لجنة عمداء كليات الصيدلة

لجنة توحيد منهاج مادة (Pharmacology III)

Pharmacology III

المرحلة الرابعة

2024

تم اعداد ومراجعة هذا المنهج الموحد للامتحان التقويمي لكليات الصيدلة للعام الدراسي 2023-2024 من قبل اساتذة متخصصين لديهم خبرة كبيرة في التدريس والعمل الاكاديمي . لقد بذل الاساتذة قصارى جهودهم في جمع المعلومات وحرصوا على ترتبها وتنظيمها لتكون واضحة يسيرة على طلبتنا الاعزاء . نأمل من طلبتنا الاعزاء الاستفادة منه في طريقهم الى النجاح والتفوق ، والله الموفق

PHARMACOLOGY III

Lec 1 Anti-inflammatory drugs

Inflammation is a normal, protective response to tissue injury caused by physical trauma, noxious chemicals, or 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.

However, inappropriate activation of the immune system can result in inflammation and immune-mediated diseases such as rheumatoid arthritis (RA). In RA, white blood cells (WBCs) initiate an inflammatory attack. WBC activation leads to stimulation of T lymphocytes, which recruit and activate monocytes and macrophages. These cells secrete proinflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-1, into the synovial cavity, ultimately leading to joint destruction and other systemic abnormalities characteristic of RA.

In addition to T lymphocyte activation, the B lymphocytes are also involved and produce rheumatoid factor and other autoantibodies to maintain inflammation.

Pharmacotherapy for RA includes anti-inflammatory and/or immunosuppressive agents that modulate/reduce the inflammatory process, with the goals of reducing inflammation and pain, and halting or slowing disease progression.

Prostaglandins: Prostaglandins are unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure. [Note: These compounds are sometimes referred to as eicosanoids].

Thromboxanes, leukotrienes, and the hydroperoxyeicosatetraenoic and hydroxyeicosatetraenoic acids (HPETEs and HETEs, respectively) are related lipids, synthesized from the same precursors as the prostaglandins, and use interrelated pathways.

Synthesis of prostaglandins

Arachidonic acid, a 20-carbon fatty acid, is the primary precursor of the prostaglandins and related compounds. There are two major pathways in the synthesis of the eicosanoids from arachidonic acid.

Cyclooxygenase pathway: **All** eicosanoids with ring structures that is, the prostaglandins, thromboxanes, and prostacyclins are synthesized via the cyclooxygenase pathway.

Two related isoforms of the cyclooxygenase enzymes have been described. **Cyclooxygenase-1 (COX-1)** is responsible for the physiologic production of prostanoids, COX-1 is described as a housekeeping enzyme that regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and kidney function whereas

Cyclooxygenase-2 (COX-2) causes the elevated production of prostanoids that occurs in sites of disease and inflammation. COX-2 is constitutively expressed in tissues such as the brain, kidney, and bone. Its expression at other sites is increased during states of inflammation.

Lipoxygenase pathway: Alternatively, several lipoxygenases can act on arachidonic acid to form leukotrienes or lipoxins, depending on the tissue.

Functions of prostaglandins in the body

Prostaglandins and their metabolites produced endogenously in tissues. They control many physiological functions, such as acid secretion and mucus production in the gastrointestinal (GI) tract, uterine contractions, and renal blood flow.

Prostaglandins are also among the chemical mediators that are released in allergic and inflammatory processes. Intradermal, intravenous, or intra-arterial injections of small amounts of prostaglandins mimic many components of inflammation. .

Non-steroidal anti-inflammatory drugs (NSAIDs)

All NSAIDs, including the traditional nonselective drugs and the subclass of selective cyclooxygenase-2 (COX-2) inhibitors, have the following actions:

Anti-inflammatory, analgesic, and antipyretic.

NSAIDs are a chemically heterogeneous group of organic acids that share certain therapeutic actions and adverse effects.

All of the NSAIDs act by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with both beneficial and unwanted effects.

Aspirin and other NSAIDs

Aspirin can be thought of as a traditional NSAID, but it exhibits anti-inflammatory activity only at relatively high doses that are rarely used.

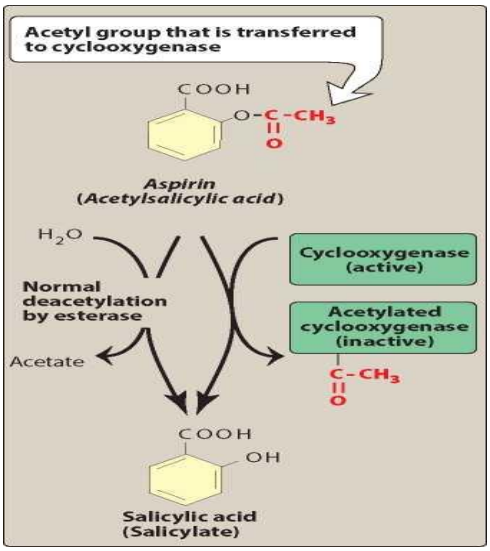
It is used more frequently at lower doses to prevent cardiovascular events such as stroke and myocardial infarction (MI).

Aspirin is often **differentiated** from other NSAIDs since it is an **irreversible** inhibitor of cyclooxygenase activity.

Mechanism of action:

Aspirin is a weak organic acid that **irreversibly** acetylates and, thus, inactivates cyclooxygenase. The **other NSAIDs are reversible** inhibitors of cyclooxygenase. The NSAIDs, including aspirin, have three major therapeutic actions:

they reduce inflammation (anti-inflammatory), pain (analgesic effect), and fever (antipyretic effect). However, not all NSAIDs are equally effective in each of these actions.



Actions of Aspirin and other NSAIDs:

1-Anti-inflammatory effect

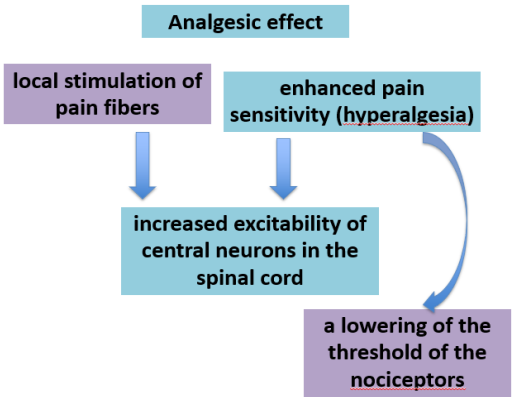
Anti-inflammatory actions: Inhibition of cyclooxygenase **diminishes** the formation of prostaglandins since PGE2 induce acute inflammation through mast cell activation via the EP3 receptors. Aspirin inhibits inflammation in arthritis, but it neither arrests the progress of the disease nor induces remission.

2-Analgesic action: PGE2 is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Thus, by decreasing PGE2 synthesis, the sensation of pain

can be decreased. As COX-2 is expressed during times of inflammation and injury, it is thought that inhibition of this enzyme is responsible for the analgesic activity of NSAIDs.

Note: No single NSAID has demonstrated superior efficacy over another, and they are generally considered to have equivalent analgesic efficacy.

The NSAIDs are used mainly for the management of **mild to moderate** pain arising from musculoskeletal disorders. One exception is ketorolac, which can be used for more severe pain, but for only a short duration.



3-Antipyretic action: Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. Lipoxygenase pathway: Alternatively, several lipoxygenases can act on arachidonic acid to form leukotrienes or lipoxins, depending on the tissue.

This can be caused by PGE2 synthesis, which is stimulated when endogenous fever-producing agents (pyrogens), such as cytokines, are released from WBCs that are activated by infection, hypersensitivity, malignancy, or inflammation.

The NSAIDs lower body temperature in patients with fever by impeding PGE2 synthesis and release, resetting the “thermostat” back toward normal.

This rapidly lowers the body temperature of febrile patients by increasing heat dissipation through peripheral vasodilation and sweating. NSAIDs have no effect on normal body temperature.

Therapeutic uses of NSAIDs

- **Anti-inflammatory and analgesic uses**: NSAIDs are used in the treatment of osteoarthritis, gout, RA, and common conditions requiring analgesia (for example, headache, arthralgia, myalgia, and dysmenorrhea).

  Combinations of opioids and NSAIDs may be effective in treating pain caused by malignancy. Furthermore, the addition of NSAIDs may lead to an opioid-sparing effect, allowing for lower doses of opioids to be utilized.

  The salicylates exhibit analgesic activity at lower doses. Only at higher doses do these drugs show anti-inflammatory activity. For example, two 325-mg aspirin tablets administered four times daily produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-inflammatory activity.

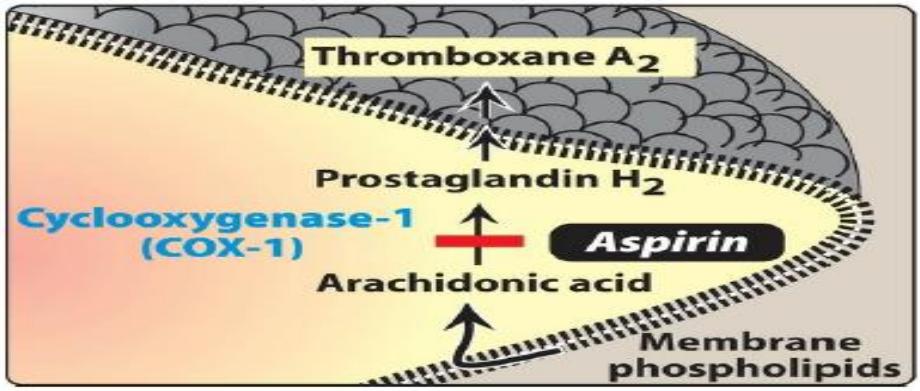
- **Antipyretic uses**: Aspirin, ibuprofen, and naproxen may be used to treat fever. **[Note:** Aspirin should be avoided in patients less than 19 years old with viral infections, such as varicella (chickenpox) or influenza, to prevent Reye syndrome—a syndrome that can cause fulminating hepatitis with cerebral edema, often leading to death.

- **Cardiovascular applications**

  Aspirin irreversibly inhibits COX-1–mediated production of TXA2, thereby reducing TXA2-mediated vasoconstriction and platelet aggregation and the subsequent risk of cardiovascular events. The antiplatelet effects persist for the life of the platelet. Low doses of aspirin (75 to 162 mg—commonly 81 mg) are used

prophylactically to reduce the risk of recurrent cardiovascular events, transient ischemic attacks (TIAs), stroke, and death in patients with a history of previous MI, TIA, or stroke.

Chronic use of aspirin allows for continued inhibition as new platelets are generated. Aspirin is also used acutely to reduce the risk of death in acute MI and in patients undergoing certain revascularization procedures.



- **External applications**: Salicylic acid is used topically to treat corns, calluses, and warts. Methyl salicylate is used externally as a cutaneous counterirritant in liniments, such as arthritis creams and sports rubs. Diclofenac is available in topical formulations (gel or solution) for treatment of osteoarthritis in the knees or hands.

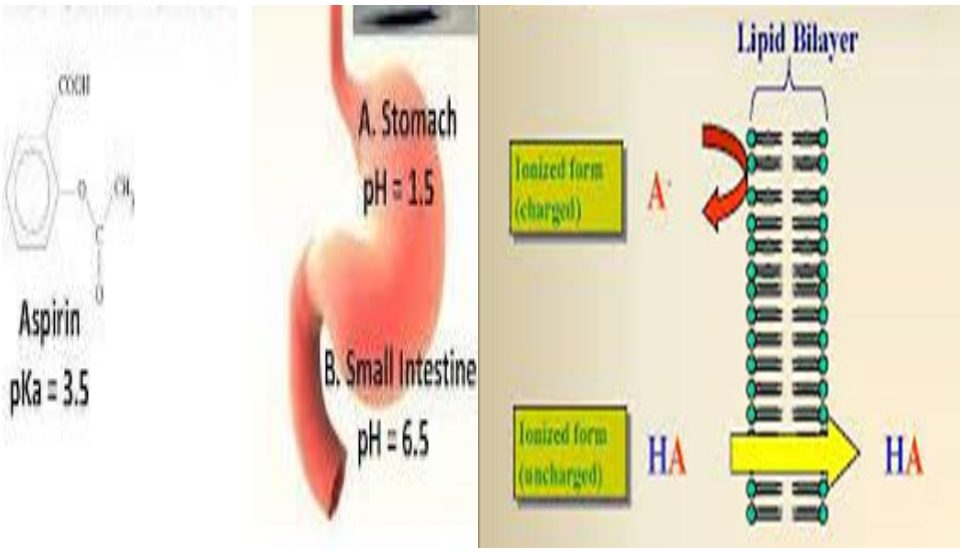
  In addition, ocular formulations of ketorolac are approved for management of seasonal allergic conjunctivitis and inflammation and pain related to ocular surgery.

