Anti-inflammatory, antipyretic and analgesic agents

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Inflammation

- Inflammation is a normal protective response to tissue injury caused by
  - Physical trauma
  - Noxious chemicals
  - Microbiologic agents

- Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair
  - When healing is complete, the inflammatory process usually subsides

Inflammation

- Occurs in response to an injury or antigen
- Inflammation limits spread of injury or antigen
  - Contains injury
  - Destroys microorganism
- Acute—8 to 10 days
- Chronic—months or years

Inflammation

- Inappropriate activation of our immune system can result in inflammation, leading to immune mediated diseases such as rheumatoid arthritis (RA)

Example: Rheumatoid Arthritis (RA)

- White blood cells (WBCs) view the synovium (tissue that nourishes cartilage and bone) as non-self and initiate an inflammatory attack
- WBC activation leads to stimulation of T lymphocytes which will recruit and activate monocytes and macrophages
- These cells secrete pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-1, into the synovial cavity leading to joint destruction and other abnormalities
- B lymphocytes are also involved and produce rheumatoid factor and other autoantibodies to maintain inflammation causing progressive tissue injury, and joint damage and erosions, functional disability, pain, and reduced quality of life.

Example: Rheumatoid Arthritis (RA)

- Pharmacotherapy in the management of RA includes:
  - Anti-inflammatory and/or immunosuppressive agents that will modulate/reduce the inflammatory process with the goals of reducing inflammation and pain, halting (or at least slowing) the progression of the disease

Prostaglandins (PGs)

- Unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure

- Also referred to as eicosanoids

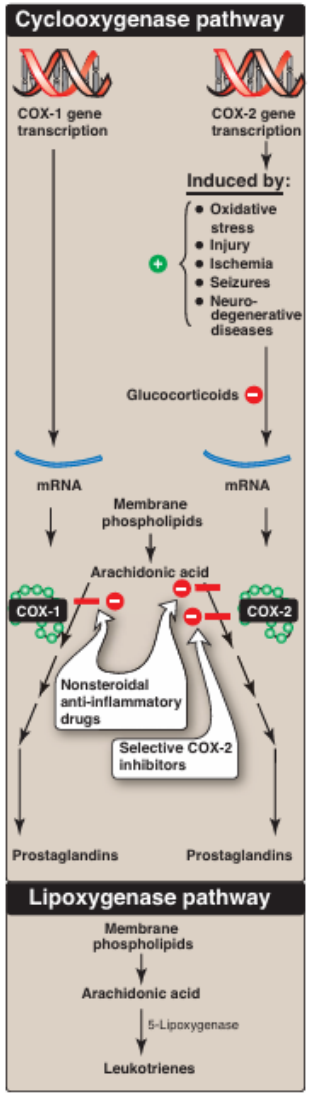
Role of prostaglandins (PGs) as local mediators

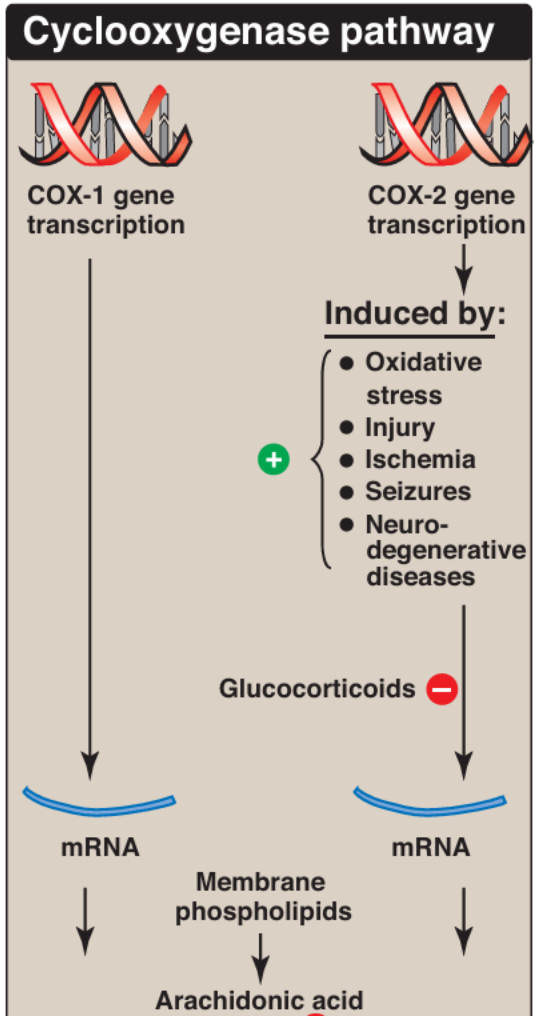
- Prostaglandins and related compounds are produced in minute quantities by virtually all tissues
- Act locally on the tissues in which they are synthesized
- Are rapidly metabolized to inactive products at their sites of action
- Thromboxanes, leukotrienes are synthesized from the same precursor (arachidonic acid)

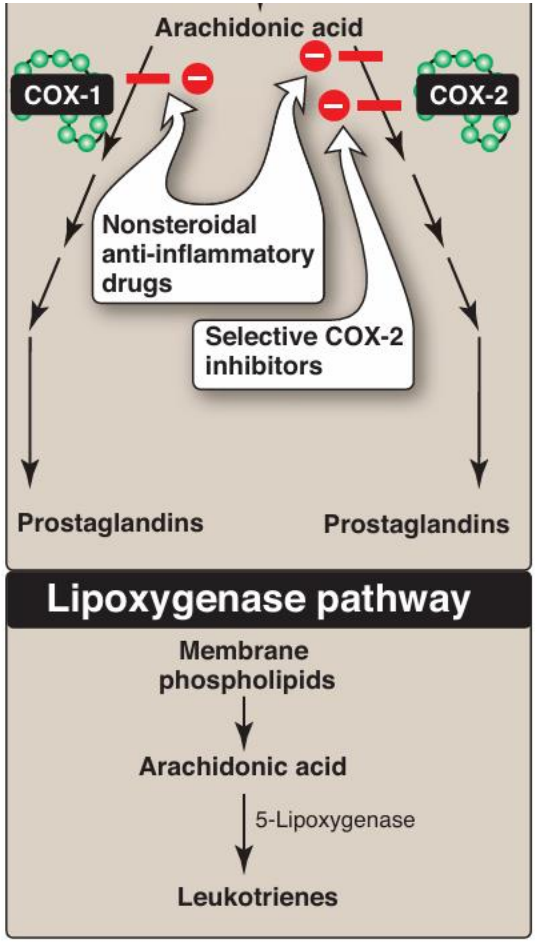
COX pathway

- Prostaglandins, thromboxanes, and prostacyclin are synthesized via the cyclooxygenase pathway.
- **Two related isoforms** of the COX enzymes exist.
  - **COX-1** is responsible for the physiologic production of prostanoids that regulate normal cellular processes
    - Gastric cytoprotection,
    - Vascular homeostasis
    - Platelet aggregation
    - Reproductive and kidney functions
  - **COX-2** causes the elevated production of prostanoids that occurs in sites of chronic disease and inflammation
    - COX-2 is constitutively expressed in tissues such as the brain, kidney, and bone.
    - Expression at other sites can be increased during states of chronic inflammation.
- Differences in binding site shape have permitted the development of selective COX-2 inhibitors

COX pathway







PG and their therapeutic uses

- PGE1 analogs
  - Alprostadil
  - Lubiprostone
  - Misoprostol
- PGF2α analogs
  - Bimatoprost
  - Latanoprost
- Prostacyclin (PGI2) analogs
  - Iloprost

Alprostadil

- PGE1 analog naturally produced in tissues such as seminal vesicles and cavernous tissues, in the placenta, and in the ductus arteriosus of the fetus.
- PGE1 maintains the patency of the ductus arteriosus during pregnancy. The ductus closes soon after delivery to allow normal blood circulation between the lungs and the heart.
- In neonates with congenital heart conditions, infusion of alprostadil keeps the ductus open, allowing time until surgical correction is possible.
- Alprostadil is also used for erectile dysfunction

Lubiprostone

- PGE1 derivative indicated for the treatment of chronic idiopathic constipation, opioid-induced constipation, and irritable bowel syndrome with constipation.

