DRUGS USED TO TREAT PAIN, INFLAMMATION & GOUT

- Pain , inflammation and gout (arthritis) are major health problems

- Drugs used in the management of pain, pyrexia and inflammation can be categorized in to two major classes;

  - Non-steroidal anti-inflammatory drugs(NSAIDs)
    - ✓ have analgesic, antipyretic and anti-inflammatory property.

  - Steroidal anti-inflammatory drugs
    - ✓ mainly used to manage severe inflammation
    - ✓Inhibit production of prostinoids & leuketrienes by inhibiting phospholipase A2

- NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)

- Have analgesic , antipyretic and at in higher doses, anti-inflammatory effects.

- Usually indicated for the treatment of acute or chronic conditions where pain and inflammation are present

- Their effects are related to inhibition of *fatty acid COX* enzyme

- **COX** is responsible for the formation of important biological mediators called prostaglandins,

- Two known isoforms COX; COX-1, COX-2.

  - COX-1 is constitutive and has a 'housekeeping' role, involved in tissue homeostasis, and is responsible for production of PGs involved in gastric cytoprotection and platelet aggregation.

  - COX-2 is induced in inflammatory cells when they are activated and inflammatory mediators are produced, so it is responsible for inflammation.

  - Most 'traditional' NSAIDs are inhibitors of both isoenzymes, although they vary in the degree to which they inhibit each isoform.

  - anti-inflammatory and analgesic actions of NSAIDs is related to their inhibition of COX-2

- NSAIDs have three major pharmacologically desirable actions, stemming from suppression of prostanoid synthesis in inflammatory cells by inhibition of COX-2.

1. ***An anti-inflammatory action***: the decrease in prostaglandin E_2 & prostacyclin reduces vasodilatation and, indirectly, oedema.

2. ***An analgesic effect***: decreased prostaglandin generation means less sensitisation of nociceptive nerve endings to inflammatory mediators.

3. ***An antipyretic effect***: interleukin-1 releases prostaglandins in the central nervous system, where they elevate hypothalamic set point for temperature control, thus causing fever. NSAIDs prevent this.

❖NSAIDs are generally indicated for the symptomatic relief of the following conditions:

- ✓Rheumatoid arthritis
- ✓Osteoarthritis
- ✓Acute gout
- ✓Dysmenorrhoea (menstrual pain)
- ✓Metastatic bone pain
- ✓Headache and migraine
- ✓Postoperative pain
- ✓Mild-to-moderate pain due to inflammation and tissue injury
- ✓Pyrexia (fever)
- ✓Renal colic

Classification

NSAIDs can be classified based on their chemical structure as;

1. Salicylates

Aspirin (acetylsalicylic acid)

2. Propionic acid derivatives

Ibuprofen

Fenoprofen

Loxoprofen

3. Acetic acid derivatives

Indomethacin

Sulindac

Diclofenac

4. Selective COX-2 inhibitors (Coxibs)

Celecoxib

Rofecoxib

Parecoxib

Cont'd anti-inflammatory

Actions of NSAIDS

- Anti pyretic
- Anti inflammatory
- Analgesic
- Anti aggregatory [Reduce platelet plug and clot formation]
- Examples of NSAIDs

	COX inhibition	Anti inflammatory activity
Aspirin	1	1
Indomethacin	100	20
Meclofenamate	200	20
(Paracetamol)	0	0

Uses of NSAIDs

- Mild analgesic
  - PGI2 and PGE2 are hyperalgesic, which means that they increase the sensitivity of pain receptors to painful stimuli (mainly bradykinin)
- NSAIDs are useful to mild or moderate pain associated with inflammation.
- Fever
- Anti inflammation
  - Inflammation associated with arthritis in joints.

Adverse effects

- Gastrointestinal
  - Local irritation because NSAIDs are acidic in nature
  - Inhibit the mucosal synthesis of PGI2 and PGE2
  - Prostanoids promote blood flow to GIT- production of mucous
  - NSAIDs decrease the defense mechanisms of the GIT
- Bleeding time
  - Decrease in TxA**2** synthesis, will prevent platelet aggregation
  - inhibit production of PGI**2** produced by endothelial cells to prevent platelet sticking.
  - However, endothelial cells can regenerate COX

Individual groups of NSAIDs

1. Salicylates

- Examples; Aspirin
- Uses:
  - Analgesic
  - Antipyretic
  - Antithrombotic, 80 mg (at low dose inhibit thxA2 without affecting prostacycline, PGI2, hence DOC for thrombosis)
  - the only NSAID able to irreversibly inhibit COX-1, indicated for inhibition of platelet aggregation.
  - Rx of thrombosis and prevention of adverse CVS events.