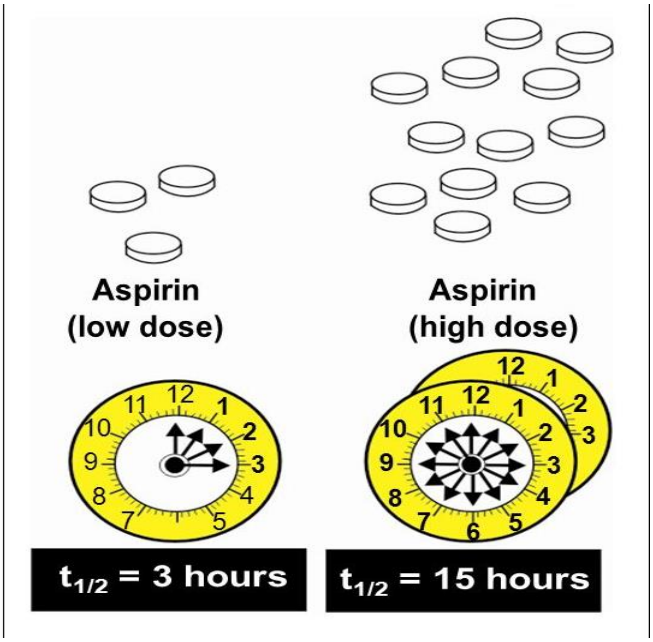
Pharmacokinetics

a. Aspirin: After oral administration, aspirin is rapidly deacetylated by esterases in the body to produce salicylate. Unionized salicylates are passively absorbed mainly from the upper small intestine. Salicylates (except for diflunisal) cross both the blood–brain barrier (BBB) and the placenta and are absorbed through intact skin (especially methyl salicylate).

Salicylate is converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney, resulting in **first-order** elimination and a serum half-life of 3.5 hours.

At anti-inflammatory dosages of aspirin (more than 4 g/day), the hepatic metabolic pathway becomes saturated, and **zero-order** kinetics are observed, leading to a half-life of 15 hours or more . Salicylate is secreted into the urine and can affect uric acid excretion. Therefore, aspirin should be **avoided** in gout, if possible, or in patients taking probenecid.





b. Other NSAIDs: Most NSAIDs are well absorbed after oral administration and circulate highly bound to plasma proteins. The majority are metabolized by the liver, mostly to inactivate metabolites. Few (for example, nabumetone and sulindac) have active metabolites. Excretion of active drug and metabolites is primarily via the urine.

Adverse effects of NSAIDs:

Because of the adverse event profile, it is preferable to use NSAIDs at the lowest effective dose for the shortest duration possible.

a)Gastrointestinal:

These are the most common adverse effects of NSAIDs, ranging from dyspepsia to bleeding. Normally, production of prostacyclin (PGI2) inhibits gastric acid secretion, and PGE2 and PGF2α stimulate synthesis of protective mucus in both

the stomach and small intestine. Agents that inhibit COX-1 reduce **beneficial** levels of these prostaglandins, resulting in increased gastric acid secretion, diminished mucus protection, and increased risk for GI bleeding and ulceration. Agents with a higher relative selectivity for COX-1 may have a higher risk for GI events compared to those with a lower relative selectivity for COX-1 (that is, higher COX-2 selectivity).

NSAIDs should be taken with food or fluids to diminish GI upset. If NSAIDs are used in patients at high risk for GI events, proton pump inhibitors or misoprostol should be used concomitantly to prevent NSAID-induced ulcers.

b) Increased risk of bleeding (antiplatelet effect):

As aspirin inhibits COX-1–mediated formation of TXA2 and reduces platelet aggregation for the lifetime of the platelet (3 to 7 days). Platelet aggregation is the first step in thrombus formation, and the antiplatelet effect of aspirin results in a prolonged bleeding time. **For this reason,** aspirin is often withheld for at least 1 week prior to surgery. NSAIDs other than aspirin are not utilized for their antiplatelet effect but can still prolong bleeding time, especially when combined with anticoagulants.

Concomitant use of NSAIDs and aspirin can prevent aspirin from binding to cyclooxygenase. Patients who take aspirin for cardioprotection should avoid concomitant NSAID use if possible or take aspirin at least 30 minutes prior to the NSAID.

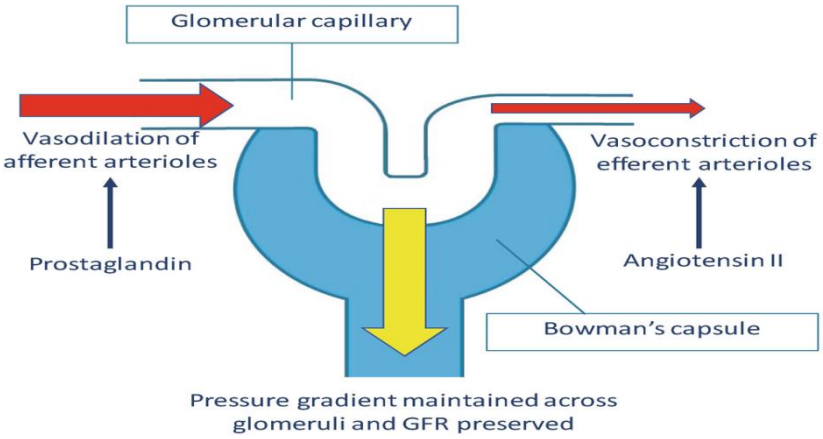
c) Renal effects:

NSAIDs prevent the synthesis of PGE2 and PGI2, prostaglandins that are responsible for maintaining renal blood flow, that the synthesis of PGE2 and PGI2

normally antagonizes the intra-renal effect of vasoconstrictors. NSAIDs leave the actions of vasoconstrictors unopposed. Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema.

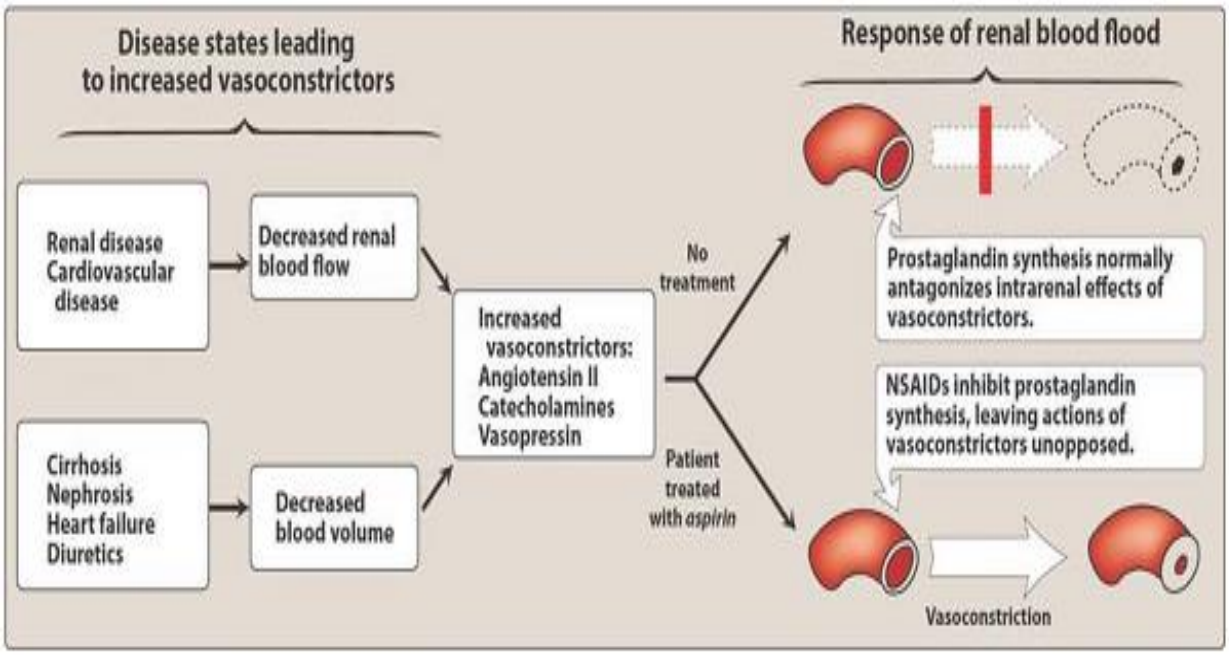
Patients with a history of heart failure or kidney disease are at particularly high risk. These effects can also decrease the beneficial effects of antihypertensive medications. In susceptible patients, NSAIDs have led to acute kidney injury.

Glomeruli and arterioles synthesize not only the vasodilatory prostaglandins PGE2 and PGI2, but also the vasoconstrictor, thromboxane A2. The primary renal cortical actions of these prostaglandins are renal vasodilatation and maintenance of GFR (PGE2 and PGI2) or renal vasoconstriction and reduction of GFR (thromboxane A2).



Vasodilatory renal prostaglandins are relatively unimportant under normal circumstances but play a modulatory role after ischemia or in the presence of increased concentrations of vasoconstrictor substances such as angiotensin II (ANG II), vasopressin or norepinephrine.

Conversely, arachidonic acid reduces the glomerular contractile effect of ANG II. It is, therefore, concluded that renal prostaglandins play an important vasoregulatory role.



.....

Lec 2 Anti-inflammatory drugs (cont.)

D) Cardiac effects:

Agents such as aspirin, with a very high degree of COX-1 selectivity at low doses, have a cardiovascular protective effect thought to be due to a reduction in the production of TXA2. Agents with higher relative COX-2 selectivity have been associated with an increased risk for cardiovascular events, possibly by decreasing PGI2 production mediated by COX-2.

An increased risk for cardiovascular events, including MI and stroke, has been associated with **all** NSAIDs **except** aspirin.

Use of NSAIDs, other than aspirin, is discouraged in patients with established cardiovascular disease .For patients with cardiovascular disease in whom NSAID treatment cannot be avoided, naproxen may be the least likely to be harmful.

E) Other adverse effects:

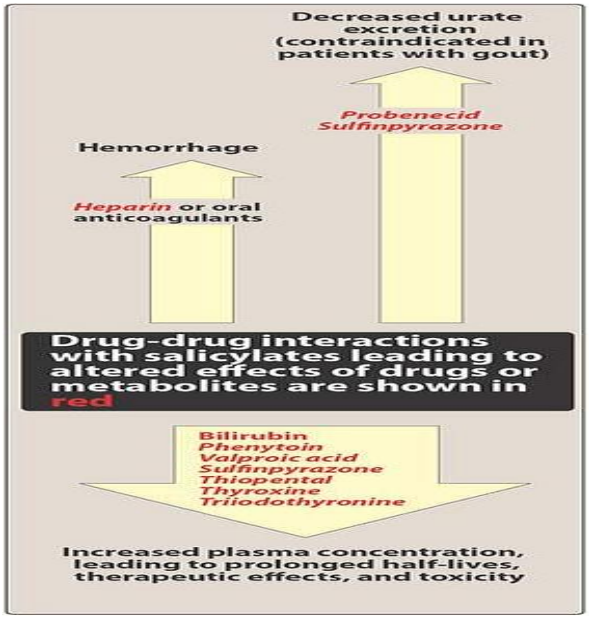
NSAIDs are inhibitors of cyclooxygenases and, therefore, inhibit the synthesis of prostaglandins but not of leukotrienes. For this reason, NSAIDs should be used with caution in patients with asthma, as inhibition of prostaglandin synthesis can cause a shift toward leukotriene production and increase the risk of asthma exacerbations.

Central nervous system (CNS) adverse events, such as headache, tinnitus, and dizziness, may occur.

Approximately 15% of patients taking aspirin experience hypersensitivity reactions. Symptoms of true allergy include urticaria, bronchoconstriction, and angioedema. Patients with severe hypersensitivity to aspirin should avoid using NSAIDs.