- Stimulates chloride channels in the luminal cells of the intestinal epithelium, thereby increasing intestinal fluid secretion

- Adverse effects:
  - Nausea (can be decreased if taken with food)
  - Diarrhea

Misoprostol

- PGE1 analog, is used to protect the mucosal lining of the stomach during chronic NSAID treatment.
- Interacts with prostaglandin receptors on parietal cells within the stomach, reducing gastric acid secretion and stimulating mucus and bicarbonate production.
- This combination of effects decreases the incidence of NSAID-induced gastric ulcers.
- Also used off-label in obstetrics for labor induction, since it increases uterine contractions by interacting with prostaglandin receptors in the uterus.
  - Misoprostol has the potential to induce abortion.
  - Contraindicated during pregnancy.
  - Adverse effects: diarrhea and abdominal pain.

Bimatoprost and Latanoprost

- Prostaglandin F2α analogs indicated for the treatment of open- angle glaucoma.
- By binding to prostaglandin receptors, they increase uveoscleral outflow, reducing intraocular pressure.
- They are administered as ophthalmic solutions once a day and are as effective as timolol or better in reducing intraocular pressure.
- Bimatoprost increases eyelash prominence, length, and darkness and is approved for the treatment of eyelash hypotrichosis.
- Adverse effects:
  - Blurred vision
  - Iris color change (increased brown pigmentation)
  - Increased number and pigment of eyelashes
  - Ocular irritation, and foreign body sensation.

Iloprost

- Prostacyclin (PGI2) analog
- Potent pulmonary vasodilator
- Used for the treatment of pulmonary arterial hypertension.
- Mimic the effects of prostacyclin in endothelial cells, producing a significant reduction in pulmonary arterial resistance with increase in cardiac index and oxygen delivery.

- Adverse effects
  - Dizziness, headache, flushing, and fainting
  - Bronchospasm and cough can also occur after inhalation of iloprost.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

- NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities

- Act primarily by inhibiting the COX enzymes that catalyze the first step in prostanoid biosynthesis
  - This leads to decreased PG synthesis with both beneficial and unwanted effects

Selective COX-2 inhibitors

- Detection of serious cardiovascular events associated with COX-2 inhibitors has led to withdrawal of rofecoxib and valdecoxib from the market
- Celecoxib is still available for the treatment of osteoarthritis, RA, pain

NSAIDs

- FDA has required that the labeling of traditional NSAIDs and celecoxib be updated to include the following:
  1. Warning of the potential risks of serious cardiovascular thrombotic events, MI, and stroke, which can be fatal, as well as a warning that these risk may increase with duration of use and that patients with cardiovascular disease or risk factors may be at greater risk
  2. Warning that use is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft surgery
  3. A notice that there is increased risk of serious GI adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal

NSAIDs

- The cardiovascular adverse events can occur at any time during use and without warning symptoms
- Elderly patients are at greater risk for serious GI events
- Aspirin has proven to be beneficial in patients for the primary and secondary prevention of cardiovascular events

Aspirin and other salicylic acid derivatives

- Aspirin is a weak organic acid that is unique among the NSAIDs in that it irreversibly acetylates (inactivates) cyclooxygenase
- The other NSAIDs, including salicylate, are all reversible inhibitors of cyclooxygenase
- Aspirin is rapidly deacetylated by esterases in the body, thereby producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects

Aspirin

- NSAIDs, including aspirin, have three major therapeutic actions:
  1. Anti-inflammatory actions
  2. Analgesic action
  3. Antipyretic action

Aspirin

- **Anti-inflammatory actions:**
- Because aspirin inhibits cyclooxygenase activity, it diminishes the formation of PGs and, thus, modulates those aspects of inflammation in which prostaglandins act as mediators

- Aspirin inhibits inflammation in arthritis, but it does not stop the progress of the disease

Aspirin

- **Analgesic action**
- PGE2 sensitizes nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process

- By decreasing PGE2 synthesis, aspirin and other NSAIDs repress the sensation of pain

- Used mainly for the management of pain of low to moderate intensity arising from musculoskeletal disorders

Aspirin

- **Antipyretic action**
- Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated, which can be caused by PGE2 synthesis

- The salicylates lower body temperature in patients with fever by decreasing PGE2 synthesis and release

- This rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating

- Aspirin has no effect on normal body temperature

Aspirin

- **Gastrointestinal effects**
- Prostacyclin (PGI2) inhibits gastric acid secretion whereas PGE2 and PGF2α stimulate synthesis of protective mucus in both the stomach and small intestine

- In the presence of aspirin, these prostanoids are not formed resulting in increased gastric acid secretion and diminished mucus protection

- This may cause epigastric distress, ulceration, hemorrhage, and iron-deficiency anemia

Aspirin

- **Gastrointestinal effects**
- Agents used for the prevention of gastric and/or duodenal ulcers include the **PGE1-derivative** misoprostol and **PPIs** like esomeprazole, lansoprazole, omeprazole

- PPIs can also be used for the treatment of an NSAID-induced ulcer especially if the patient will need to continue NSAID treatment

Aspirin

- **Actions on the kidney**
- Cyclooxygenase inhibitors prevent the synthesis of PGE2 and PGI2 which are responsible for maintaining renal blood flow
- Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema and hyperkalemia in some patients
- Interstitial nephritis can also occur with all NSAIDs