Cont'd anti-inflammatory

- **Adverse effects:**
  - The same as for all NSAIDs, but in addition to:
- Reyes syndrome
  - encephalopathy leading to coma in children using aspirin to treat fever in certain types of infection. [chicken pox, measles and mumps]
  - Not recommended in children less than 14 years with these types of infections and fever.
- Tinnitus
- Uric acid retention
  - Aspirin at low dose competes for uric acid excretion in kidney tubules but at high dose has minimal effect, so used for gout at higher dose.

Cont’d anti-inflammatory

- **Pharmacokinetics of salicylates**
  - Aspirin (and all other NSAIDs) is acidic- well absorbed in the stomach
  - Distribution of aspirin is predominantly in plasma, 80-90% ppb.
  - Slow to enter CNS
  - To reduce the irritation on the stomach- buffered preparations can be used (e.g. Asproclear)
  - An alternative to a buffered solution is to have an enteric coating

Cont'd anti-inflammatory

2. Propionic acids

- More potent than aspirin and hence better at inhibiting COX, but comes with more side effects.
- Naproxen (naprogesic)]
  - Used to treat menstrual pain

- Ibuprofen
- Metabolised in liver & little excreted unchanged in urine
- GI iritation less frequently than aspirin
- Prutitis, rash, tinnitus, dizziness, fluid retention
- Rarely agranulocytosis, aplastic anemia.

Cont'd anti-inflammatory

3. Acetic acids

- Indomethacin
  - Treatment of acute gouty arthritis, ankylosing spongylitis.
- Sulindac
  - Prodrug of Diclofenac
  - Longer halflife
- Diclifenac
  - Potent cyclooxygenase inhibitor
  - Accumulates in synovial fluid
  - Used in RA, osteoarrthritis, acute muscloskeltal pain

- Both are highly potent drugs.
- Increase in adverse effects [GI problems]
- Predominantly used as anti-inflammatory, not as antipyretics or analgesics.
- Can be given rectally to reduce gastric irritation.

Cont’d anti-inflammatory

Selective COX 2 inhibitors [COXIBS]

- Meloxicam
- Celecoxib
- Etoricoxib
- Rofecoxib

- Less adverse effects???
- Reduces the PGs produced in pathological situations

- Coxibs
  - Have analgesic, antipyretic and anti-inflammatory effect similar to nonselective NSAIDs but with fewer GI side effect
  - No impact on platelet aggregation

Cont’d anti-inflammatory

Acetaminophen (paracetamol)