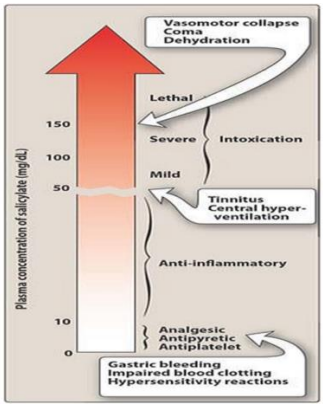
F) Drug interactions:

Salicylate is roughly 80% to 90% plasma protein bound (albumin) and can be displaced from protein-binding sites, resulting in increased concentration of free salicylate. Alternatively, aspirin can displace other highly protein-bound, drugs, such as warfarin, phenytoin, or valproic acid, resulting in higher free concentrations of these agents .



G) Toxicity:

Mild salicylate toxicity is called **salicylism** and is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears). When large doses of salicylate are administered, severe salicylate intoxication may result). Restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure may occur. Children are particularly prone to salicylate intoxication; ingestion of as little as 10 g of aspirin can be fatal.



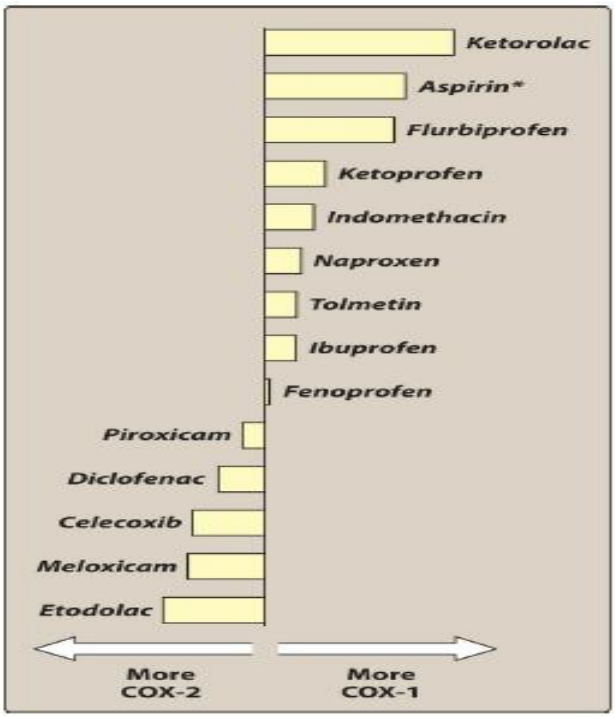
H) Pregnancy

NSAIDs should be used in pregnancy only if benefits outweigh risks to the developing fetus. [Note: Acetaminophen is preferred if analgesic or antipyretic effects are needed during pregnancy.] In the third trimester, NSAIDs should generally be avoided due to the risk of premature closure of the ductus arteriosus.

Selective COX-2 inhibitor,

Celecoxib : a selective COX-2 inhibitor, is significantly more selective for inhibition of COX-2 than COX-1. Unlike the inhibition of COX-1 by aspirin (which is irreversible), the inhibition of COX-2 is reversible.

Therapeutic uses: Celecoxib is approved for the treatment of RA, osteoarthritis, and acute pain. Celecoxib has similar efficacy to NSAIDs in the treatment of pain.



Pharmacokinetics

Celecoxib is readily absorbed after oral administration. It is extensively metabolized in the liver by cytochrome P450 (CYP2C9), and the metabolites are excreted in feces and urine. The half-life is about 11 hours, and the drug may be dosed once or twice daily. The dosage should be reduced in those with moderate hepatic impairment, and celecoxib should be avoided in patients with severe hepatic or renal disease.

Adverse effects

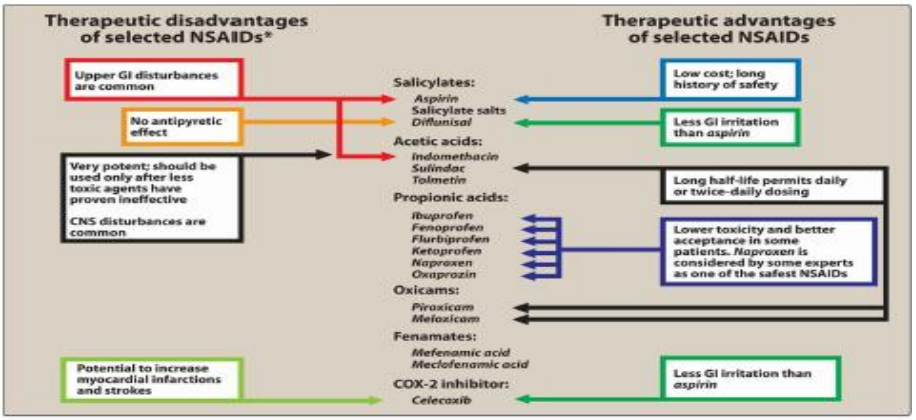
Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects.

Celecoxib is associated with **less** GI bleeding and dyspepsia than other NSAIDs. However, this benefit is lost when aspirin is added to celecoxib therapy. Patients who are at high risk of ulcers and require aspirin for cardiovascular prevention should avoid the use of celecoxib.

Patients who have had anaphylactoid reactions to aspirin or nonselective NSAIDs may be at risk for similar effects with celecoxib.

Inhibitors of CYP2C9, such as fluconazole, may increase serum levels of celecoxib.

Like other NSAIDs, celecoxib has a similar risk for cardiovascular events.



Acetaminophen

Acetaminophen (N-acetyl-p-aminophenol or APAP) inhibits prostaglandin synthesis in the CNS, leading to antipyretic and analgesic effects.

Acetaminophen has **less** effect on cyclooxygenase in **peripheral** tissues (due to peripheral inactivation), which accounts for its weak anti-inflammatory activity. Acetaminophen does not affect platelet function or increase bleeding time. It is not considered an NSAID.

Therapeutic uses: Acetaminophen is used for the treatment of fever and the relief of pain. It is useful in patients with gastric complaints/risks with NSAIDs and those who do not require the anti-inflammatory action of NSAIDs.
Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox (due to the risk of Reye syndrome with aspirin).

Pharmacokinetics:

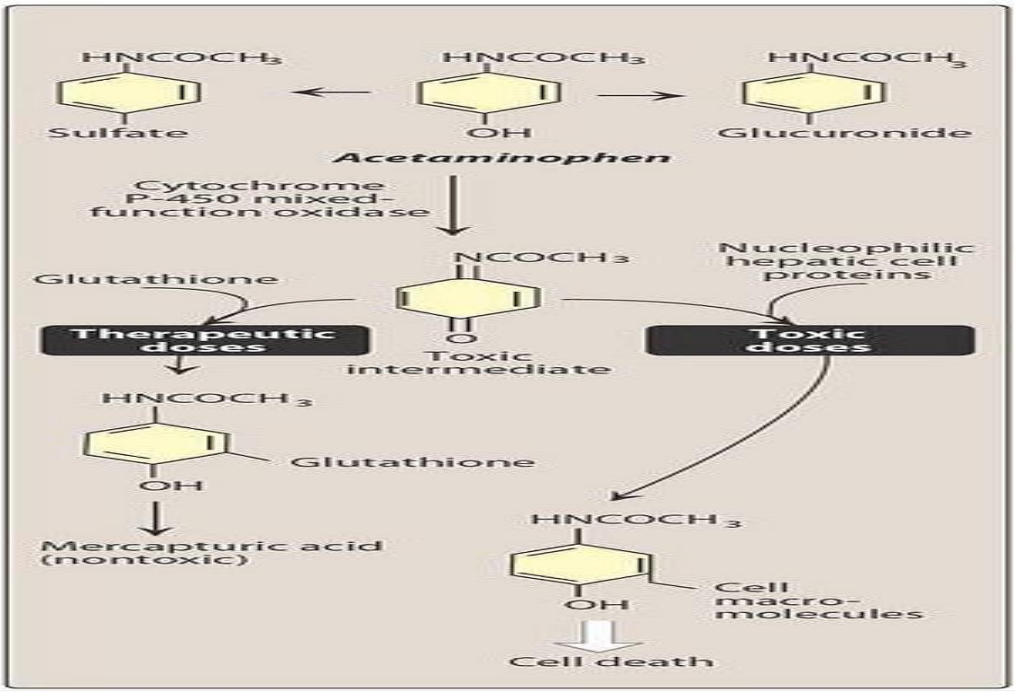
Acetaminophen is rapidly absorbed from the GI tract and undergoes significant first-pass metabolism. It is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of acetaminophen is hydroxylated to form N-acetyl-p-benzoquinoneimine, or NAPQI, a highly reactive metabolite that can react with sulfhydryl groups and cause liver damage.
At normal doses of acetaminophen, NAPQI reacts with the sulfhydryl group of glutathione produced by the liver, forming a nontoxic substance.
Acetaminophen and its metabolites are excreted in urine.
The drug is also available in intravenous and rectal formulations.

Adverse effects:

At normal therapeutic doses, acetaminophen has few significant adverse effects.

With large doses of acetaminophen, the available glutathione in the liver becomes depleted, and NAPQI reacts with the sulfhydryl groups of hepatic proteins. Hepatic necrosis, a serious and potentially life-threatening condition, can result.

Patients with hepatic disease, viral hepatitis, or a history of alcoholism are at higher risk of acetaminophen-induced hepatotoxicity. [Note: N-acetylcysteine is an antidote in cases of overdose.] Acetaminophen should be avoided in patients with severe hepatic impairment.



Traditional Disease-Modifying Antirheumatic Drugs

Traditional DMARDs (methotrexate, hydroxychloroquine, leflunomide, or sulfasalazine) are used in the treatment of RA, slow the course of the disease,

Induce remission, and prevent further destruction of the joints and involved tissues.

Following diagnosis of RA, these agents should be started as soon as possible to delay progression of the disease.

Choice of drug

Mono-therapy may be initiated with any of the traditional DMARDs, although

Methotrexate is generally preferred.

For patients with inadequate response to monotherapy, a combination of traditional DMARDs, or use of a TNF inhibitor or non-TNF biologic agent may be needed.

Combination therapies are both safe and efficacious, NSAIDs or glucocorticoids can also be used for their anti-inflammatory actions.

Methotrexate

Methotrexate is a folic acid antagonist that inhibits cytokine production and purine nucleotide biosynthesis, leading to immunosuppressive and anti-inflammatory effects. Other traditional DMARDs, TNF inhibitors, or non-TNF biologic agents can be added to methotrexate if there is inadequate response to mono-therapy with this agent.

Mainstay of treatment in patients with rheumatoid or psoriatic arthritis.Response to methotrexate occurs within 3 to 6 weeks of starting treatment. Doses of methotrexate required for this treatment are much lower than those needed in cancer chemotherapy and are given once a week, thereby minimizing adverse effects.

adverse effects: mucosal ulceration and nausea .Cytopenias (particularly depression of the WBC count), cirrhosis of the liver, and an acute pneumonia-like syndrome Taking leucovorin once daily after methotrexate reduces the severity of the adverse effects

[Note: Supplementation with folic acid may improve tolerability of methotrexate and reduce GI and hepatic adverse effects.] Periodic liver function tests, complete blood counts, and monitoring for signs of infection are recommended. Methotrexate is contraindicated in pregnancy.

Hydroxychloroquine

Hydroxychloroquine is used for early, mild RA, and may be combined with methotrexate.

Its mechanism of action in autoimmune disorders is unknown, and onset of effects takes 6 weeks to 6 months. Hydroxychloroquine has less adverse effects on the liver and immune system than other DMARDs.

However, it may cause

- ocular toxicity, including irreversible retinal damage and corneal deposits,
- CNS disturbances,
- GI upset, and
- skin discoloration and eruptions.

Leflunomide

Leflunomide is an immune-modulatory agent, causes cell arrest of the autoimmune lymphocytes through its action on dihydroorotate dehydrogenase (DHODH), after biotransformation, leflunomide becomes a reversible inhibitor of DHODH, an enzyme necessary for pyrimidine synthesis. It not only reduces pain and inflammation associated with the disease but also appears to slow the progression of structural damage.

Leflunomide 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.

Common adverse effects include

Headache, diarrhea, and nausea. Other effects are weight loss, allergic reactions, including a flu-like syndrome, skin rash, alopecia, and hypokalemia.

The drug is not recommended in patients with liver disease as it can be hepatotoxic. Leflunomide is **contraindicated** in pregnancy.

Monitoring parameters include signs of infection, complete blood count, electrolytes, and liver enzymes.

Sulfasalazine

Sulfasalazine has recommendations for use similar to leflunomide in the treatment of RA. Its mechanism of action in treating RA is unclear.

Onset of activity is 1 to 3 months. it is associated with GI adverse effects (nausea, vomiting, anorexia) and leukopenia.