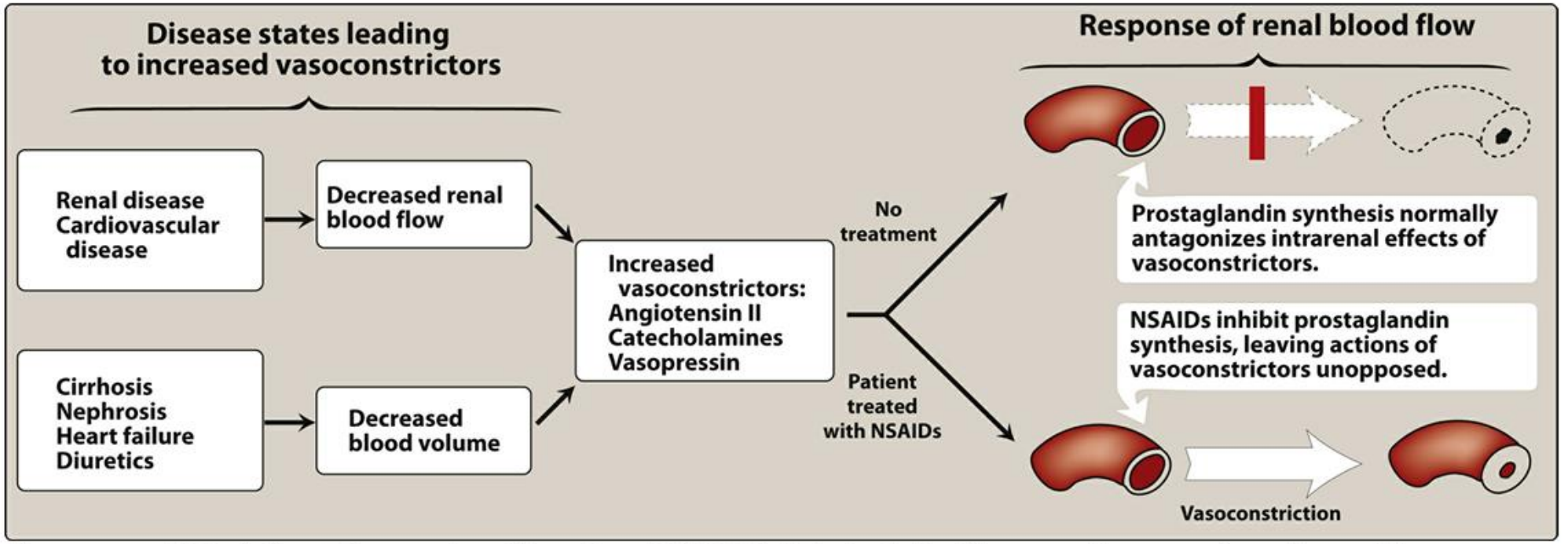


Figure 40.13 Renal effect of NSAID inhibition of prostaglandin synthesis.NSAIDs = nonsteroidal anti-inflammatory drugs.

Aspirin and other salicylic acid derivatives: therapeutic uses

- Antipyretic, anti-inflammatory and analgesic
- External applications
  - Salicylic acid is used topically for acne, corns, calluses, and warts
- Cardiovascular applications

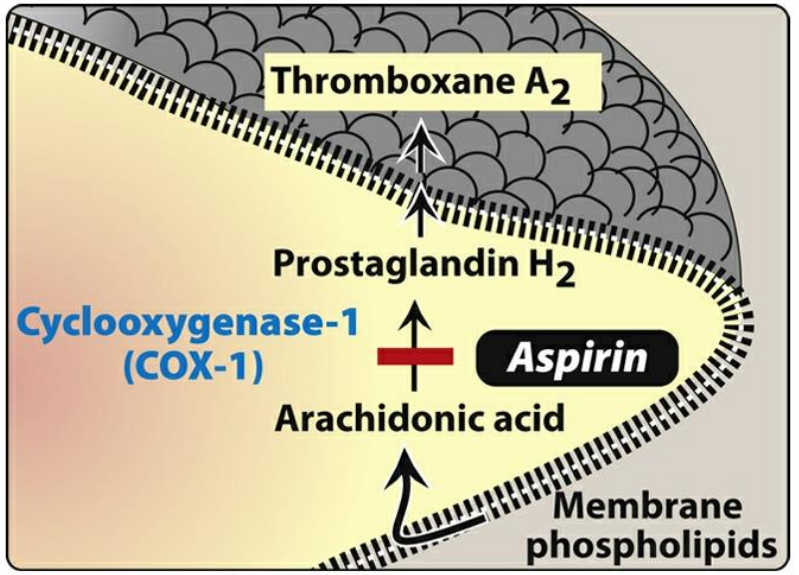


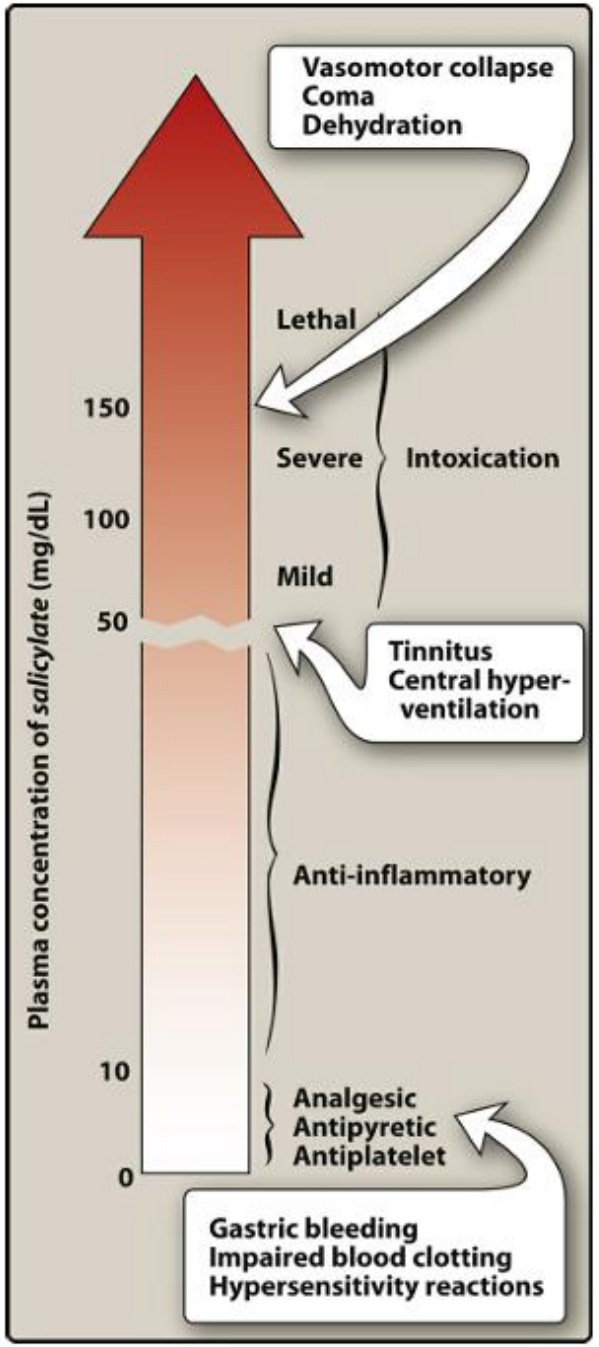
Figure 40.11 *Aspirin* irreversibly inhibits platelet cyclooxygenase-1.

Aspirin and other salicylic acid derivatives

- Salicylates must be avoided in children and teenagers (<20 years old) with viral infections, such as varicella (chickenpox) or influenza, to prevent Reye syndrome.

Aspirin adverse effects

- GI: Epigastric distress, nausea, and vomiting.
  - Microscopic GI bleeding.
- Blood: The irreversible acetylation of platelet cyclooxygenase reduces the level of platelet TXA2 resulting in inhibition of platelet aggregation and a prolonged bleeding time
- Respiration: In toxic doses, salicylates cause respiratory depression
- Metabolic processes: Large doses of salicylates uncouple oxidative phosphorylation, the energy normally used for ATP production is dissipated as heat causing hyperthermia at toxic quantities
- Hypersensitivity: (urticaria, bronchoconstriction)



