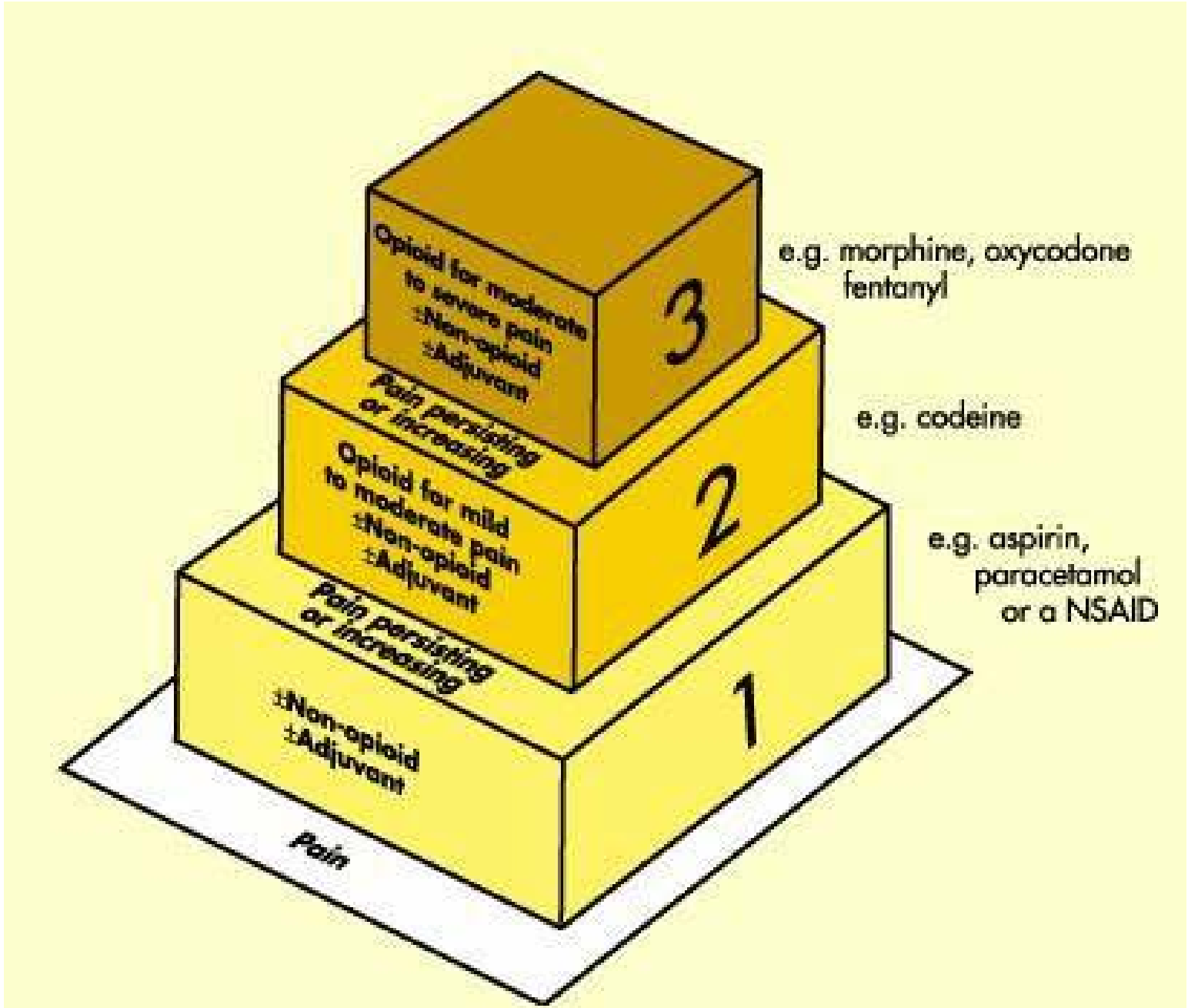
Non-Steroidal Anti-Inflammatory Drugs

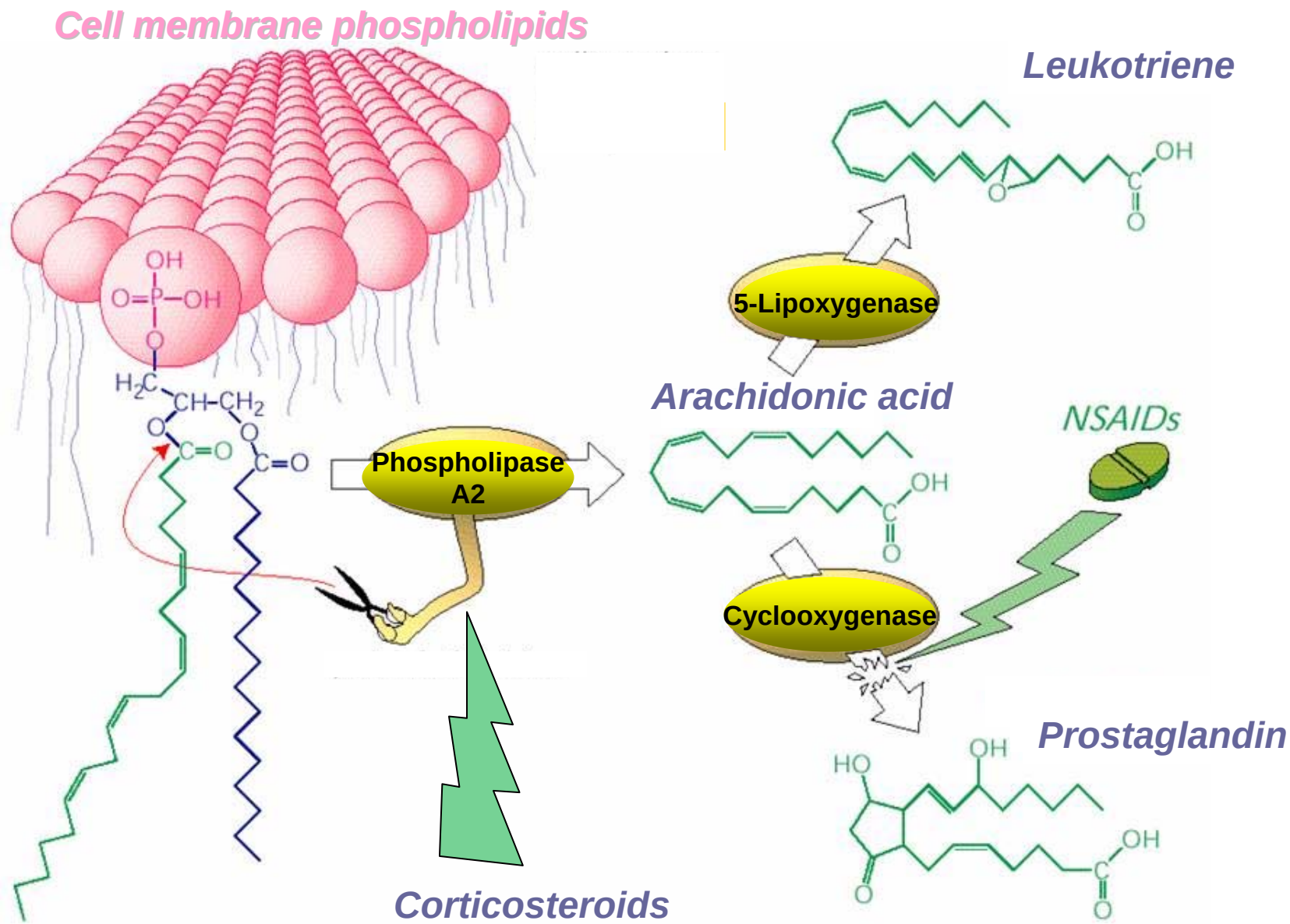
(NSAIDs)

NSAIDs

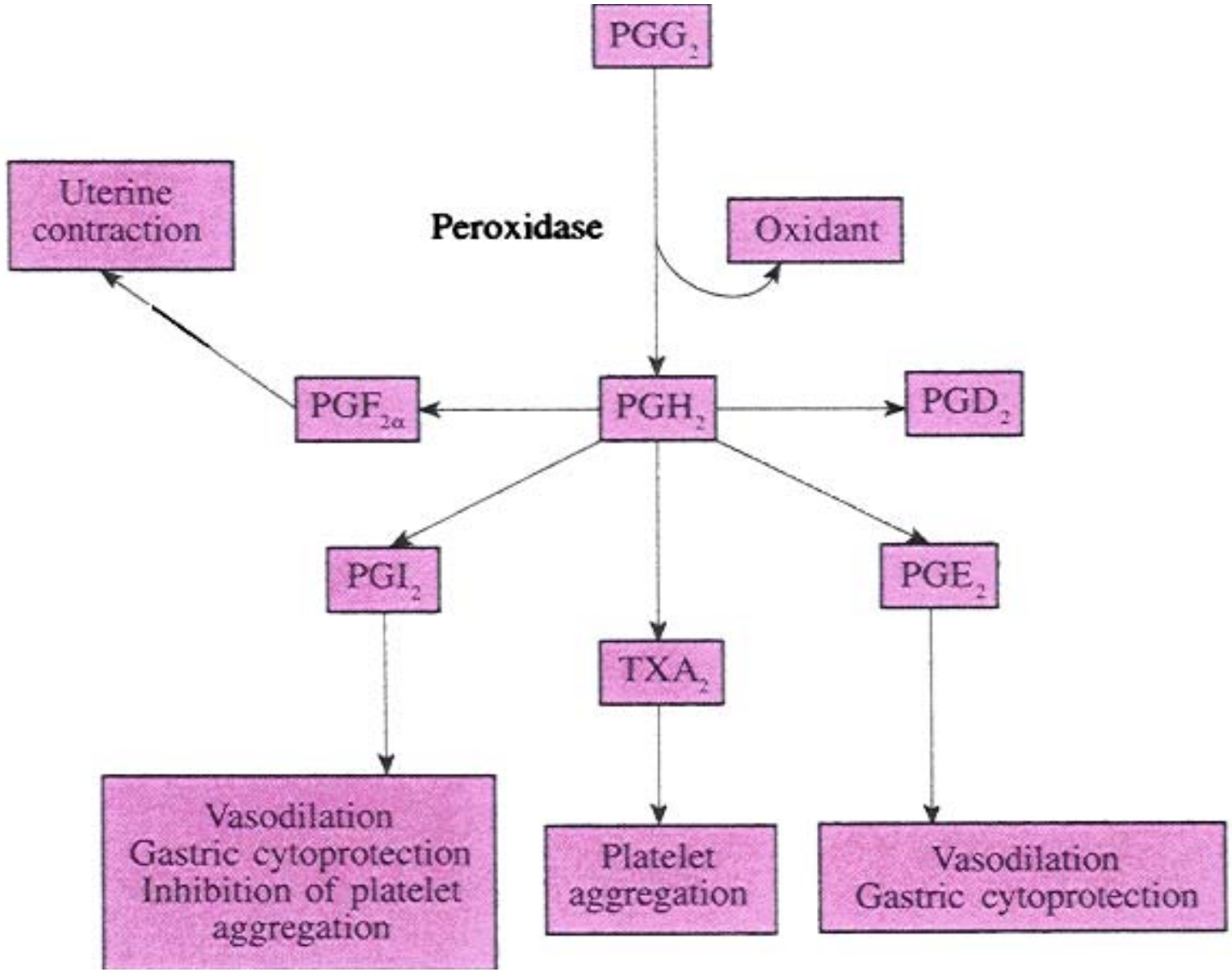
- “Non-steroidal” to distinguish them from corticosteroids
- Actions:
  1. Antipyresis
  2. Analgesia (mild to moderate pain)
  3. Anti-inflammation
  4. Anticoagulation (Aspirin)
- Uses:
  1. Minor aches and pains (moderate doses)
  2. Rheumatoid arthritis (higher, chronic doses)