Glucocorticoids

Glucocorticoids are potent anti-inflammatory drugs that are commonly used in patients with RA to provide symptomatic relief and bridge the time until other DMARDs become effective.

Glucocorticoids should always be used at the lowest dose and for the shortest duration possible to avoid adverse effects associated with long-term use.

……..

Lec 3 Biologic Disease-Modifying Antirheumatic Drugs

IL-1 and TNF-α are proinflammatory 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, thereby

- degrading cartilage,
- stimulating bone resorption, and
- Inhibiting proteoglycan synthesis.

Biologic DMARDs include the TNF-α inhibitors, as well as the non-TNF biologic agents (abatacept, rituximab, tocilizumab).

The TNF-α inhibitors (adalimumab, certolizumab, etanercept, golimumab, and infliximab) are biologic DMARDs which have been shown to

- decrease signs and symptoms of RA,
- reduce progression of structural damage,
- and improve physical function.

Clinical response can be seen within **2** weeks of therapy.

TNF-α inhibitors should be used cautiously in those with heart failure, as they can cause and/or worsen preexisting heart failure. An increased risk of lymphoma and other cancers has been observed with the use of TNF-α inhibitors.

Like TNF-α inhibitors, non-TNF biologics are generally used in RA after a patient has an inadequate response to traditional DMARDs.

Patients receiving biologic DMARDs are at increased risk for infections, such as tuberculosis, fungal opportunistic infections, and sepsis.

[Note: TNF-α inhibitors and non-TNF biologic agents should not be used together due to the risk of severe infections.]

Reactivation of hepatitis B may occur with the use of these agents. Live vaccinations should not be administered to patients taking any of the biologic DMARDs.

Adalimumab : Adalimumab is a recombinant monoclonal antibody that binds to TNF-α and interferes with its activity by blocking interaction of TNF-α with cell surface receptors. Adalimumab is administered subcutaneously weekly or every other week. It may cause headache, nausea, agranulocytosis, rash, reaction at the injection site, and increased risk of infections.

Certolizumab

Certolizumab is a humanized antibody that neutralizes biological actions of TNF-α.

It is combined with polyethylene glycol (pegylated) and is administered every 2 weeks via subcutaneous injection. Adverse effects are similar to other TNF-α inhibitors.

Etanercept

Etanercept is a genetically engineered fusion protein that binds to TNF-α, thereby blocking its interaction with cell surface TNF-α receptors. Etanercept is given subcutaneously once weekly and is generally well tolerated.

Golimumab

Golimumab neutralizes the biological activity of TNF-α by binding to it and blocking its interaction with cell surface receptors. It is administered subcutaneously once a **month** in combination with methotrexate. Golimumab may increase hepatic enzymes.

Infliximab

Infliximab is a chimeric monoclonal antibody composed of human and murine regions. The antibody binds specifically to human TNF-α and inhibits binding with its receptors. This agent is **not** indicated for monotherapy, as this leads to the development of anti-infliximab antibodies and reduced efficacy. Infliximab should be administered with methotrexate. Infliximab is administered as an IV infusion every **8 weeks**. Infusion-related reactions, such as fever, chills, pruritus, and urticaria, may occur.

Abatacept

T lymphocytes need two interactions to become activated:

1) the antigen-presenting cell (macrophages or B cells) must interact with the receptor on the T cell and

2) the CD80/CD86 protein on the antigen-presenting cell must interact with the CD28 protein on the T cell.

Abatacept is a recombinant fusion protein and co- stimulation modulator that competes with CD28 for binding on CD80/CD86 protein, thereby preventing full T cell activation and reducing the inflammatory response. Abatacept is administered

as an IV infusion every 4 weeks. Common adverse effects include infusion-related reactions, headache, upper respiratory infections, and nausea.

Rituximab

In RA, B lymphocytes can perpetuate the inflammatory process in the syovium by

1) Activating T lymphocytes,
2) producing autoantibodies and rheumatoid factor, and
3) Producing proinflammatory cytokines, such as TNF-α and IL-1.

Rituximab is a chimeric murine/human 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. Rituximab is 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. Infusion reactions (urticaria, hypotension, and angioedema) are the most common complaints and typically occur during the first infusion.

Tocilizumab and sarilumab

Tocilizumab and sarilumab are recombinant monoclonal antibodies that bind to IL-6 receptors and inhibit activity of the proinflammatory cytokine IL-6. Both tocilizumab and sarilumab are administered as a subcutaneous injection every 2 weeks. Tocilizumab may also be administered as an intravenous infusion every 4 weeks.

Adverse reactions include

- elevated liver function tests,
- hyperlipidemia,
- neutropenia,
- hypertension, and
- infusion-related and injection site reactions.

Other Drugs for Rheumatoid Arthritis

Janus kinases are intracellular enzymes that modulate immune cell activity in response to the binding of inflammatory mediators to the cellular membrane.

Tofacitinib is a synthetic small molecule that is an oral inhibitor of Janus kinases. It is indicated for the treatment of moderate to severe established RA in patients who have had an inadequate response or intolerance to methotrexate.

Hemoglobin concentrations must be greater than 9 g/dL to start Tofacitinib and must be monitored during therapy due to the risk for anemia. Likewise, lymphocyte and neutrophil counts should be checked prior to initiation of therapy and monitored during treatment. Tofacitinib treatment may also increase the risk for new primary malignancy and opportunistic infections.

Due to long-term safety concerns, Tofacitinib is usually reserved for patients who have inadequate response or intolerance to other agents.

[Note: Anakinra, azathioprine, cyclosporine, gold, and minocycline are other agents used infrequently in the treatment of RA due to their adverse effect profile or the availability of other agents with more proven efficacy.]

Drugs Used for the Treatment of Gout

Gout is a metabolic disorder characterized by high levels of uric acid in the blood (hyperuricemia). Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney. The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize

the urate crystals. Acute flares of gout usually present as pain, swelling, tenderness, and redness in the affected joints (for example, big toe, knees, ankles, wrists, or elbows). The cause of hyperuricemia in gout is an imbalance between overproduction of uric acid and/or the inability to excrete uric acid renally.

Most therapeutic strategies for gout involve **lowering** the uric acid level below the saturation point (6 mg/dL). This can be accomplished by interfering with uric acid synthesis or increasing uric acid excretion.

Treatment of acute gout: Acute gout attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease.

NSAIDs, corticosteroids, and colchicine are effective agents for the management of acute gouty arthritis.

Patients are candidates for prophylactic urate-lowering therapy if they have more than two attacks per year or they have chronic kidney disease, kidney stones, or tophi (deposit of urate crystals in the joints, bones, cartilage, or other body structures).

Treatment of chronic gout

Urate-lowering therapy for chronic gout aims to reduce the frequency of attacks and complications of gout.

Treatment strategies include the use of xanthine oxidase inhibitors to reduce the synthesis of uric acid or use of uricosuric drugs to increase its excretion.

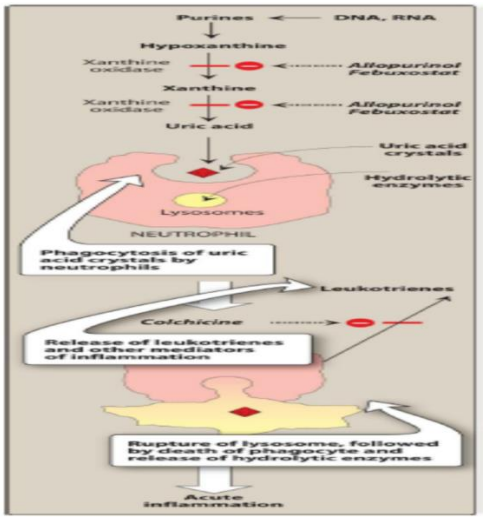
- Xanthine oxidase inhibitors (allopurinol, febuxostat) are first-line urate lowering agents.

- Uricosuric agents (probenecid) may be used in patients who are intolerant to xanthine oxidase inhibitors or fail to achieve adequate response with those agents.

[Note: Initiation of urate-lowering therapy can precipitate an acute gout attack due to rapid changes in serum urate concentrations. Medications for the prevention of an acute gout attack (low-dose colchicine, NSAIDs, or corticosteroids) should be initiated with urate-lowering therapy and continued for at least 6 months.]

Colchicine

Colchicine, a plant alkaloid, is used for the treatment of acute gouty attacks. It is **neither** a uricosuric **nor** an analgesic agent, although it relieves pain in acute attacks of gout.Mechanism of action: Colchicine binds to tubulin, a microtubular protein, causing its depolymerization. This disrupts cellular functions, such as the mobility of neutrophils, thus decreasing their migration into the inflamed joint. Furthermore, colchicine blocks cell division by binding to mitotic spindles.



Therapeutic uses: The anti-inflammatory activity of colchicine is specific for gout, usually alleviating the pain of acute gout within 12 hours. [Note: Colchicine must be administered within 36 hours of onset of attack to be effective.]

NSAIDs have largely replaced colchicine in the treatment of acute gouty attacks for safety reasons. Colchicine is also used as a prophylactic agent to prevent acute attacks of gout in patients initiating urate-lowering therapy.

Pharmacokinetics: Colchicine is administered orally and is rapidly absorbed from the GI tract. Colchicine is metabolized by hepatic CYP450 3A4 and other tissues.

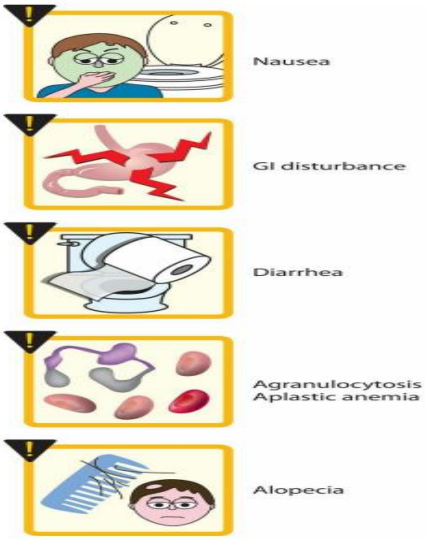
It undergoes enterohepatic recirculation and exhibits high interpatient variability in the elimination half-life. A portion of the drug is excreted unchanged in the urine.

Adverse effects

- Nausea, vomiting, abdominal pain, and diarrhea.
- Chronic administration may lead to myopathy,
- neutropenia, aplastic anemia,
- And alopecia.

The drug should not be used in pregnancy and should be used with caution in patients with hepatic, renal, or cardiovascular disease.

Dosage adjustments are required in patients taking CYP3A4 inhibitors (for example, clarithromycin and itraconazole) or P-glycoprotein efflux pump inhibitors (for example, amiodarone and verapamil) and those with severe renal impairment.



Allopurinol

Allopurinol, a xanthine oxidase inhibitor, is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase.

Therapeutic uses: Allopurinol is an effective urate-lowering therapy in the treatment of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after chemotherapy) or in renal disease.

Pharmacokinetics: Allopurinol is completely absorbed after oral administration.

The primary metabolite alloxanthine (oxypurinol) is also a xanthine oxidase inhibitor with a half-life of 15 to 18 hours. Thus, effective inhibition of xanthine oxidase can be maintained with once-daily dosing.

The drug and its active metabolite are excreted in the urine. Dose adjustment is needed if estimated glomerular filtration rate is less than 30 mL/min/1.73 m2.

Adverse effects: Allopurinol is well tolerated by most patients. Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions. The risk is increased in those with reduced renal function.

Febuxostat

Febuxostat is an oral xanthine oxidase inhibitor structurally **un**related to allopurinol. Its adverse effect profile is similar to that of allopurinol, although the risk for rash and hypersensitivity reactions may be reduced.

Febuxostat does not have the same degree of renal elimination as allopurinol and thus requires less adjustment in those with reduced renal function.

Febuxostat should be used with caution in patients with a history of heart disease or stroke, as this agent may be associated with a greater risk of these events as compared to allopurinol.

Probenecid

Probenecid is an 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. At therapeutic doses, it blocks proximal tubular reabsorption of uric acid.

Probenecid should be avoided if the creatinine clearance is less than 50 mL/min.

Adverse effects include

- nausea, vomiting, and
- dermatologic reactions, and,
- Rarely, anemia or anaphylactic reactions.

Pegloticase

Pegloticase is a recombinant form of the enzyme urate oxidase or uricase. It acts by converting uric acid to allantoin, a water-soluble nontoxic metabolite that is excreted primarily by the kidneys. Pegloticase is indicated for patients with gout who fail treatment with standard therapies such as xanthine oxidase inhibitors. It is administered as an IV infusion every 2 weeks. Infusion-related reactions and anaphylaxis may occur with pegloticase, and patients should be premedicated with antihistamines and corticosteroids.