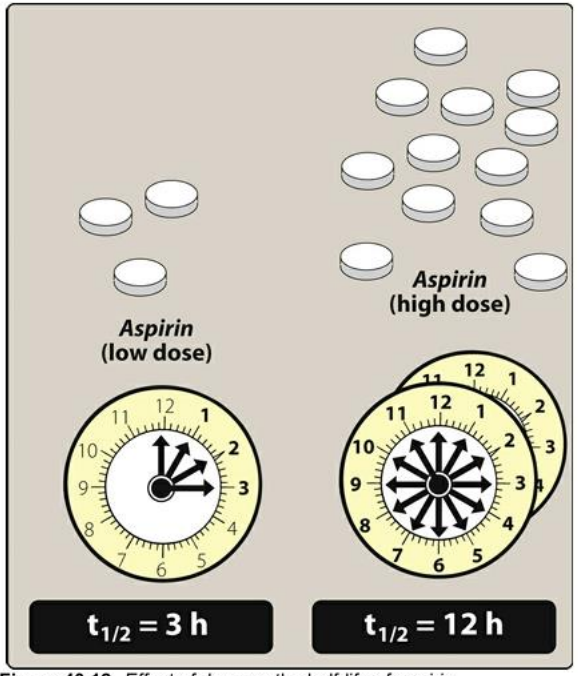
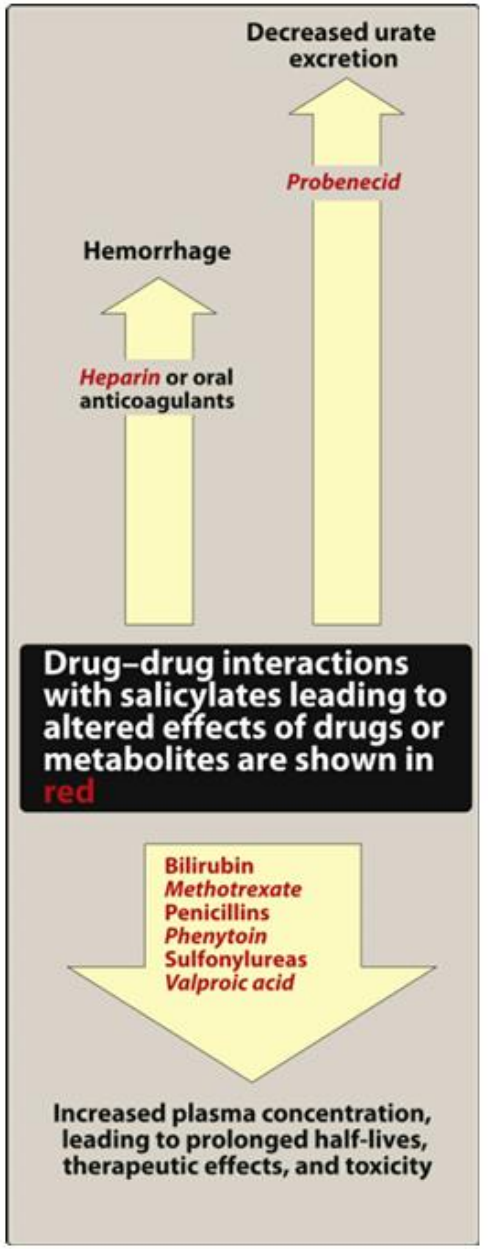


Figure 40.12 Effect of dose on the half-life of *aspirin*.

Aspirin drug interactions

- Salicylate is roughly 80-90% plasma protein bound
- Aspirin could displace other highly protein- bound drugs, such as warfarin, phenytoin, or valproic acid
- Chronic aspirin use should be avoided in patients receiving probenecid or sulfinpyrazone, because they increase renal excretion of uric acid, while aspirin (less than 2 g/day) causes reduced clearance of uric acid
- Concomitant use of ketorolac and aspirin is contraindicated because of increased risk of GI bleeding and platelet aggregation inhibition



Aspirin in pregnancy

- Aspirin is classified as FDA pregnancy category C risk during the first and second trimesters
- Category D during the third trimester

- Because salicylates are excreted in breast milk, aspirin should be avoided during pregnancy and while breastfeeding

Propionic acid derivatives

- Ibuprofen (Trufen®, Adex®, Ibufen®, Advil®, Isofen, Nurofen®, Ultrafen®, Artofen®)
- Naproxen (Naprex®, Naxyn®, Naproxi®)
- Ketoprofen (Profenid®)

Propionic acid derivatives

- All of these drugs possess anti-inflammatory, analgesic, and antipyretic activity
- They can alter platelet function and prolong bleeding time
- Used in the chronic treatment of RA and osteoarthritis, because their GI effects are generally less intense than those of aspirin
- Reversible inhibitors of the cyclooxygenases, inhibit PG synthesis

- Adverse effects:
  - GI, ranging from dyspepsia to bleeding
  - Tinnitus, dizziness

- Ibuprofen is used IV to close a patent ductus arteriosus (PDA)

Acetic acid derivatives

- Indomethacin (Indocaps®, Indocin®, Indolin®, Indomed®)
- Sulindac (Mobicol®)
- Etodolac (Etodolac Teva®, Etopan®)

Acetic acid derivatives

- All have anti-inflammatory analgesic and antipyretic activity
- Act by reversibly inhibiting cyclooxygenase
- Generally not used to lower fever
- Toxicity of indomethacin limits its use to the treatment of acute gouty arthritis, to close a PDA in neonates, in ankylosing spondylitis, and in osteoarthritis of the hip
- Sulindac is an inactive prodrug that is closely related to indomethacin
- Adverse effects
  - Transient renal insufficiency
  - Jaundice
  - Elevated liver function test values

Heteroaryl acetic acids

- Diclofenac (Diclofen®, Rufenal®, Voltaren®, Abitern®, Betaren®, Anaflam®, Cataflam®)
- Ketorolac

Heteroaryl acetic acids

- Approved for treatment of RA, osteoarthritis, and ankylosing spondylitis
- Diclofenac is more potent than indomethacin or naproxen
- Adverse effects: GI, renal and hepatic side effects
- Ketorolac is a potent analgesic but has moderate anti-inflammatory effect
- Ketorolac can cause fatal peptic ulcers as well as GI bleeding

Oxicam derivatives

- Piroxicam (Pirox®)
- Meloxicam (Movalis®)
- Used to treat RA, ankylosing spondylitis, and osteoarthritis
- They have long half lives, which permits once-daily administration
- Excreted in urine
- Adverse effects: GI disturbances