3
Opioid for moderate to severe pain
±Non-opioid
±Adjuvant
e.g. morphine, oxycodone fentanyl
Pain persisting or increasing
2
Opioid for mild to moderate pain
±Non-opioid
±Adjuvant
e.g. codeine
Pain persisting or increasing
1
±Non-opioid
±Adjuvant
e.g. aspirin, paracetamol or a NSAID
Pain

NSAIDs


Cell membrane phospholipids
Leukotriene
5-Lipoxygenase
Arachidonic acid
NSAIDs
Phospholipase A2
Cyclooxygenase
Prostaglandin
Corticosteroids

Properties of Prostaglandins



Excessive prostaglandins

1. Inflammation:

- Increased prostaglandin synthesis is usually detected at the site of local inflammation.

- Certain types of prostaglandins cause
  - Vasodilatation
  - Increase blood flow
  - Increase capillary and vascular permeability (edema)
  - and increase the effect of histamne and bradykinin.

Excessive prostaglandins

2. Pain:

- Prostaglandins help mediate painful stimuli

- They don’t directly produce pain

- They sensitize pain receptors to bradykinin, a local mediator of pain released during inflammation

Excessive prostaglandins

3. Fever:

- Fever is often initiated by pyrogen interleukin-1 released from leukocytes in the inflammation process.
- In the hypothalamus, pyrogen-IL-1 stimulates the generation of PGEs (e.g. PGE2)
- PGEs cause elevation of the set-point for temperature.
- NSAIDs reduce elevated temperature by:
  - peripheral vasodilatation of blood vessels and enhanced sweating
  - inhibit PGEs production in the hypothalamus.
- Normal body temperature is not affected by NSAIDs

Excessive prostaglandins

4. Thrombus Formation:

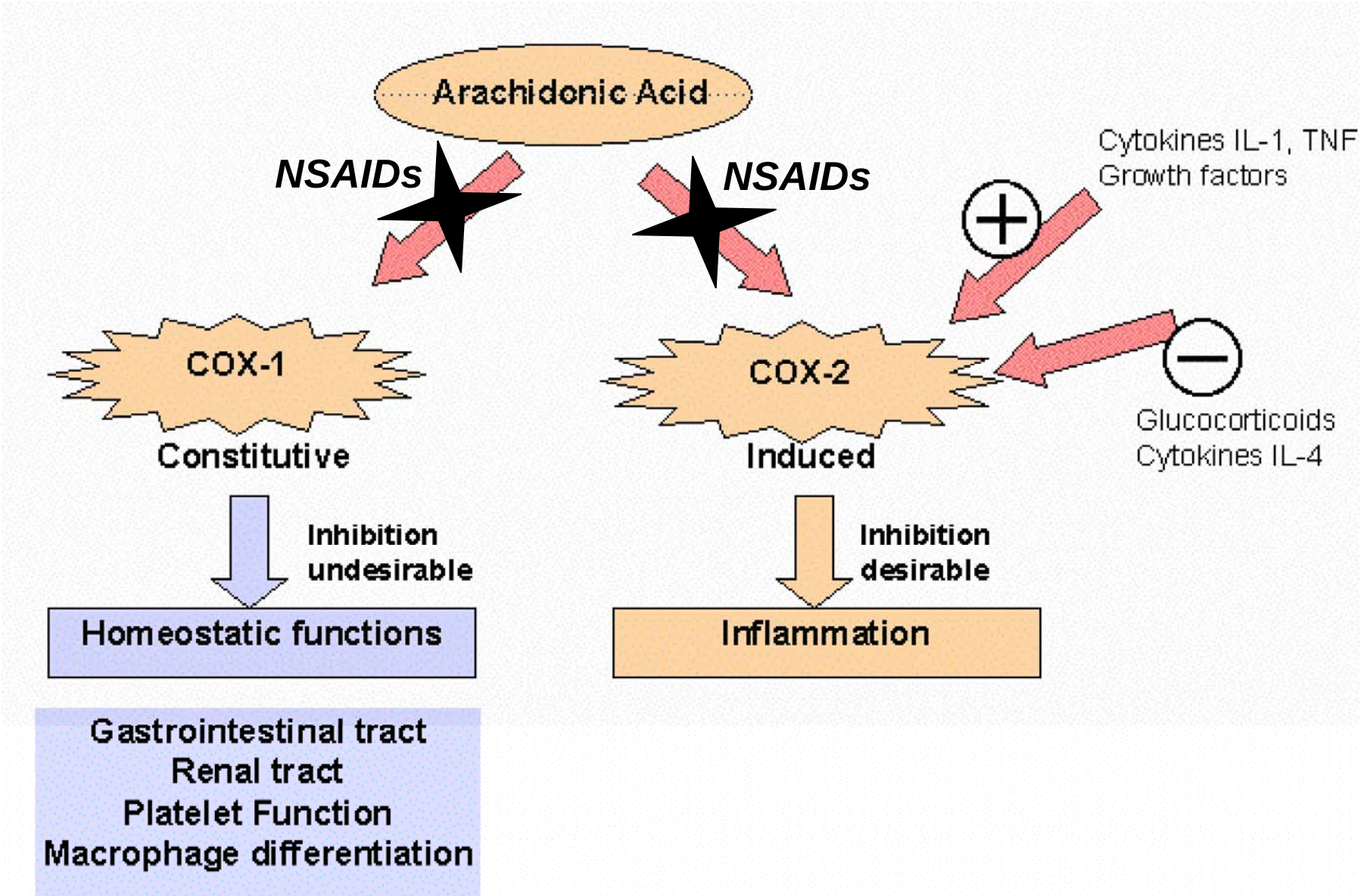
- Blood clot formation is associated with a prostaglandin called thromboxanes or TXA_2