Lec 4 Drugs affecting bone metabolism

Osteoporosis, Paget disease, and **Osteomalacia** are disorders of the bone.
Osteoporosis is characterized by progressive loss of bone mass and skeletal fragility. Patients with osteoporosis have an increased risk of fractures, which can cause significant morbidity. Osteoporosis occurs most frequently in postmenopausal women and older adults of both sexes.

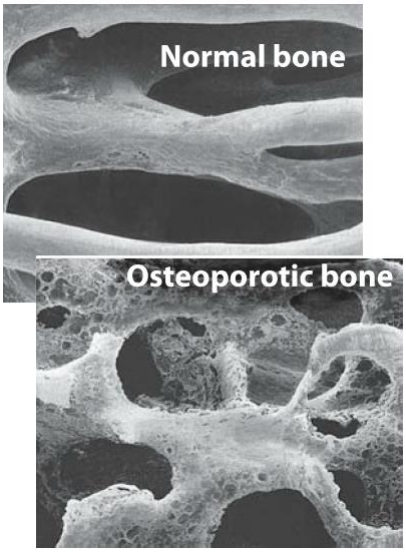
Paget disease is a disorder of bone remodeling that results in disorganized bone formation and enlarged or misshapen bones. Unlike osteoporosis, Paget disease is usually limited to one or a few bones. Patients may experience bone pain, bone deformities, or fractures.

Osteomalacia is softening of the bones that is most often attributed to vitamin D deficiency.

[Note: Osteomalacia in children is referred to as rickets].

Bone remodeling

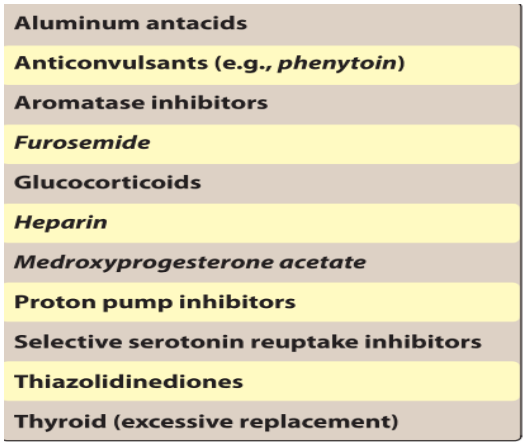
Throughout life, bone undergoes continuous remodeling, with about 10% of the skeleton replaced each year. Bone remodeling serves to remove and replace damaged bone and to maintain calcium homeostasis. **Osteoclasts** are cells that break down bone, a process known as bone resorption. Following bone resorption, **osteoblasts** or bone-building cells synthesize new bone. Crystals of calcium phosphate known as **hydroxyapatite** are deposited in the new bone matrix during the process of bone mineralization. Bone loss occurs when bone resorption exceeds bone formation during the remodeling process.



Prevention of osteoporosis

Strategies to reduce bone loss in postmenopausal women include adequate dietary **intake of calcium and vitamin D, weight-bearing exercise, smoking cessation, and avoidance of excessive alcohol intake**. Patients with inadequate dietary intake of calcium should receive calcium supplementation. Calcium carbonate is an inexpensive and commonly used calcium supplement. It contains 40% elemental

calcium and should be taken with meals for best absorption. Calcium citrate (21% elemental calcium) is better tolerated and may be taken with or without food. **Adverse effects** of calcium supplementation include gas and bloating. Calcium may interfere with absorption of **iron preparations, thyroid replacement, and fluoroquinolone and tetracycline antibiotics,** and administration of these drugs should be separated by several hours. Vitamin D is essential for absorption of calcium and bone health, and older patients are often at risk for vitamin D deficiency. Supplementation with vitamin D2 (ergocalciferol) or vitamin D3 (cholecalciferol) is used for treatment.



Treatment of osteoporosis

Pharmacologic therapy for osteoporosis is warranted in postmenopausal women and men aged 50 years or over who have a previous osteoporotic fracture, a bone mineral density that is 2.5 standard deviations or more below that of a healthy young adult, or a low bone mass (osteopenia) with a high probability of future fractures.

Bisphosphonates

Bisphosphonates including **alendronate**, **risedronate**, and **zoledronic acid** are preferred agents for treatment of postmenopausal osteoporosis. These

bisphosphonates, along with **etidronate**, **ibandronate**, **pamidronate**, and **tiludronate**, comprise an important drug group used for the treatment of bone disorders such as osteoporosis and Paget disease, as well as for treatment of bone metastases and hypercalcemia of malignancy.

Mechanism of action: Bisphosphonates bind to hydroxyapatite crystals in the bone and decrease osteoclastic bone resorption, resulting in a small increase in bone mass and a decreased risk of fractures in patients with osteoporosis. The beneficial effects of alendronate persist over several years of therapy, but discontinuation results in a gradual loss of effects.

Pharmacokinetics: The oral bisphosphonates alendronate, risedronate, and ibandronate are dosed on a daily, weekly, or monthly basis depending on the drug.

BISPHOSPHONATE	FORMULATION	DOSING FREQUENCY*
Alendronate	Oral tablet Effervescent tablet	Daily or weekly Weekly
Ibandronate	Oral tablet Intravenous	Daily or monthly Every 3 months
Risedronate	Oral tablet Oral delayed-release tablet	Daily, weekly, or monthly Weekly
Zoledronic acid	Intravenous	Yearly

DOSING INSTRUCTIONS FOR ORAL BISPHOSPHONATES

- Take with 6 to 8 ounces of plain water only
  [Note: Take *risedronate* delayed-release tablet with at least 4 ounces of plain water]
- Take at least 30 minutes (60 minutes for *ibandronate*) BEFORE other food, drink, or medications
  [Note: Take *risedronate* delayed-release tablet immediately AFTER breakfast]
- Remain upright and do not lie down or recline for at least 30 minutes (60 minutes for *ibandronate*) after taking

Absorption after oral administration is poor, with less than 1% of the dose absorbed. Food and other medications significantly interfere with absorption of oral bisphosphonates. Bisphosphonates are rapidly cleared from the plasma, primarily because they avidly bind to hydroxyapatite in the bone. Elimination is predominantly via the kidney, and bisphosphonates should be avoided in severe

renal impairment. For patients unable to tolerate oral bisphosphonates, intravenous ibandronate and zoledronic acid are alternatives.

Adverse effects: These include diarrhea, abdominal pain, and musculoskeletal pain. Alendronate, risedronate, and ibandronate are associated with esophagitis and esophageal ulcers. To minimize esophageal irritation, patients should remain upright after taking oral bisphosphonates. Although uncommon, osteonecrosis of the jaw and atypical femur fractures may occur with use of bisphosphonates. The risk of atypical fractures seems to increase with long-term use of bisphosphonates. Therefore, current guidelines recommend a drug holiday for some patients after 5 years of oral bisphosphonates or 3 years of zoledronic acid.

Figure below show relative potencies of the bisphosphonates.

Bisphosphonate	Antiresorptive activity
Etidronate	1
Tiludronate	10
Pamidronate	100
Alendronate	1000
Risedronate	5000
Ibandronate	10,000
Zoledronic acid	10,000

Denosumab: **Denosumab** is a monoclonal antibody that targets receptor activator of nuclear factor kappa-8 ligand and inhibits osteoclast formation and function. Denosumab is approved for the treatment of postmenopausal osteoporosis in women at high risk of fracture. It is administered via subcutaneous injection every 6 months. Denosumab is considered a first-line agent for osteoporosis, particularly in patients at higher risk of fractures. The drug has been

associated with an increased risk of infections, dermatological reactions, hypocalcemia, and rarely, osteonecrosis of the jaw, and atypical fractures.

Parathyroid agents

Teriparatide is a recombinant form of human parathyroid hormone and **abaloparatide** is an analog of parathyroid hormone-related peptide. These drugs act as agonists at the parathyroid hormone receptor, and once-daily subcutaneous administration results in stimulation of osteoblastic activity and increased bone formation and bone strength. By contrast, other drugs for osteoporosis inhibit bone resorption. These agents should be reserved for patients at high risk of fractures and those who have failed or cannot tolerate other osteoporosis therapies. Both drugs have been associated with hypercalcemia, orthostatic hypotension, and an increased risk of osteosarcoma in rats. Cumulative lifetime use of either agent for more than 2 years is not recommended.

Selective estrogen receptor modulators

Lower estrogen levels after menopause promote proliferation and activation of osteoclasts, and bone mass can decline rapidly. Estrogen replacement is effective for the prevention of postmenopausal bone loss. However, since estrogen may increase the risk of endometrial cancer, breast cancer, stroke, venous thromboembolism, and coronary events, it is no longer recommended as a preventive therapy for osteoporosis. **Raloxifene** is a selective estrogen receptor modulator approved for the prevention and treatment of osteoporosis. It has estrogen-like effects on bone and estrogen antagonist effects on breast and endometrial tissue. Therefore, raloxifene increases bone density without increasing the risk of endometrial cancer, raloxifene should be used as an alternative to bisphosphonates or denosumab in the treatment of postmenopausal osteoporosis.

Adverse effects include hot flashes, leg cramps, and increased risk of venous thromboembolism.

Calcitonin

Salmon calcitonin is indicated for the treatment of osteoporosis in women who are at least 5 years postmenopausal. The drug reduces bone resorption, but it is less effective than other agents, and is no longer routinely recommended for the treatment of osteoporosis.. The intranasal formulation is most commonly used in osteoporosis, and adverse effects include rhinitis and other nasal symptoms.

.....

Lec 5 Drugs For Diabetes :

The pancreas produces the peptide hormones **insulin, glucagon, and somatostatin.** The peptide hormones are secreted from cells in the islets of Langerhans (**β-cells produce insulin, α-cells produce glucagon, and delta-cells produce somatostatin).** These hormones play an important role in regulating metabolic activities of the body, particularly glucose homeostasis. A relative or absolute lack of insulin, as seen in diabetes mellitus, can cause serious hyperglycemia. Left untreated, retinopathy, nephropathy, neuropathy, and cardiovascular complications may result. Administration of insulin preparations or other glucose-lowering agents can reduce morbidity and mortality associated with diabetes.

Diabetes mellitus

The incidence of diabetes is growing rapidly in the United States and worldwide. An estimated 30.3 million people in the United States and 422 million people

worldwide are afflicted with diabetes. Diabetes is not a single disease. Rather, it is a heterogeneous group of syndromes characterized by elevated blood glucose attributed to a relative or absolute deficiency of insulin. The American Diabetes Association (ADA) recognizes four clinical classifications of diabetes:

Type 1 diabetes, type 2 diabetes, gestational diabetes, and diabetes due to other causes such as genetic defects or medications.

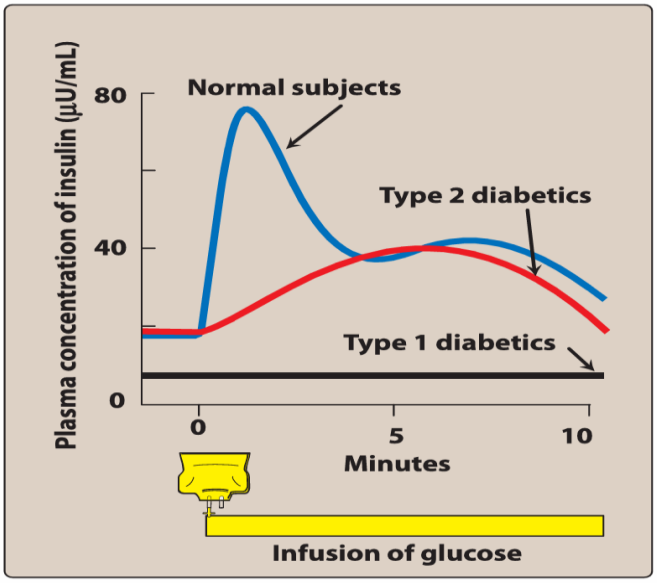
Gestational diabetes is defined as carbohydrate intolerance with onset or first recognition during pregnancy.