Nabumetone

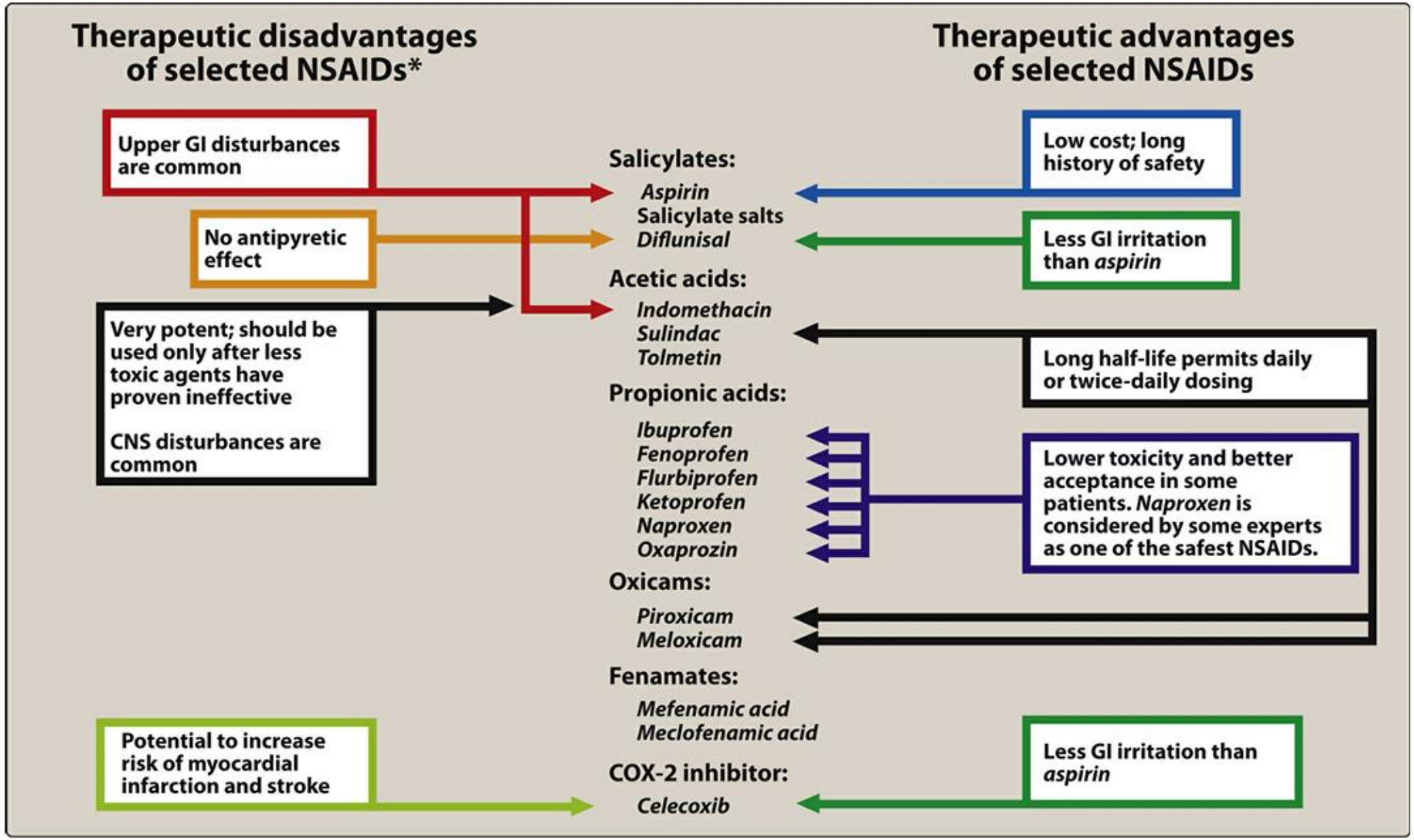
- Nabumetone (Nabuco®, Reliefex®)
- Indicated for the treatment of RA and osteoarthritis
- Associated with a low incidence of adverse effects
- Metabolized by the liver to the active metabolite
- Excreted by urine
- Dose should be adjusted in low creatinine clearance

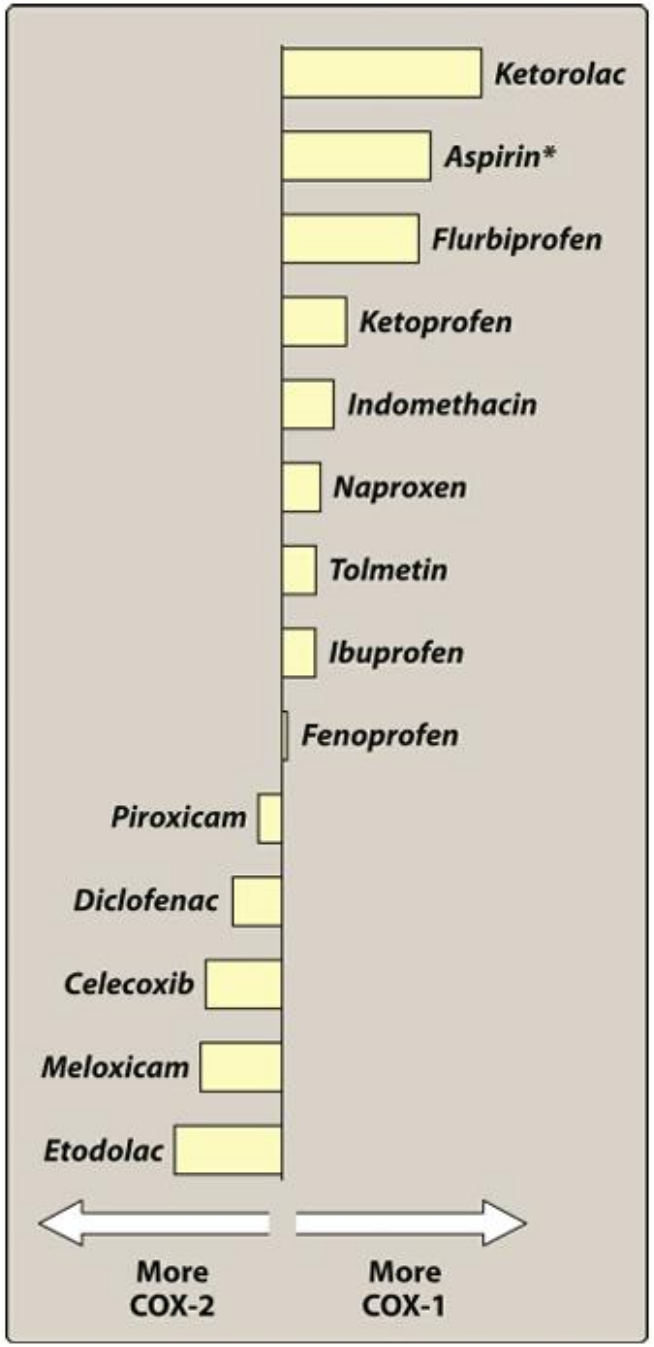
Celecoxib

- Celecoxib (Celebra®, Celcox®)
- Significantly more selective for inhibition of COX-2 than of COX-1
- This selectivity provides a therapeutic advantage over nonselective COX inhibitors, allowing the proper management of chronic inflammatory conditions
- Approved for treatment of RA, osteoarthritis, acute to moderate pain
- Celecoxib has both similar efficacy to NSAIDs in the treatment of pain and in the risk for cardiovascular events
- When used without concomitant aspirin therapy, has been shown to be associated with less GI bleeding and dyspepsia
- Etoricoxib (Arcoxia®, Tericox®) is also more selective for COX-2 inhibition

Celecoxib Adverse effects:

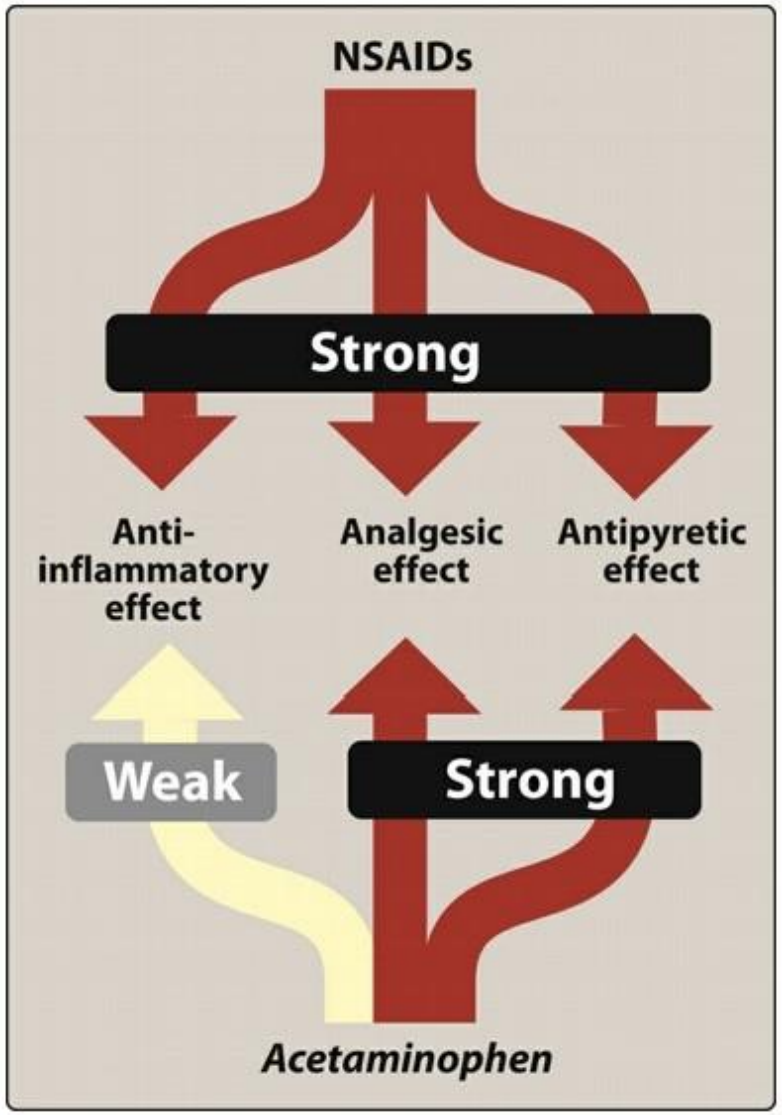
- Diarrhea
- As with other NSAIDs, kidney toxicity may occur
- Celecoxib should be avoided in patients with chronic renal insufficiency, severe heart disease, hepatic failure
- Inhibitors of CYP2C9, such as fluconazole, fluvastatin, and zafirlukast, may increase serum levels of celecoxib.
- Celecoxib inhibits CYP2D6 and can lead to elevated levels of some β-blockers (propranolol), antidepressants (amitriptyline), and antipsychotic drugs (risperidone)





Acetaminophen

- N-acetyl-p-aminophenol, or (APAP) = Paracetamol (Febramol®, Sedamol®, Otamol®, Paramol®, Tailol®, Panadol®, Dexamol®, Acamol®)
- Inhibits prostaglandin synthesis in the CNS
- This explains its antipyretic and analgesic properties
- Acetaminophen has less effect on cyclooxygenase in peripheral tissues, which accounts for its weak anti- inflammatory activity
- Acetaminophen does not affect platelet function or increase blood-clotting time
- Acetaminophen is not considered to be an NSAID

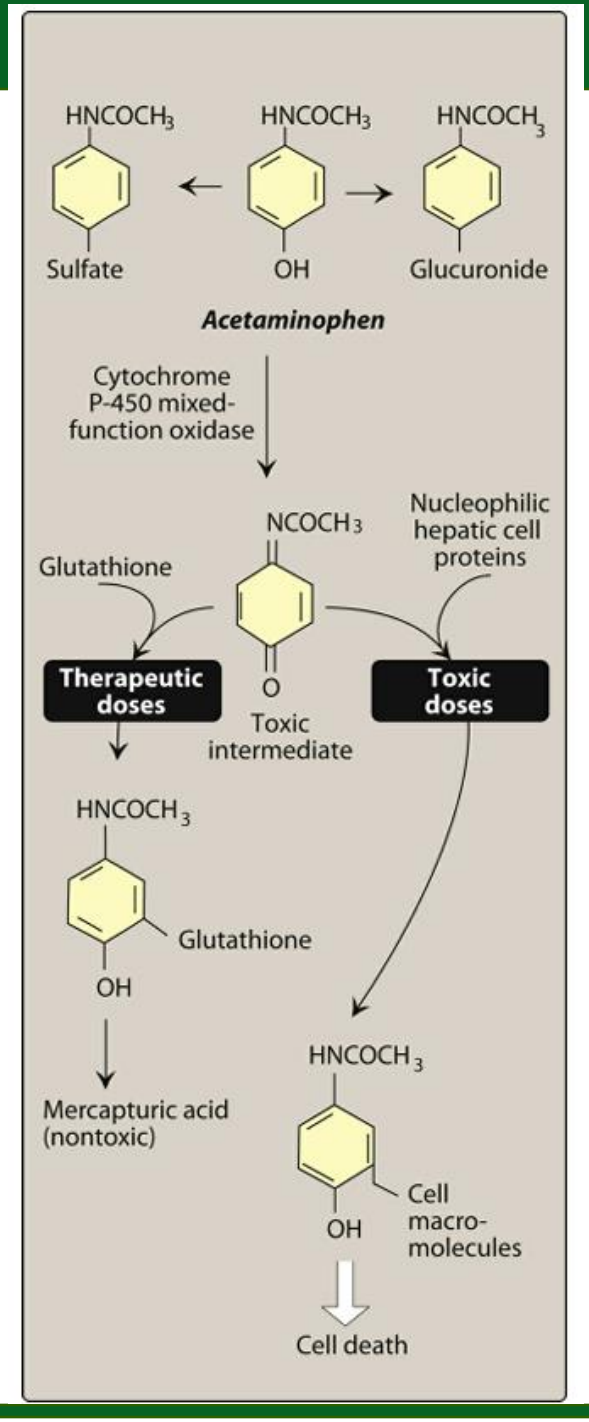


Acetaminophen therapeutic uses:

- Analgesic
- Antipyretic
- Suitable for those patients with gastric complaints, those in whom prolongation of bleeding time would be a disadvantage, and those who do not require the anti- inflammatory action
- Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox
- Acetaminophen does not antagonize the uricosuric agents like probenecid and may be used in patients with gout

Acetaminophen

- Under normal circumstances, acetaminophen is conjugated in the liver to form inactive glucuronidated or sulfated metabolites
- A portion of acetaminophen is hydroxylated to form N-acetylbenzoiminoquinone, (N-acetyl-p- benzoquinoneimine, or NAPQI), a highly reactive and potentially dangerous metabolite that reacts with sulfhydryl groups and causes liver damage
- At normal doses of acetaminophen, the N-acetylbenzoiminoquinone reacts with glutathione, forming a nontoxic substance
- Acetaminophen and its metabolites are excreted in urine



Acetaminophen adverse effects

- With normal therapeutic doses, acetaminophen is virtually free of any significant adverse effects
- Skin rash and minor allergic reactions occur
- With large doses of acetaminophen, hepatic necrosis, a very serious and potentially life- threatening condition, can result.
- Renal tubular necrosis may also occur.

- Antidote: N-acetylcysteine

Disease modifying antirheumatic agents (DMARDs)

- DMARDs are used in the treatment of RA and have been shown to slow the course of the disease, induce remission, and prevent further destruction of the joints and involved tissues
- When a patient is diagnosed with RA the initiation of therapy with DMARDs is recommended within 3 months of diagnosis (in addition to NSAIDs, low-dose corticosteroids, physical therapy, and occupational therapy)
- DMARDs is initiated rapidly to help stop the progression of the disease at the earlier stages

DMARDs

- Methotrexate (Abitrexate®, Metoject®)
- Hydroxychloroquine (Plaquenil®)
- Leflunomide
- Sulfasalazine
- Glucocorticoids

Methotrexate

- Used alone or in combination therapy
- Has become the mainstay of treatment in patients with rheumatoid or psoriatic arthritis
- Slows the appearance of new erosions within joints
- Response to methotrexate occurs within 3 to 6 weeks of starting treatment
- It is an immunosuppressant
- Given once a week

Methotrexate

- Side effects:
  - Mucosal ulceration and nausea
  - Cytopenias (depression of the WBC count)
  - Liver cirrhosis of the liver
  - Acute pneumonia-like syndrome may occur with chronic administration

- Taking leucovorin once daily after methotrexate reduces adverse effects severity
- Periodic monitoring for signs of infections, complete blood counts, and liver enzymes tests are recommended

Hydroxychloroquine

- Also used in the treatment of malaria
- Used for early mild RA
- Often combined with methotrexate
- When used alone it does not slow joint damage
- Mechanism of action may include
  - Inhibition of phospholipase A2 and platelet aggregation
  - Membrane stabilization
  - Effects on the immune system
  - Antioxidant activity

Hydroxychloroquine

- Side effects
  - Ocular toxicity, including irreversible retinal damage as well as corneal deposits
  - CNS disturbances,
  - GI upset
  - Skin discoloration and eruptions.