- TXA_2 causes platelet aggregation resulting in clot formation.

Cyclooxygenase (COX)

- 3 isoforms of cyclooxygenase:
  - COX-1:
    - Constitutive enzyme expressed in all tissues
    - Inhibition of COX-1 may be responsible for many adverse effects of NSAIDs (prevents beneficial effects of prostaglandins)
  - COX-2:
    - Inducible enzyme stimulated by inflammatory factors.
    - Inhibition of COX-2 (inducible) may be responsible for therapeutic effects of NSAIDs
  - COX-3

NSAIDs


Arachidonic Acid
NSAIDs
NSAIDs
Cytokines IL-1, TNF
Growth factors
COX-1
COX-2
Constitutive
Induced
Glucocorticoids
Cytokines IL-4
Inhibition
undesirable
Inhibition
desirable
Homeostatic functions
Inflammation
Gastrointestinal tract
Renal tract
Platelet Function
Macrophage differentiation

Selectivity of NSAIDs to COX

- Aspirin
- Indomethacin
- Piroxicam
- Sulindac

} More effective in inhibiting COX-1

- Ibuprofen
- Meclofenamate

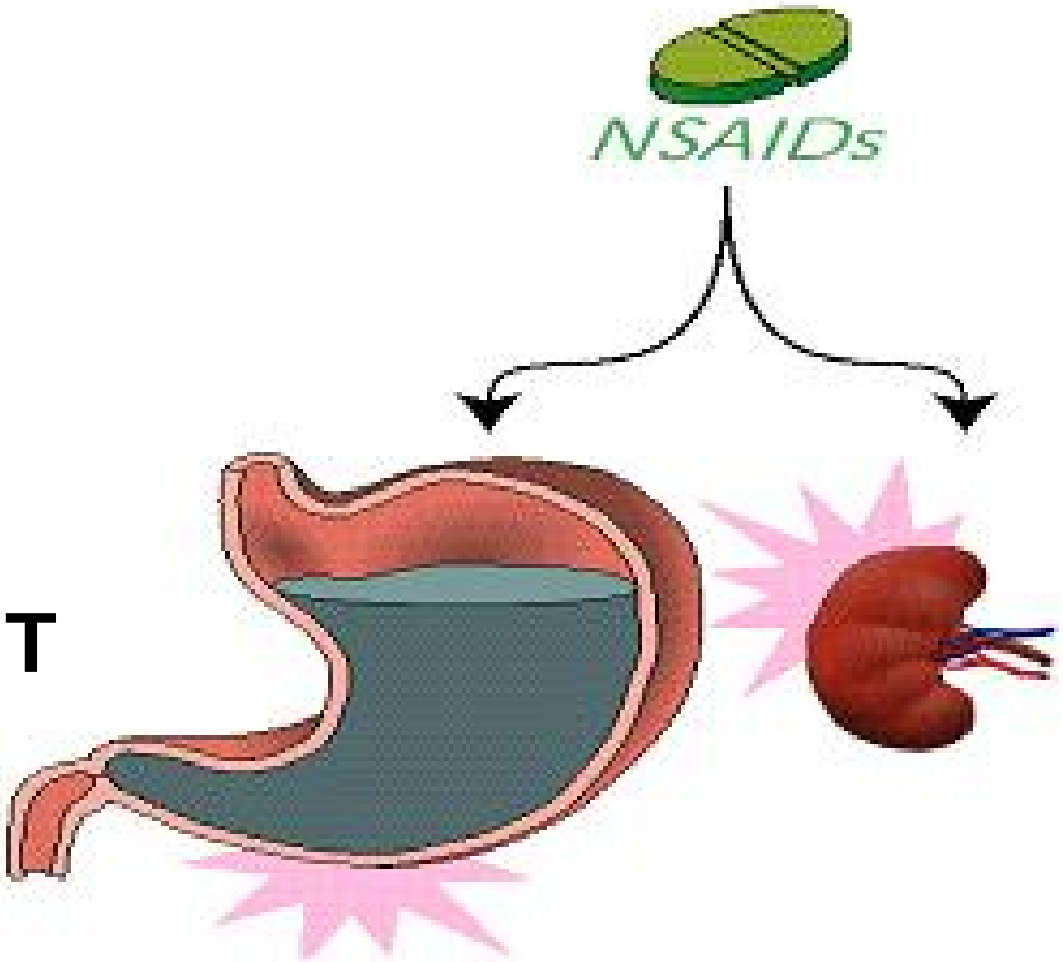
} Inhibit both enzymes equally

- Indomethacin and diclofenac both reduce the synthesis of PGs and LTs

NSAIDs

- Paracetamol (acetaminophen) has little or no anti-inflammatory action
- Indomethacin and piroxicam are more strongly anti-inflammatory than the others
- Sulindac has strong oxygen-radical-scavenging effects (decrease tissue damage).

Common unwanted effects of NSAIDs

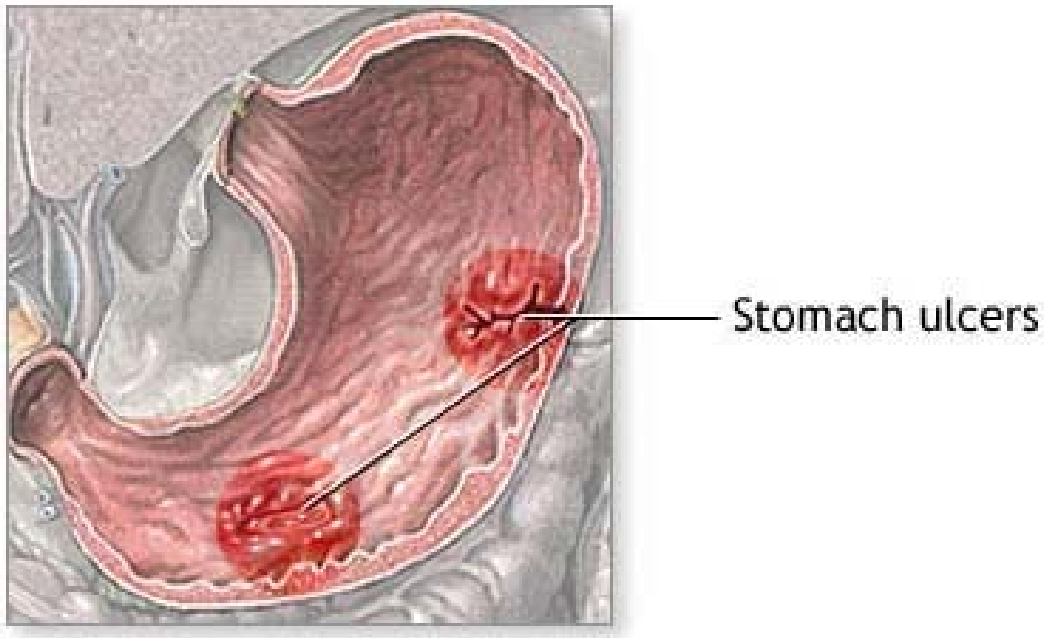


GIT

Renal

Common unwanted effects of NSAIDs

GIT:



- Dyspepsia, diarrhea, nausea, vomiting, gastric bleeding and ulceration

- Oral misoprostol (PG analogues) or proton pump inhibitor can diminish this effect

Common unwanted effects of NSAIDs

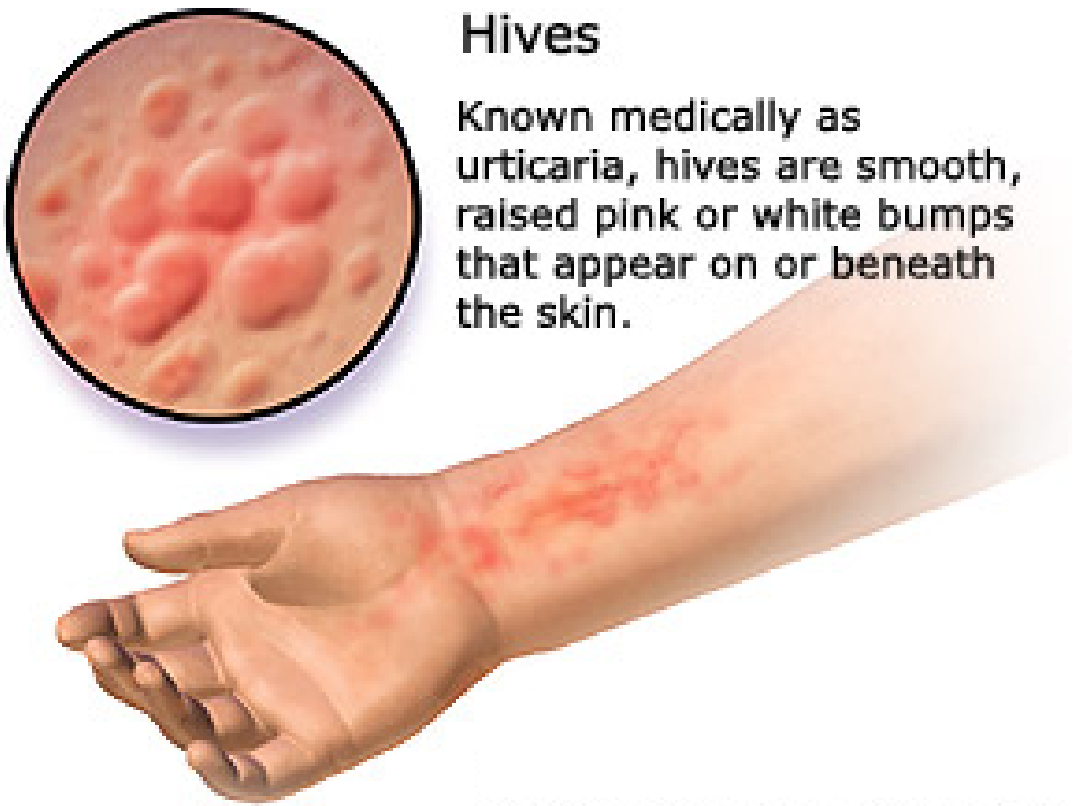
Renal:

- Reduced kidney function (revesible)
- Nephrotoxicity
- Analgesic nephropathy (esp. chronic and high doses of phenacetin and acetaminophene)

Common unwanted effects of NSAIDs

Skin reaction:

- Rashes, urticaria and photosensitivity



Common unwanted effects of NSAIDs

Less common side effects:

- Liver disorder
- Bone marrow depression

General pharmacokinetic of NSAIDs

- Most of them are well absorbed
- Food does not substantially change their bioavailability
- Highly metabolized in the liver (CYP3A and CYP2C)
- Renal excretion is the most important route for final elimination.
- Most of NSAIDs are highly protein-bound (>98%) to albumin
- All NSAIDs can be found in synovial fluid after repeated doses

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

Aspirin

- Low dose of aspirin (81 mg) is effective in some cardiovascular disorders (reduces risk of transient ischemic attacks, stroke, or MI)

- Inhibits platelet aggregation by blocking thromboxane A2 (antiplatelet action)

- Aspirin should be stopped 1 week prior to surgery to avoid bleeding complications

Pharmacokinetics of Aspirin

- Rapidly absorbed
- Rapidly hydrolyzed to acetic acid and salicylate by esterase in tissue and blood
- Salicylate bind to albumin (saturable)
- When the total body load of salicylate exceeds 600 mg this will lead to increase unbound fraction, metabolic pathway become saturated and the drug excreted unchanged
- As dose increase the elimination half-life increase

Unwanted Effects of Aspirin

- Salicylism (chronic and high doses)
  - Ringing in the ears (tinnitus)
  - Vertigo
  - Decrease hearing
  - Nausea, vomiting

- Reye's syndrome
  - Liver disorder
  - CNS disturbance (encephalopathy)
  - Should not be used in children with viral infection

Unwanted Effects of Aspirin

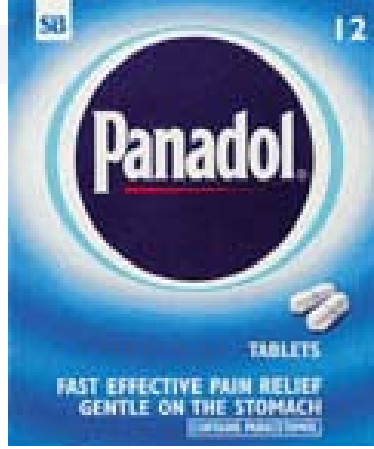
- Interactions:
  - Increase the risk of bleeding with warfarin
  - Should not be used in gout (reduces urate excretion)
  - Contraindicated in patients with hemophilia
  - Not recommended during pregnancy

Aspirin

- In the previous, aspirin was the standard against which other NSAIDs are compared but now ibuprofen is the standard

- Aspirin is now less often used as an anti-inflammatory medication (Ibuprofen as effective as aspirin but safer than aspirin)

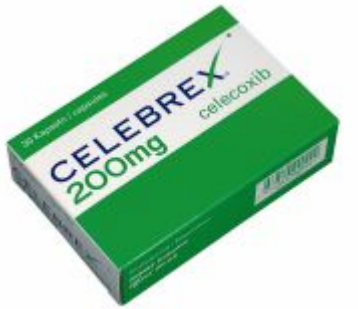
Acetaminophen (paracetamol)



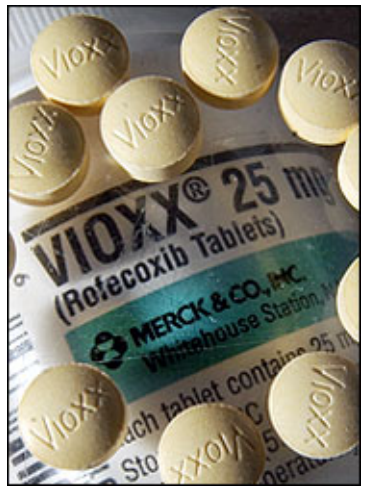
- Weak anti-inflammatory
- Selective inhibitor of COX-3 (hypothalamus?)
- Chronic and large doses may increase the risk of kidney damage
- Toxic doses cause a fatal hepatotoxicity (nausea & vomiting). Treated by gastric lavage followed by activated charcoal
- Soon after ingestion, N-acetylcysteine (IV) or methionine (oral) can prevent liver damages by increasing glutathione formation in the liver