	Type 1	Type 2
Age at onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence among diagnosed diabetics	5%–10%	90%–95%
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β Cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

A. Type 1 diabetes

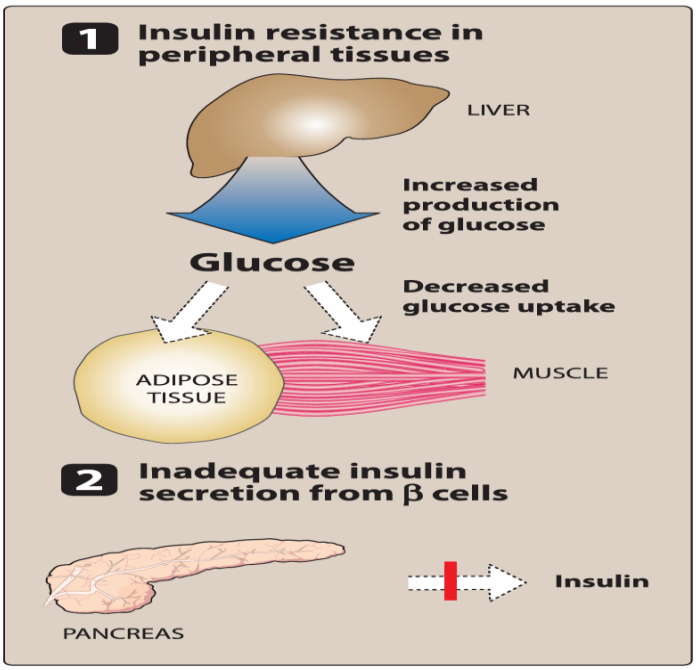
Type 1 diabetes most commonly afflicts children, adolescents, or young adults, but some latent forms occur later in life. The disease is characterized by an absolute deficiency of insulin due to destruction of β cells. Without functional β cells, the pancreas fails to respond to glucose, and a person with type 1 diabetes shows classic symptoms of insulin deficiency (polydipsia, polyphagia, polyuria, and weight loss).

Causes: Loss of β -cell function in type 1 diabetes results from autoimmune-mediated processes that may be triggered by viruses or other environmental toxins. In normal subjects (without diabetes), constant β -cell secretion of insulin suppresses lipolysis, proteolysis, and glycogenolysis. A burst of insulin secretion occurs within 2 minutes after ingesting a meal, in response to transient increases in circulating glucose and amino acids. This lasts for up to 15 minutes, followed by the postprandial secretion of insulin. However, without functional β cells, those with type 1 diabetes can neither maintain basal secretion of insulin nor respond to variations in circulating glucose.



Treatment: A person with type 1 diabetes must rely on exogenous insulin to control hyperglycemia, avoid ketoacidosis, and maintain acceptable levels of glycosylated hemoglobin (HbA1c). [Note: HbA1c is a marker of overall glucose control and is used to monitor diabetes in clinical practice.

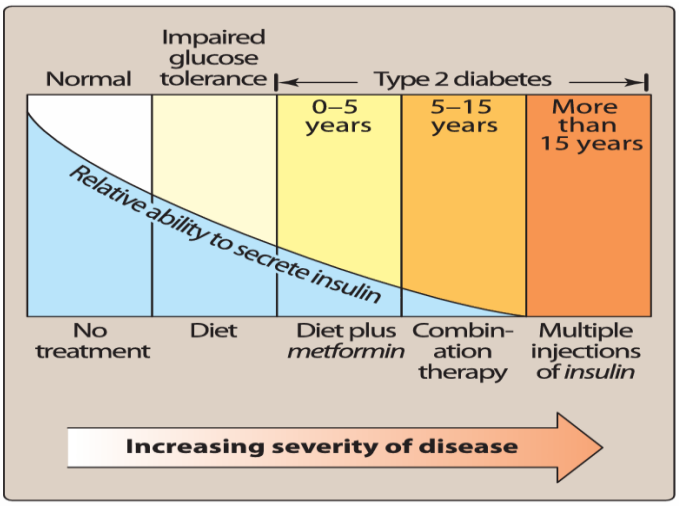
The rate of formation of HbA1c is proportional to the average blood glucose concentration over the previous 3 months. A higher average glucose results in a higher HbA1c·l the goal of insulin therapy in type 1 diabetes is to: maintain blood glucose as close to normal as possible and to avoid wide fluctuations in glucose. The use of home blood glucose monitors facilitates frequent self-monitoring and treatment with insulin.



B. Type 2 diabetes Type 2 diabetes accounts for greater than 90% of cases. Type 2 diabetes is influenced by genetic factors, aging, obesity, and peripheral insulin resistance, rather than autoimmune processes.

The metabolic alterations are generally milder than those observed with type 1 diabetes (for example, patients with type 2 diabetes typically are not ketotic), but the long-term clinical consequences are similar.

Cause: Type 2 diabetes is characterized by a lack of sensitivity of target organs to insulin. In type 2 diabetes, the pancreas retains some β -cell function, but insulin secretion is insufficient to maintain glucose homeostasis in the face of increasing peripheral insulin resistance. The β-cell mass may gradually decline over time in type 2 diabetes. In contrast to patients with type 1 diabetes, those with type 2



diabetes are often obese. Obesity contributes to insulin resistance, which is considered the major underlying defect of type 2 diabetes.

Treatment: The goal in treating type 2 diabetes is to maintain blood glucose within normal limits and to prevent the development of long-term complications. Weight reduction, exercise, and dietary modification decrease insulin resistance and correct hyperglycemia in some patients with type 2 diabetes. However, most patients require pharmacologic intervention with oral glucose-lowering agents. As the disease progresses, β-cell function declines, and insulin therapy is often needed to achieve satisfactory glucose levels.

Insulin and Insulin analogs

Insulin is a polypeptide hormone consisting of two peptide chains that are connected by disulfide bonds. It is synthesized as a precursor (proinsulin) that undergoes proteolytic cleavage to form insulin and C-peptide, both of which are secreted by the β cells of the pancreas.

[Note: Because insulin undergoes significant hepatic and renal extraction, plasma insulin levels may not accurately reflect insulin production. Thus, measurement of C-peptide provides a better index of insulin levels.]

Insulin secretion is regulated by blood glucose levels, certain amino acids, other hormones, and autonomic mediators. Secretion is most often triggered by increased blood glucose, which is taken up by the glucose transporter into the β cells of the pancreas. There, it is phosphorylated by glucokinase, which acts as a glucose sensor. The products of glucose metabolism enter the mitochondrial respiratory chain and generate adenosine triphosphate (ATP). The rise in ATP levels causes a blockade of K+ channels, leading to membrane depolarization and an influx of Ca2 +. The increase in intracellular Ca2 + causes pulsatile insulin exocytosis.

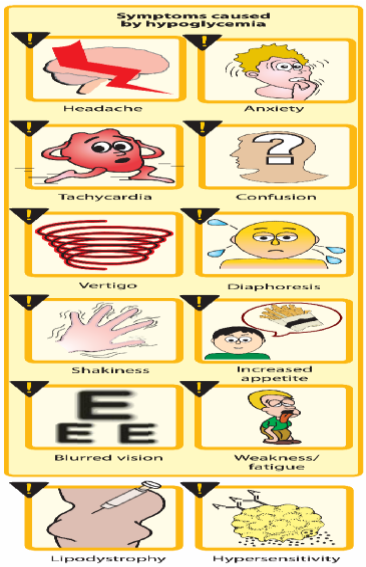
A. Mechanism of action

Exogenous insulin is administered to replace absent insulin secretion in type 1 diabetes or to supplement insufficient insulin secretion in type 2 diabetes.

B. Pharmacokinetics

Human insulin is produced by recombinant DNA technology using strains of Escherichia coli or yeast that are genetically altered to contain the gene for human insulin. Modification of the amino acid sequence of human insulin produces

insulins with different pharmacokinetic properties. Insulin preparations vary primarily in their onset and duration of activity. Dose, injection site, blood supply, temperature, and physical activity can also affect the onset and duration of various insulin preparations. Because insulin is a polypeptide, it is degraded in the gastrointestinal tract if taken orally. Therefore, it is generally administered by subcutaneous injection, although an inhaled insulin formulation is also available. **[Note:** In a **hyperglycemic emergency**, **regular insulin** is administered intravenously (IV).] Continuous subcutaneous insulin infusion (also called the insulin pump) is another method of insulin delivery. This method of administration may be more convenient for some patients, eliminating multiple daily injections of insulin. The pump is programmed to deliver a basal rate of insulin. In addition, it allows the patient to deliver a bolus of insulin to cover mealtime carbohydrate intake and compensate for high blood glucose.



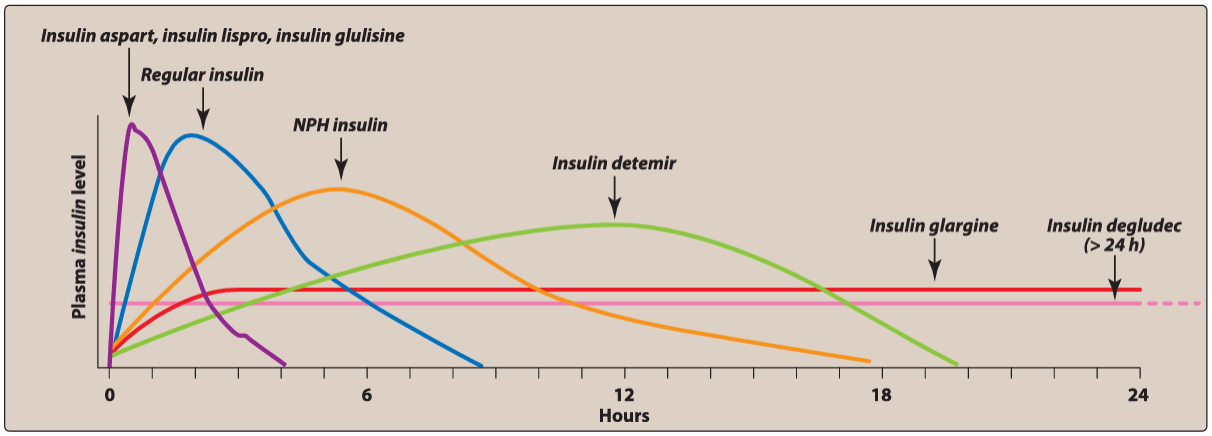
C. Adverse effects

Hypoglycemia is the most serious and common adverse reaction to insulin.

Other adverse effects include **weight gain,** local injection site reactions, and lipodystrophy. **Lipodystrophy** can be minimized by rotation of injection sites. Diabetics with renal insufficiency may require a decrease in insulin dose. Due to the potential for bronchospasm with inhaled insulin, patients with asthma, chronic obstructive pulmonary disease, and smokers should not use this formulation.

Insulin preparations and treatment

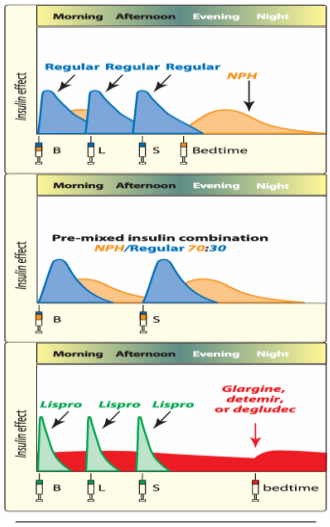
Insulin preparations are classified as **rapid-, short-, intermediate-, or long-acting.** It is important that clinicians exercise caution when adjusting insulin treatment, paying strict attention to the dose and type of insulin.



A. Rapid-acting and short-acting insulin preparations

Five preparations fall into this category: **regular insulin**, **insulin lispro**, **insulin aspart, insulin glulisine, and inhaled insulin**. Regular insulin is a short-acting, soluble, crystalline zinc insulin. Insulin lispro, aspart, and glulisine are classified as rapid-acting insulins. Modification of the amino acid sequence of regular insulin produces analogs that are rapid-acting insulins. This modification results in more rapid absorption, a quicker onset, and a shorter duration of action after subcutaneous injection. Peak levels of insulin lispro are seen at 30 to 90 minutes, as compared with 50 to 120 minutes for regular insulin. Insulin aspart and insulin glulisine have pharmacokinetic and pharmacodynamic properties similar to those of insulin lispro. Inhaled insulin is also considered rapid-acting. This dry powder formulation is inhaled and absorbed through pulmonary tissue, with peak levels

achieved within 45 to 60 minutes. Rapid- or short-acting insulins are administered to mimic the prandial (mealtime) release of insulins and to control postprandial glucose. They may also be used in cases where swift correction of elevated glucose is needed. Rapid- and short-acting insulins are usually used in conjunction with a longer-acting basal insulin that provides control of fasting glucose. Regular insulin should be injected subcutaneously 30 minutes before a meal, whereas rapid-acting insulins are administered in the 15 minutes preceding a meal or within 15 to 20 minutes after starting a meal. Rapid-acting insulin suspensions are commonly used in external insulin pumps, and they are suitable for IV administration, although regular insulin is most commonly used when the IV route is needed.