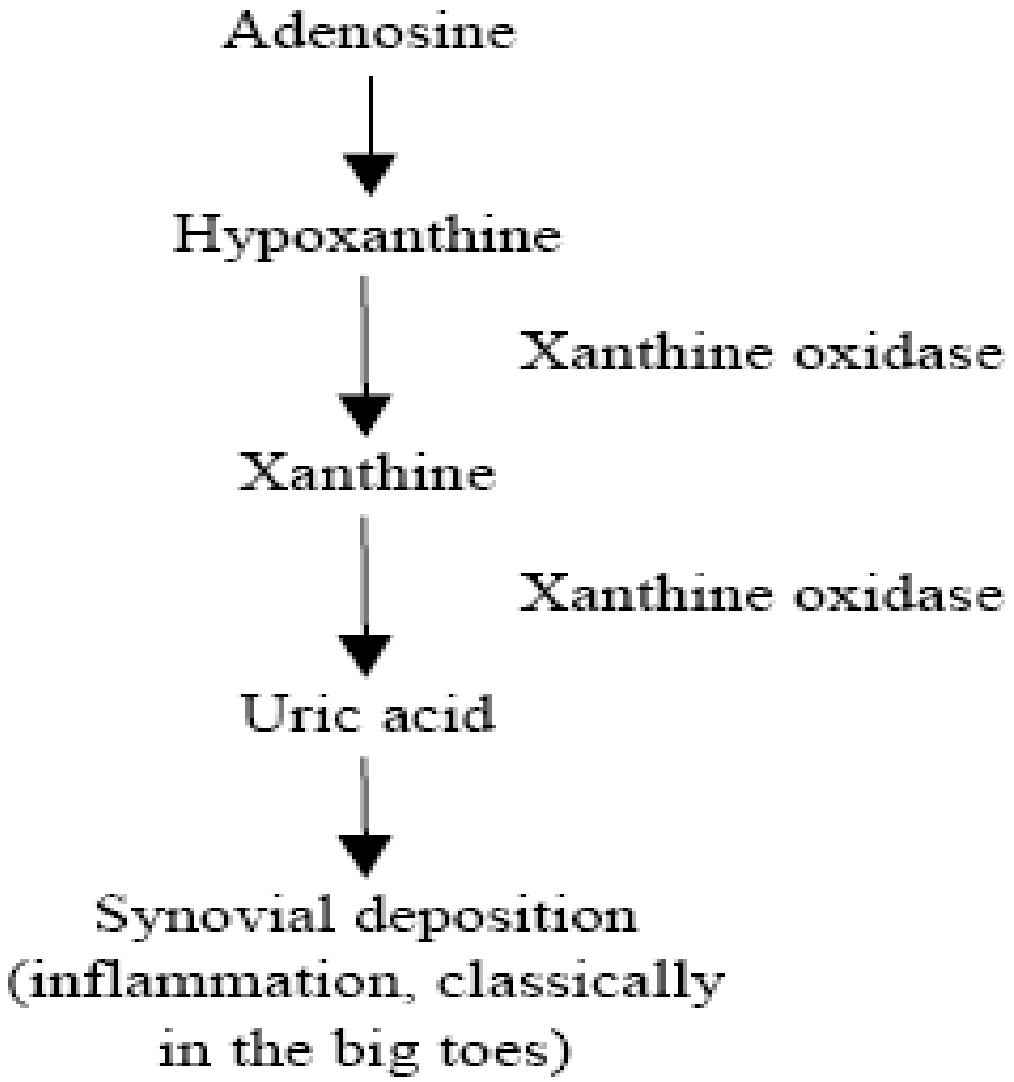
- Active metabolite of phenacetin
- Weak PG synthesis inhibitor in peripheral tissues and possesses no significant anti-inflammatory effect
- Effective analgesic and antipyretic agent
- Useful in mild to moderate pain such as head ache, myalgia, postpartum pain
- Adverse effect: hepatotoxic, hemolytic anemia and methemoglobinemia

Drugs used in the treatment of gout

- Gout is due to an accumulation of uric acid (a breakdown product of adenosine).

- High concentrations of uric acid lead to crystallisation and deposition in the synovium of joints, resulting in arthritic pain.

Cont’d anti-inflammatory



Cont’d anti-inflammatory

- Acute treatment of gout involves:
  - NSAIDs
  - Colchicine
  - Glucocorticoids
- Chronic treatment involves:
  - Allopurinol
  - Colchicine
  - Probenecid

Cont’d anti-inflammatory

- **Colchicine**
  - Antimitotic agent; It interferes with tubulin- prevents leukocyte migration
  - Reduced leukocytes in the synovial joints affected by gout would reduce the pain and discomfort
  - Can be used as an acute treatment
  - Also can be used as a chronic treatment as prevention (prophylactically) in conjunction with allopurinol

Cont’d anti-inflammatory

- **Allopurinol**
  - analogue of hypoxanthine
  - inhibits xanthine oxidase, preventing hypoxanthine from binding formed.
  - product of allopurinol with xanthine oxidase is alloxanthine
  - Alloxanthine is an irreversible inhibitor of xanthine oxidase.
  - decreased synthesis of uric acid and the concentrations fall.

Cont’d anti-inflammatory

- **Probenecid**
  - uricosuric agent (increases excretion of uric acid)
  - inhibits tubular reabsorption of uric acid in kidneys
  - limited use, not as effective as allopurinol
  - It is used when a person has an inability to excrete uric acid (in most patients, an increased uric acid is mainly due to an increase in production and so allopurinol is better suited).