Selective COX-2 Inhibitors

- Celecoxib
  - Celebrex



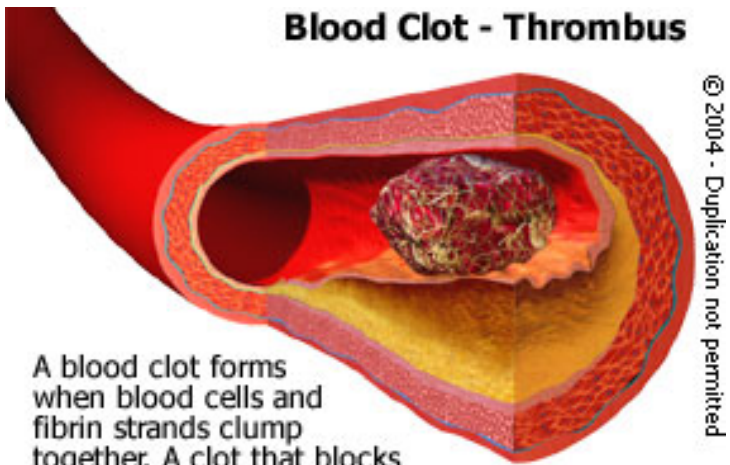
- Rofecoxib
  - Vioxx withdrawn from market
  - Two-fold increase in CV morbidity and mortality

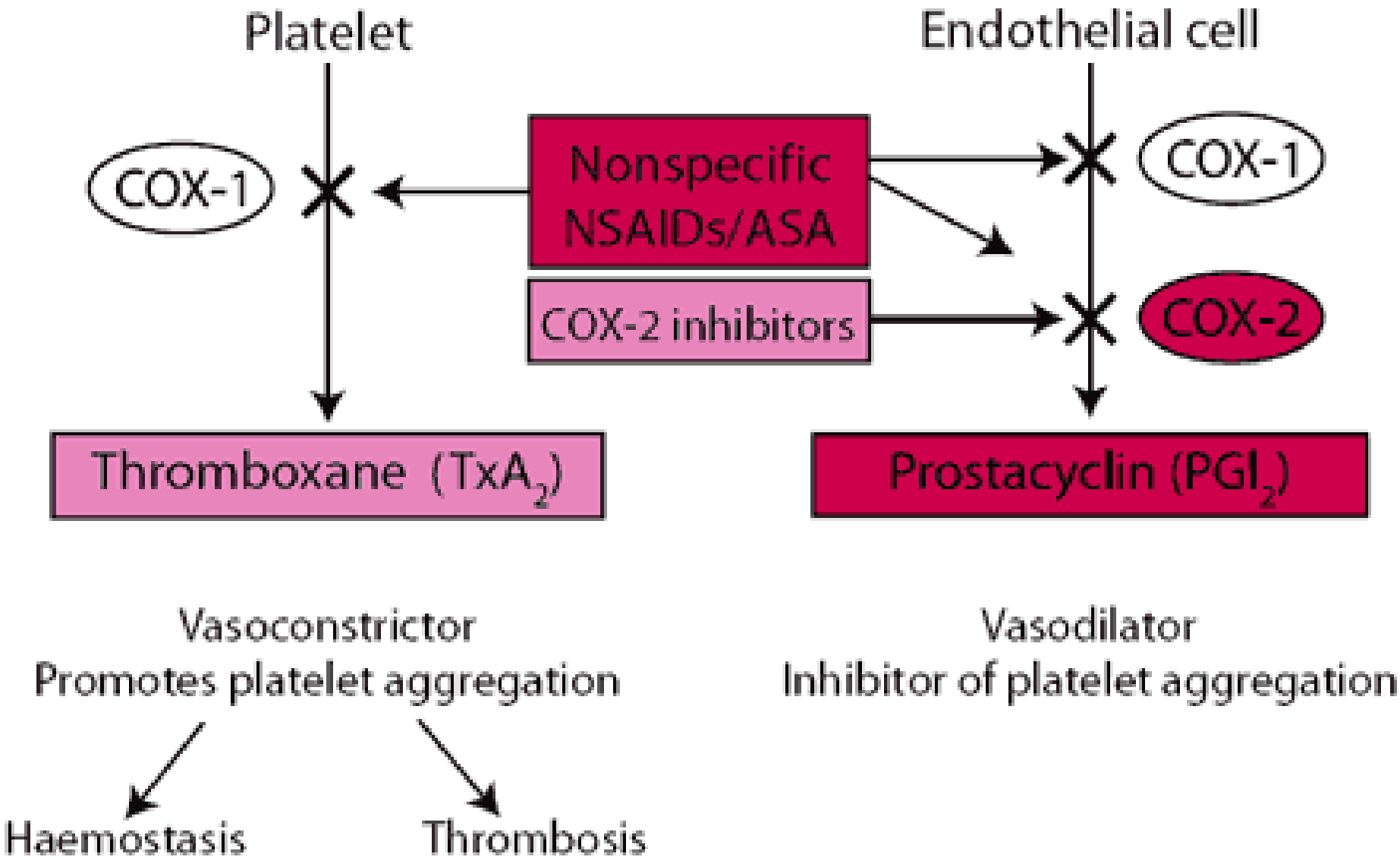


- Valdecoxib
  - Bextra

Selective COX-2 Inhibitors

- Reduced GI adverse effects (but can occur)
- Anti-inflammatory but not antiplatelet activity.
- Antiarthritic agents.
- Analgesic (dysmenorrhea and after dental and orthopedic surgery)
- Increased thrombotic cardiovascular adverse events