B. Intermediate-acting insulin

Neutral protamine Hagedorn (NPH) insulin is an intermediate-acting insulin formed by the addition of **zinc and protamine** to regular insulin. [Note: Another name for this preparation is insulin isophane.] The combination with protamine forms a complex that is less soluble, resulting in delayed absorption and a longer duration of action. NPH insulin is used for basal (fasting) control in type 1 or 2 diabetes and is usually given along with rapid- or short-acting insulin for mealtime control. NPH insulin should be given only subcutaneously (never IV), and it should not be used when rapid glucose lowering is needed (for example, diabetic ketoacidosis).

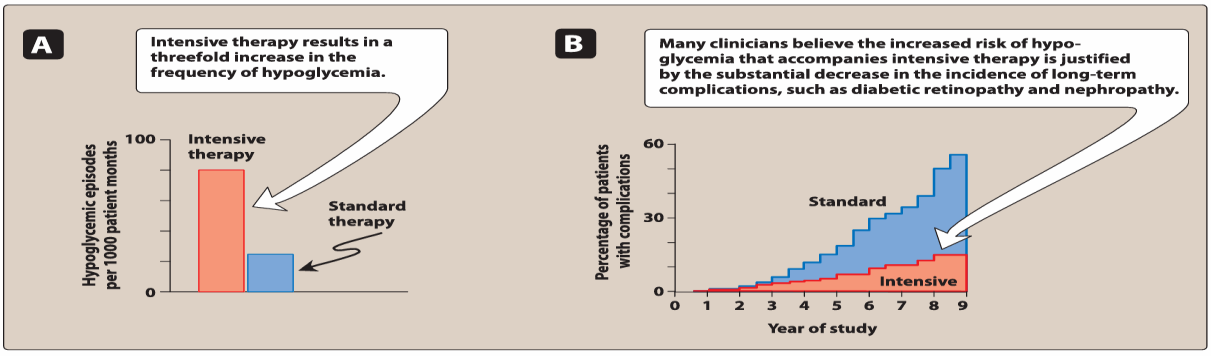
C. Long-acting insulin preparations : The isoelectric point of insulin **glargine** is lower than that of human insulin, leading to formation of a precipitate at the injection site that releases insulin over an extended period. It has a slower onset than NPH insulin and a flat, prolonged hypoglycemic effect with no peak. Insulin **detemir** has a fatty acid side chain that enhances association to albumin. Slow dissociation from albumin results in long-acting properties similar to those of insulin glargine.l nsulin **degludec** remains in solution at physiologic pH, with a slow release over an extended period. It has the longest half-life of the long-acting insulins. As with NPH insulin, insulin glargine, insulin detemir, and insulin degludec are used for basal control and should only be administered subcutaneously. Longacting insulins should not be mixed in the same syringe with other insulins, because doing so may alter the pharmacodynamic profile.

D. Insulin combinations

Various premixed combinations of human insulins, such as 70% NPH insulin plus 30% regular insulin or 50% of each of these, are also available. Use of premixed combinations decreases the number of daily injections but makes it more difficult to adjust individual components of the insulin regimen.

E. Standard treatment versus intensive treatment

Standard insulin therapy involves twice daily injections. In contrast, intensive treatment utilizes three or more injections daily with frequent monitoring of blood glucose levels. The ADA recommends a target mean blood glucose level of 154 mg/dl or less (HbA1c :S 7%) for most patients, and intensive treatment is more likely to achieve this goal. The frequency of hypoglycemic episodes, coma, and seizures is higher with intensive insulin regimens.



However, patients on intensive therapy show a significant reduction in microvascular complications of diabetes such as retinopathy, nephropathy, and neuropathy compared to patients receiving standard care. Intensive therapy should not be recommended for patients with long-standing diabetes, significant microvascular complications, advanced age, and those with hypoglycemic unawareness.

Synthetic amylin analog

Amylin is a hormone that is co-secreted with insulin from β cells following food intake. It delays gastric emptying, decreases postprandial glucagon secretion, and improves satiety. **Pramlintide** is a synthetic amylin analog that is indicated as an adjunct to mealtime insulin therapy in patients with type 1 and type 2 diabetes. Pramlintide is administered by subcutaneous injection immediately before meals. When pramlintide is initiated, the dose of mealtime insulin should be decreased by 50% to avoid a risk of severe hypoglycemia. Other adverse effects include nausea, anorexia, and vomiting. Pramlintide may not be mixed in the same syringe with insulin, and it should be avoided in patients with diabetic gastroparesis (delayed stomach emptying), cresol hypersensitivity, or hypoglycemic unawareness.

Glucagon-like peptide receptor agonists

Oral intake of glucose results in a higher secretion of insulin than occurs when an equal load of glucose is given IV. This effect is referred to as the **"incretin effect"** and is markedly reduced in type 2 diabetes. The incretin effect occurs because the gut releases incretin hormones, notably **glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP),** in response to a meal. Incretin hormones are responsible for 60% to 70% of postprandial insulin secretion. **Albiglutide**, **dulaglutide**, **exenatide**, **liraglutide**, **lixisenatide**, and **semaglutide** are injectable GLP-1 receptor agonists used for the treatment of type 2 diabetes. Liraglutide is also approved to reduce the risk of cardiovascular events and cardiovascular mortality in patients with type 2 diabetes and cardiovascular disease. Two premixed preparations of long-acting insulins and GLP-1 receptor agonists are available: insulin glargine plus lixisenatide and insulin degludec plus liraglutide. Use of these combinations may decrease daily insulin requirements and the number of daily injections.

Mechanism of action These agents are analogs of GLP-1 that exert their activity by improving glucose-dependent insulin secretion, slowing gastric emptying time, reducing food intake by enhancing satiety (a feeling of fullness), decreasing postprandial glucagon secretion, and promoting β-cell proliferation. Consequently, postprandial hyperglycemia is reduced, HbA1c levels decline, and weight loss may occur.

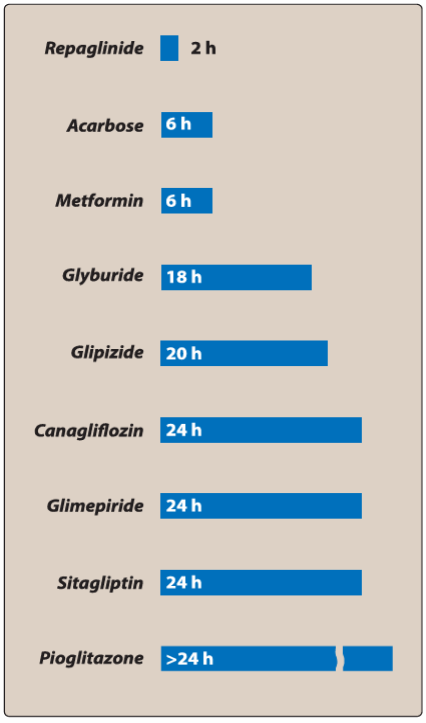
Pharmacokinetics GLP-1 receptor agonists are administered subcutaneously, since they are polypeptides. Albiglutide, dulaglutide, liraglutide, and semaglutide are considered long-acting GLP-1 receptor agonists. Albiglutide, dulaglutide, and semaglutide are dosed **once weekly**, while liraglutide is available as a **once-daily**

injection. Lixisenatide is a short-acting GLP-1 receptor agonist that is dosed once daily. Exenatide is available as both a short-acting (dosed twice daily) and extended-release preparation (dosed once weekly). Exenatide should be avoided in patients with severe renal impairment.

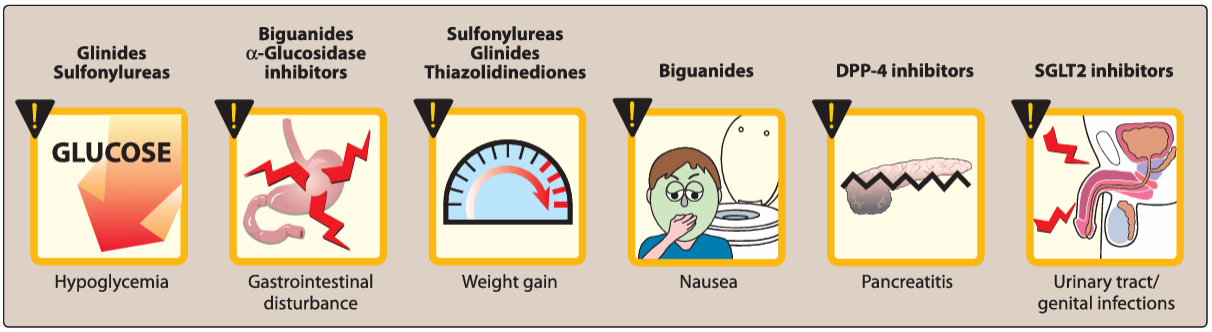
Adverse effects: The main adverse effects of the incretin mimetics consist of N, V,D and constipation. GLP-1 receptor agonists have been associated with pancreatitis and should be avoided in patients with chronic pancreatitis. Longer-acting agents have been associated with thyroid C-cell tumors in rodents. It is unknown if GLP-1 receptor agonists cause these tumors or thyroid carcinoma in humans, although they are contraindicated in patients with a history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.

Oral hypoglycemic drugs

Oral agents are useful in the treatment of patients who have type 2 diabetes that is not controlled with diet. Patients who developed diabetes after age 40 and have had diabetes less than 5 years are most likely to respond well to oral glucose-lowering agents. Patients with long-standing disease may require a combination of oral agents with or without insulin to control hyperglycemia.



The duration of action of some of the oral glucose-lowering drugs and some of the common adverse effects are shown in the figers.



A. Sulfonylureas

These agents are classified as insulin **secretagogues,** because they promote insulin release from the β cells of the pancreas. The sulfonylureas most used in clinical practice are the second-generation drugs **glyburide, glipizide**, and **glimepiride**.

Mechanism of action: These agents stimulate insulin release from the β cells of the pancreas. Sulfonylureas block ATP-sensitive K+ channels, resulting in depolarization, Ca2+ influx, and insulin exocytosis. In addition, sulfonylureas may reduce hepatic glucose production and increase peripheral insulin sensitivity.

Pharmacokinetics: Given orally, these drugs bind to serum proteins, are metabolized by the liver, and are excreted in the urine and feces. The duration of action ranges from 12 to 24 hours.

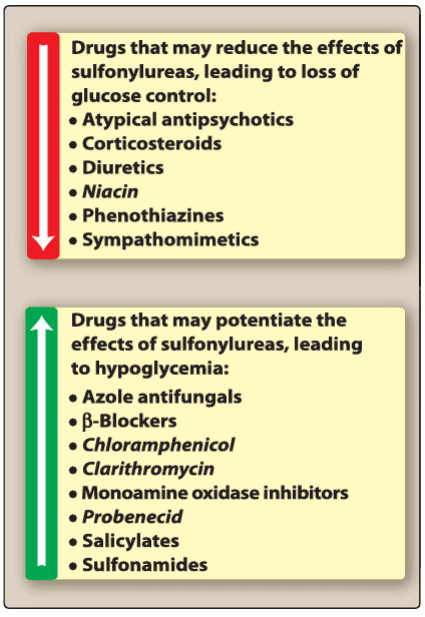
Adverse effects: Adverse effects of the sulfonylureas include hypoglycemia, hyperinsulinemia, and weight gain. They should be used with caution in hepatic or renal insufficiency, since accumulation of sulfonylureas may cause hypoglycemia. Renal impairment is a particular problem for glyburide, as it may increase the duration of action and increase the risk of hypoglycemia significantly. Glipizide or glimepiride are safer options in renal dysfunction and in elderly patients.

B. Glinides

This class of agents includes **repaglinide and nateglinide**. Glinides are also considered insulin secretagogues.

1. Mechanism of action: Like the sulfonylureas, the glinides stimulate insulin secretion. In contrast to the sulfonylureas, the glinides have **a rapid onset and a short duration of action.** They are particularly effective in the early release of insulin that occurs after a meal and are categorized as postprandial glucose regulators. Glinides should not be used in combination with sulfonylureas due to overlapping mechanisms of action and increased risk of serious hypoglycemia.