Leflunomide

- An immunomodulatory agent that preferentially causes cell arrest of the autoimmune lymphocytes through inhibition of dihydroorotate dehydrogenase (DHODH), an enzyme necessary for pyrimidine synthesis

- May be used as monotherapy in patients who have intolerance or contraindications to use of methotrexate in RA, or it may be used in combination with methotrexate for patients with suboptimal response to methotrexate alone.

Leflunomide

- Adverse effects:
  - Headache
  - Diarrhea
  - Nausea.
  - Allergic reactions, a flu-like syndrome; skin rash
  - Alopecia; and
  - Hypokalemia.

- The drug is not recommended in patients with liver disease as it can be hepatotoxic.
- Contraindicated in pregnancy.
- Monitoring parameters: signs of infection, CBC, electrolytes, and liver enzymes.

Sulfasalazine

- Used for early, mild RA in combination with hydroxycholoroquine and methotrexate
- Associated with leukopenia
- Mechanism of action in treating RA is unclear

Glucocorticoids

- Used in patients with RA until DMARDs are effective
- Doses up to 10 mg of prednisone are usually used
- Dose reductions and cessation are necessary to avoid adverse effects associated with long-term use

DMARDs

- No one DMARD is efficacious and safe in every patient
- Trials of several different drugs may be necessary
- Most experts begin DMARD with methotrexate or hydroxychloroquine
  - (Efficacious and are generally well tolerated)
- Inadequate response to them may be followed by use of newer DMARDs
- Combination therapies are both safe and efficacious
  - In most cases, methotrexate is combined with another DMARD
- In patients who do not respond to combination therapy with methotrexate plus TNF inhibitors, or other combinations, rituximab or abatacept may be tried
- Most are contraindicated for use in pregnant women

Biologic therapies in RA

- Interleukin-1 and TNF-α are pro-inflammatory cytokines involved in the pathogenesis of RA
- When secreted by synovial macrophages, IL-1 and TNF-α stimulate synovial cells to proliferate and synthesize collagenase, degrading cartilage and stimulating bone resorption
- In RA, B lymphocytes can perpetuate the inflammatory process in the synovium by:
    1. activating T lymphocytes
    2. producing autoantibodies and rheumatoid factor
    3. producing proinflammatory cytokines, such as TNF-α and IL-1

TNF inhibitors

- The TNF inhibitors decrease signs and symptoms of RA, reduce progression of structural damage, and improve physical function
  - Adalimumab (Humira®)
  - Certolizumab
  - Etanercept
  - Golimumab
  - Infliximab
- A TNF inhibitor plus methotrexate be considered as standard therapy for patients with rheumatoid and psoriatic arthritis
- TNF inhibitors increase risk for infections (Tuberculosis, sepsis)
- Demyelinating disorders and bone marrow suppression may occur (rare)
- Should be used very cautiously in those with heart failure, because they can cause and worsen preexisting heart failure

IL-6 inhibitors

- Tocilizumab
- Sarilumab
- Recombinant monoclonal antibodies that bind to IL-6 receptors and inhibit activity of the proinflammatory cytokine IL-6.
- Administered as a subcutaneous injection every 2 weeks.
- Tocilizumab may be administered as an intravenous infusion every 4 weeks.
- Adverse reactions:
  - Elevated liver function tests
  - Hyperlipidemia
  - Neutropenia
  - Hypertension
  - Infusion-related and injection site reactions

Abatacept

- Competes with CD28 for binding on CD80/CD86 protein, preventing full T cell activation and reducing the inflammatory response
- Administered as an IV infusion every 4 weeks
- Adverse effects:
  - Infusion-related reactions
  - Headache
  - Upper respiratory infections
  - Nausea.

Rituximab

- Monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes.
- Administration of rituximab results in B cell depletion.
- Administered as an intravenous infusion every 16 to 24 weeks.
- To reduce infusion reactions, methylprednisolone, acetaminophen, and an antihistamine are administered prior to each infusion.

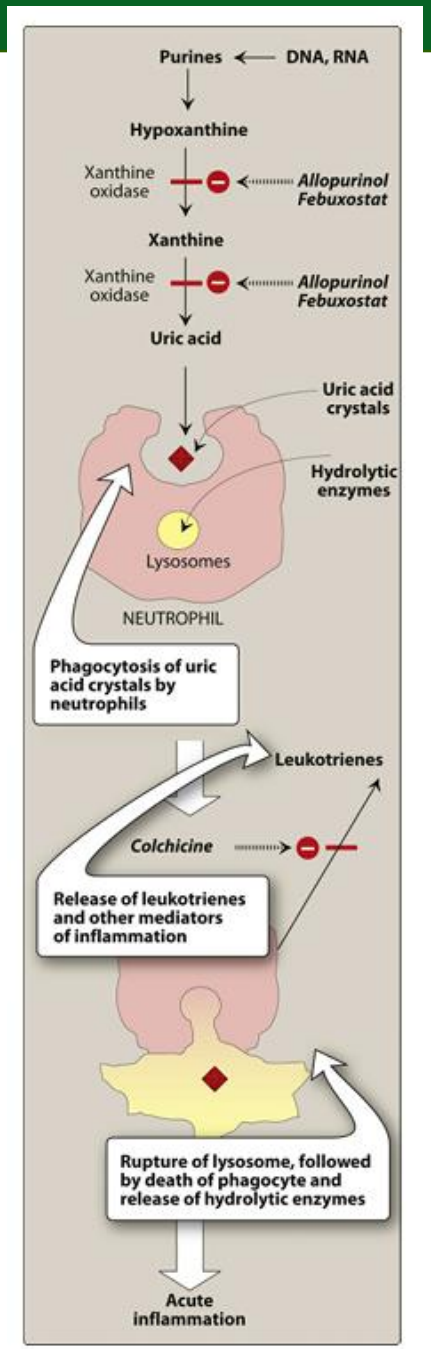
- Adverse effects:
  - Infusion reactions (urticaria, hypotension, and angioedema)
    - typically occur during the first infusion.