Platelet
Endothelial cell
COX-1
Nonspecific
NSAIDs/ASA
COX-1
COX-2 inhibitors
COX-2
Thromboxane (TxA2)
Prostacyclin (PGI2)
Vasoconstrictor
Promotes platelet aggregation
Vasodilator
Inhibitor of platelet aggregation
Haemostasis
Thrombosis

NSAIDs

- **Diclofenac and Sulindac** :
  - Potent analgesic
  - Nonselective COX inhibitor
  - Diclofenac and misoprostol combination reduce upper GI ulceration but may result in diarrhea
  - Ophthalmic preparation to prevent post operative ophthalmic inflammation
  - Available also as IM and topical

NSAIDs

- **Diflunisal:**
  - Effective for cancer pain with bone metastases
  - Because its clearance depends on renal function, its use should be limited in patients with significant renal impairment.
- **Etodolac**:
  - Slightly more COX-2 selective than most other NSAIDs
  - Less gastric side effects than other NSAIDs

NSAIDs

- **Flurbiprofen**:
  - Nonselective COX inhibitor
  - Affects TNF-α and nitric oxide synthesis

- **Ibuprofen**:
  - 2400 mg daily is equivalent to 4 gm of aspirin in anti-inflammatory effect
  - Low doses (<2400 mg/d) has analgesic but not anti-inflammatory effects

NSAIDs

- **Indomethacin**:
  - Potent
  - Nonselective COX inhibitor
  - May also inhibit phospholipase A and C
  - Reduces polymorphonuclear leukocyte migration
  - Decreases T cell and B cell proliferation
  - Probenecid prolongs its half-life by inhibiting both renal and biliary clearance

NSAIDs

- **Ketoprofen**:
  - Nonselective COX inhibitor
  - Inhibits lipoxygenase
  - Probenecid prolongs its half-life
  - Slow-release formulation is available (once-daily)

NSAIDs

- **Ketorolac**:
  - Mainly as an analgesic (not as an anti-inflammatory)
  - Used successfully to replace morphine in some situations involving mild to moderate post surgical pain
  - Use of ketorolac for more than 5 days is associated with a significant incidence of peptic ulceration and renal impairment.

NSAIDs

- **Meclofenamate & mefenamic acid:**
  - Inhibit both COX and phospholipase A2
  - Diarrhea and abdominal pain are more common
  - Meclofenamate is contraindicated in pregnancy
  - Mefenamic acid is less effective than aspirin as an anti-inflammatory agent and is more toxic. It should not be used for longer than 1 week and should not be used in children.

NSAIDs

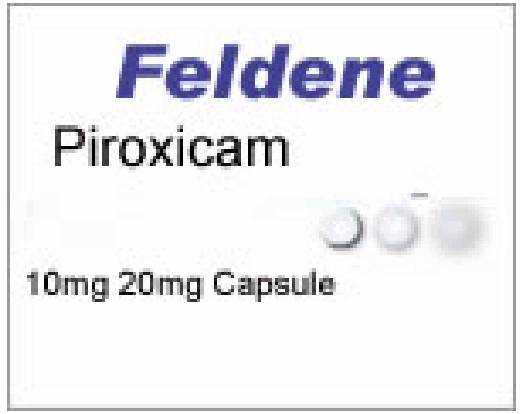
- **Meloxicam**:
  - Slightly selective to COX-2

- **Nabumetone**:
  - Less side effects
  - May cause photosensitivity

NSAIDs

- **Naproxen**:
  - Nonselective COX inhibitor
  - Available in a slow-release formulation
- **Oxaprozin**:
  - Very long half-life (Once daily)
- **Phenylbutazone**:
  - May cause aplastic anemia
  - Withdrawn.

NSAIDs



- **Piroxicam and Tenoxicam** :
  - Nonselective COX inhibitor
  - Long half-life (50-60 hours), administered once-daily.
  - Can be used in renal impairment.
  - At high dose inhibits leukocyte migration, decreases oxygen radical production and inhibits lymphocyte function

NSAIDs

- **Tiaprofen**:
  - Short half-life
  - Inhibits renal uric acid reabsorption (decreases serum uric acid)

- **Tolmetin**:
  - Nonselective COX inhibitor
  - Short half-life

Choice of an NSAID

- The choice of an NSAID requires a balance of:
  - Efficacy
  - Cost-effectiveness
  - Toxicity
  - Personal factors

Drugs	**Analgesic**	**Antipyretic**	**Anti-inflammatory**	**Toxicities & *Special features***
Acetylsalicylic Acid	+	+	+	GI/Salicylism/ Reyes Synd./ Resp. Suppress./ *Prophylactic uses*
Acetaminophen	+	+	-	Little GI tox. Hepatotox. Chronic kidney tox. *CNS Action*
Ibuprofen	+	+	+	Modest GI tox. Chronic kidney tox.
Indomethacin	+	+	++	Potent, but high incid. of GI, Salicylism
Piroxicam	+	+	++	Modest GI tox. Chronic kidney tox. *1x daily dosing*
Etodoloc	+	+	+	Less GI tox. *1x daily dosing*
Nabumetone	+	+	+	Less GI tox. *(COX2 inhibitor)*
Celecoxib	+	+	+	Little GI tox. *(first true COX2 selective agent)*