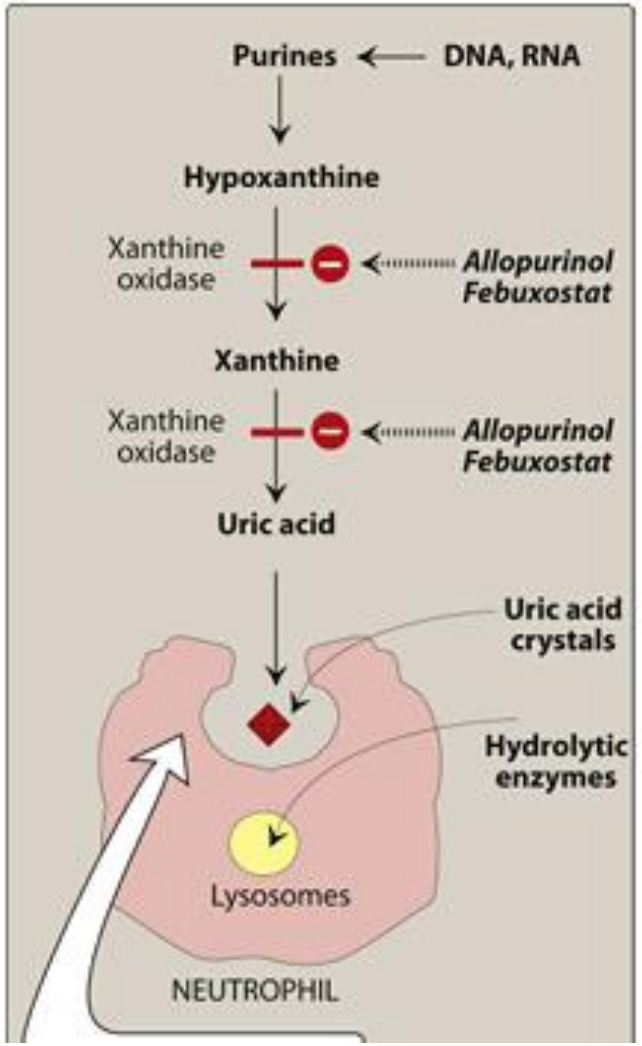
Drugs used for Gout

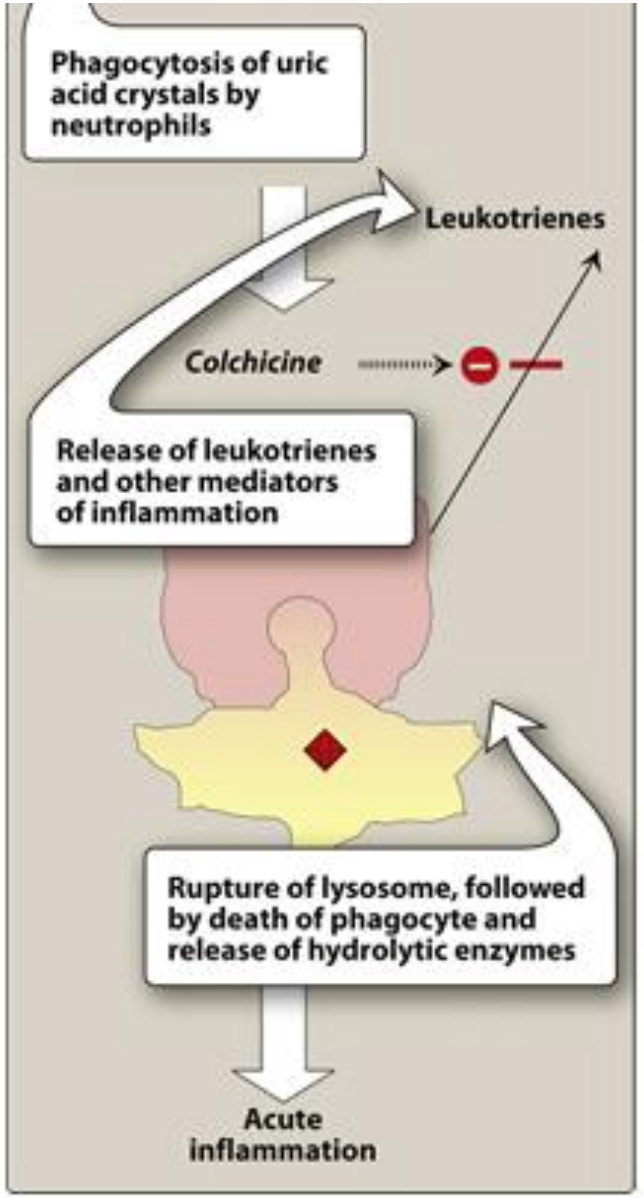
- Gout is a metabolic disorder characterized by high levels of uric acid in the blood.
- Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney
- The cause of hyperuricemia is an overproduction of uric acid relative to the patient's ability to excrete it
- Sodium urate is the end product of purine metabolism
- The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals
  - This process generates oxygen metabolites, which damage tissues

Drugs used for Gout

- Most therapeutic strategies for gout involve lowering uric acid level below the saturation point (below 6 mg/dL) thus preventing the deposition of urate crystals by
  1. Interfering with uric acid synthesis with allopurinol
  2. Increasing uric acid excretion with probenecid or sulfinpyrazone
  3. Inhibiting leukocyte entry into the affected joint with colchicine
  4. Administration of NSAIDs







Acute Gout Treatment

- Acute gouty attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease.
- Acute attacks are treated with indomethacin to decrease movement of granulocytes into the affected area and reduce pain and inflammation
- Intraarticular administration of glucocorticoids (when only one or two joints are affected) is also appropriate in the acute setting

Chronic Gout Treatment

- Treatment strategies for chronic gout include:
  - The use of uricosuric drugs like probenecid that increase the excretion of uric acid reducing its concentration in plasma
  - The use of allopurinol, which is a selective inhibitor of the terminal steps in the biosynthesis of uric acid

Colchicine

- Used for the treatment of acute gouty attacks as well as chronic gout
  - It is neither a uricosuric nor an analgesic agent
  - Relieves pain in acute attacks of gout
- Does not prevent the progression of gout to acute gouty arthritis
- Has a suppressive, prophylactic effect that reduces the frequency of acute attacks and relieves pain

Colchicine Mechanism of action

- Colchicine binds to tubulin, a microtubular protein, causing its depolymerization
- This disrupts the mobility of granulocytes decreasing their migration into the affected area
- Colchicine blocks cell division by binding to mitotic spindles
- Colchicine also inhibits the synthesis and release of the leukotrienes
- Therapeutic uses
- The anti-inflammatory activity of colchicine is specific for gout, alleviating the pain of acute gout within 12 hours
- NSAIDs have largely replaced colchicine in the treatment of acute gouty attacks
- Colchicine is currently used for prophylaxis of recurrent attacks

Colchicine Adverse effects

- Nausea, vomiting, abdominal pain, and diarrhea
- Myopathy
- Aplastic anemia
- Alopecia

- Should not be used in pregnancy
- Should be used with caution in patients with hepatic, renal diseases

Allopurinol

- Alloril ®, Zylol®, Zyloric®
- A purine analog
- Xanthine oxidase inhibitor
- Reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis catalyzed by xanthine oxidase

Allopurinol

- Therapeutic uses
  - Effective in the treatment of primary hyperuricemia of gout and hyperuricemia secondary to other conditions such as that associated with certain malignancies
  - Acute attacks of gout may occur more frequently during the first several weeks of therapy, colchicine or NSAIDs should be administered concurrently

- Adverse effects
  - Hypersensitivity reactions, especially skin rashes
  - GI side effects, such as nausea and diarrhea

Probenecid

- Oral uricosuric drug.
- It is a weak organic acid that promotes renal clearance of uric acid by inhibiting the urate-anion exchanger in the proximal tubule, blocking proximal tubular reabsorption of uric acid.
- Probenecid should be avoided if the creatinine clearance is less than 50 mL/min.

- Adverse effects:
  - Nausea, vomiting
  - Dermatologic reactions
  - Anemia (Rare)
  - Anaphylactic reactions (Rare)