2. Pharmacokinetics: Glinides should be taken prior to a meal and are well absorbed after oral administration. Both glinides are metabolized to inactive products by cytochrome P450 3A4 in the liver and are excreted through the bile.



3. Adverse effects: Although glinides cause hypoglycemia and weight gain, the incidence is lower than that with sulfonylureas. By inhibiting hepatic

metabolism, the lipid-lowering drug gemfibrozil may significantly increase the effects of repaglinide, and concurrent use is contraindicated. These agents should be used with caution in patients with hepatic impairment.

C. Biguanides

Metformin, the only biguanide, is classified as an insulin **sensitizer**. It increases glucose uptake and use by target tissues, thereby decreasing insulin resistance. Unlike sulfonylureas, metformin does not promote insulin secretion. Therefore, the risk of hypoglycemia is far less than that with sulfonylureas. Metformin is also useful in the treatment of **polycystic ovary syndrome**, as it reduces insulin resistance seen in this disorder.

Mechanism of action: The main mechanism of action of metformin is reduction of hepatic gluconeogenesis. [Note: Excess glucose produced by the liver is a major source of high blood glucose in type 2 diabetes, accounting for high fasting blood glucose.] Metformin also slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization. Weight loss may occur because metformin causes loss of appetite. The ADA recommends metformin as the initial drug of choice for type 2 diabetes. Metformin may be used alone or in combination with other oral agents or insulin. Hypoglycemia may occur when metformin is taken in combination with insulin or insulin secretagogues, so adjustment in dosage may be required.

Pharmacokinetics: Metformin is well absorbed after oral administration, is not bound to serum proteins, and is not metabolized. Excretion is via the urine.

Adverse effects: These are largely gastrointestinal, including NVD. These effects can be reduced by titrating the dose of metformin slowly and administering

doses with meals. Metformin is contraindicated in renal dysfunction due to the risk of lactic acidosis. It should be discontinued in cases of acute myocardial infarction, exacerbation of heart failure, sepsis, or other disorders that can cause acute renal failure. Metformin should be used with caution in patients older than 80 years and in those with heart failure or alcohol abuse. It should be temporarily discontinued in patients undergoing procedures requiring IV radiographic contrast. **Rarely**, potentially fatal lactic acidosis has occurred. Long-term use may be associated with vitamin B12 deficiency, and periodic measurement of vitamin B12 1evels is recommended, especially in patients with anemia or peripheral neuropathy.

D. Thiazolidinediones

The thiazolidinediones (TZDs) are also insulin sensitizers. The two agents in this class are **pioglitazone** and **rosiglitazone.** Although insulin is required for their action, the TZDs do not promote its release from the β cells, so hyperinsulinemia is not a risk.

Mechanism of action: The TZDs lower insulin resistance by acting as agonists for the peroxisome proliferator-activated receptor-γ (PPARγ), a nuclear hormone receptor. Activation of PPARγ regulates the transcription of several insulin responsive genes, resulting in increased insulin sensitivity in adipose tissue, liver, and skeletal muscle. The TZDs can be used as monotherapy or in combination with other glucose-lowering agents or insulin. The dose of insulin may have to be lowered when used in combination with these agents. The ADA recommends pioglitazone as a second- or third line agent for type 2 diabetes. Rosiglitazone is less utilized due to concerns regarding cardiovascular adverse effects.

Pharmacokinetics: Pioglitazone and rosiglitazone are well absorbed after oral administration and are extensively bound to serum albumin. Both undergo extensive metabolism by different CYP450 isozymes. Some metabolites of pioglitazone have activity. Renal elimination of pioglitazone is negligible, with the majority of active drug and metabolites excreted in the bile and eliminated in the feces. Metabolites of rosiglitazone are primarily excreted in the urine. No dosage adjustment is required in renal impairment.

3. Adverse effects: Liver toxicity has occasionally been reported with these drugs, and baseline and periodic monitoring of liver function is recommended. Weight gain can occur because TZDs may increase subcutaneous fat and cause fluid retention. [Note: **Fluid retention can worsen heart failure. These drugs should be avoided in patients with severe heart failure**.] TZDs have been associated with osteopenia and increased fracture risk in women. Pioglitazone may also increase the risk of bladder cancer. Additionally, rosiglitazone increased risk of myocardial infarction and angina with the use of this agent.

E. α-Glucosidase inhibitors

Acarbose and miglitol are oral agents used for the treatment of type 2 diabetes.

Mechanism of action: Located in the intestinal brush border, α-glucosidase enzymes break down carbohydrates into glucose and other simple sugars that can be absorbed. Acarbose and miglitol reversibly inhibit α -glucosidase enzymes. When taken at the start of a meal, these drugs delay the digestion of carbohydrates, resulting in lower postprandial glucose levels. Since they do not stimulate insulin release or increase insulin sensitivity, these agents do not cause hypoglycemia when used as monotherapy. However, when used with insulin secretagogues or insulin, hypoglycemia may develop. [Note: It is important that hypoglycemia in

this context be treated with glucose rather than sucrose, because sucrase is also inhibited by these drugs.]

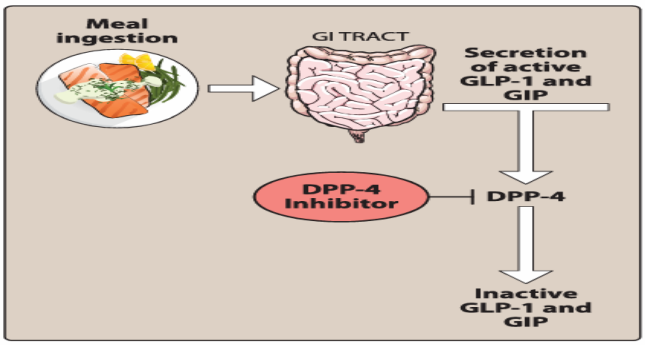
Pharmacokinetics: Acarbose is poorly absorbed. lt is metabolized primarily by intestinal bacteria, and some of the metabolites are absorbed and excreted into the urine. Miglito is very well absorbed but has no systemic effects. It is excreted unchanged by the kidney.

Adverse effects: The most common adverse effects are flatulence, diarrhea, and abdominal cramping. Adverse effects limit the use of these agents in clinical practice. Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.

F. Dipeptidyl peptidase-4 inhibitors

Alogliptin, linagliptin, saxagliptin, and sitagliptin are oral dipeptidyl peptidase-4 (DPP-4) inhibitors used for the treatment of type 2 diabetes.

Mechanism of action: These drugs inhibit the enzyme DPP4, which is responsible for the inactivation of incretin hormones such as GLP-1.



Prolonging the activity of incretin hormones increases release of insulin in response to meals and reduces inappropriate secretion of glucagon. DPP-4 inhibitors may be used as monotherapy or in combination with sulfonylureas, metformin, TZDs, or insulin. Treatment guidelines do not recommend the combination of DPP-4 inhibitors with GLP-1 receptor agonists for management of diabetes due to overlapping mechanisms and toxicity. Unlike GLP-1 receptor agonists, these drugs do not cause satiety or fullness and are weight neutral.

Pharmacokinetics: The DPP-4 inhibitors are well absorbed after oral administration. Food does not affect the extent of absorption. Alogliptin and sitagliptin are mostly excreted unchanged in the urine. Saxagliptin is metabolized via CYP450 to an active metabolite. The primary route of elimination for saxagliptin and the metabolite is renal. Linagliptin is primarily eliminated via the enterohepatic system. All DPP-4 inhibitors except linagliptin require dosage adjustments in renal dysfunction.

Adverse effects: In general, DPP-4 inhibitors are well tolerated, with the most common adverse effects being nasopharyngitis and headache. Although infrequent, pancreatitis has occurred with the use of DPP-4 inhibitors.

Agents in this class may also increase the risk of severe, disabling joint pain. Alogliptin and saxagliptin have also been shown to increase the risk of heart failure hospitalizations and should be used with caution in patients with or at risk for heart failure.

G. Sodium-glucose cotransporter 2 inhibitors

Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are oral agents for the treatment of type 2 diabetes. Empagliflozin is also indicated to reduce the risk of cardiovascular death in patients with type 2 diabetes and cardiovascular disease.

Mechanism of action: The sodium-glucose cotransporter 2 (SGLT2) is responsible for reabsorbing filtered glucose in the tubular lumen of the kidney. By inhibiting SGLT2, these agents decrease reabsorption of glucose, increase urinary glucose excretion, and lower blood glucose. Inhibition of SGLT2 also decreases reabsorption of sodium and causes osmotic diuresis. Therefore, SGLT2 inhibitors may reduce systolic blood pressure. However, they are not indicated for the treatment of hypertension.

Pharmacokinetics: These agents are given once daily in the morning. Canagliflozin should be taken before the first meal of the day. All drugs are mainly metabolized by glucuronidation to inactive metabolites. These agents should be avoided in patients with renal dysfunction.

Adverse effects: The most common adverse effects with SGLT2 inhibitors are female genital mycotic infections (for example, vulvovaginal candidiasis), urinary tract infections, and urinary frequency. Hypotension has also occurred, particularly in the elderly or patients on diuretics. Thus, volume status should be evaluated prior to starting these agents. Ketoacidosis has been reported with use of SGLT2 inhibitors, and these agents should be used with caution in patients with risk factors that predispose to ketoacidosis (for example, alcohol abuse and caloric restriction related to surgery or illness)

H. Other agents

Both the dopamine agonist **bromocriptine** and the bile acid sequestrant **colesevelam** produce modest reductions in HbA1c. The mechanism of action of glucose lowering is **unknown** for both of these drugs. Although bromocriptine and colesevelam are indicated for the treatment of type 2 diabetes, their modest efficacy, adverse effects, and pill burden limit their use in clinical practice. Figures below summary of the oral antidiabetic agents and GLP-1 receptor agonists and treatment guidelines for type 2 diabetes.

DRUG CLASS	MECHANISM OF ACTION	EFFECT ON PLASMA INSULIN	RISK OF HYPO-GLYCEMIA	COMMENTS
Sulfonylureas *Glimepiride* *Glipizide* *Glyburide*	Stimulates insulin secretion	↑	Yes	Well-established history of effectiveness. Weight gain can occur. Hypoglycemia most common with this class of oral agents.
Glinides *Nateglinide* *Repaglinide*	Stimulates insulin secretion	↑	Yes (rarely)	Taken with meals. Short action with less hypoglycemia. Postprandial effect.
Biguanides *Metformin*	Decreases hepatic production of glucose	↓	No	Preferred agent for type 2 diabetes. Well-established history of effectiveness. Weight loss may occur. Monitor renal function and vitamin B_{12} levels.
Thiazolidinediones *Pioglitazone* *Rosiglitazone*	Binds to peroxisome proliferator–activated receptor-γ in muscle, fat and liver to decrease insulin resistance	↓↓	No	Effective in highly insulin-resistant patients. Once-daily dosing for *pioglitazone*. Check liver function before initiation. Avoid in liver disease or heart failure.
α-Glucosidase inhibitors *Acarbose* *Miglitol*	Decreases glucose absorption	⟺	No	Taken with meals. Adverse gastrointestinal effects. Not a preferred therapy. Reserve for patients unable to tolerate other agents.
DPP-4 inhibitors *Alogliptin* *Linagliptin* *Sitagliptin* *Saxagliptin*	Increases glucose-dependent insulin release; decreases secretion of glucagon	↑	No	Once-daily dosing. May be taken with or without food. Well tolerated. Risk of pancreatitis.
SGLT2 inhibitors *Canagliflozin* *Dapaglifozin* *Empagliflozin* *Ertugliflozin*	Increases urinary glucose excretion	⟺	No	Once-daily dosing in the morning. Risk of hypotension, genitourinary infections. Avoid in severe renal impairment. *Empagliflozin* is approved to reduce cardiovascular events in patients with type 2 diabetes.
GLP-1 receptor agonists *Albiglutide* *Dulaglutide* *Exenatide* *Liraglutide* *Lixisenatide* *Semaglutide*	Increases glucose-dependent insulin release; decreases secretion of glucagon; slows gastric emptying; increases satiety	↑	No	Injection formulation. *Liraglutide* and *lixisenatide* are dosed once daily. *Albiglutide*, *dulaglutide*, and *semaglutide* are dosed once weekly. *Exenatide* is dosed twice daily and extended-release *exenatide* is dosed once weekly. *Liraglutide* is approved to reduce cardiovascular events in patients with type 2 diabetes. Weight loss may occur. Risk of pancreatitis. Contraindicated in patients with a history of medullary thyroid carcinoma.

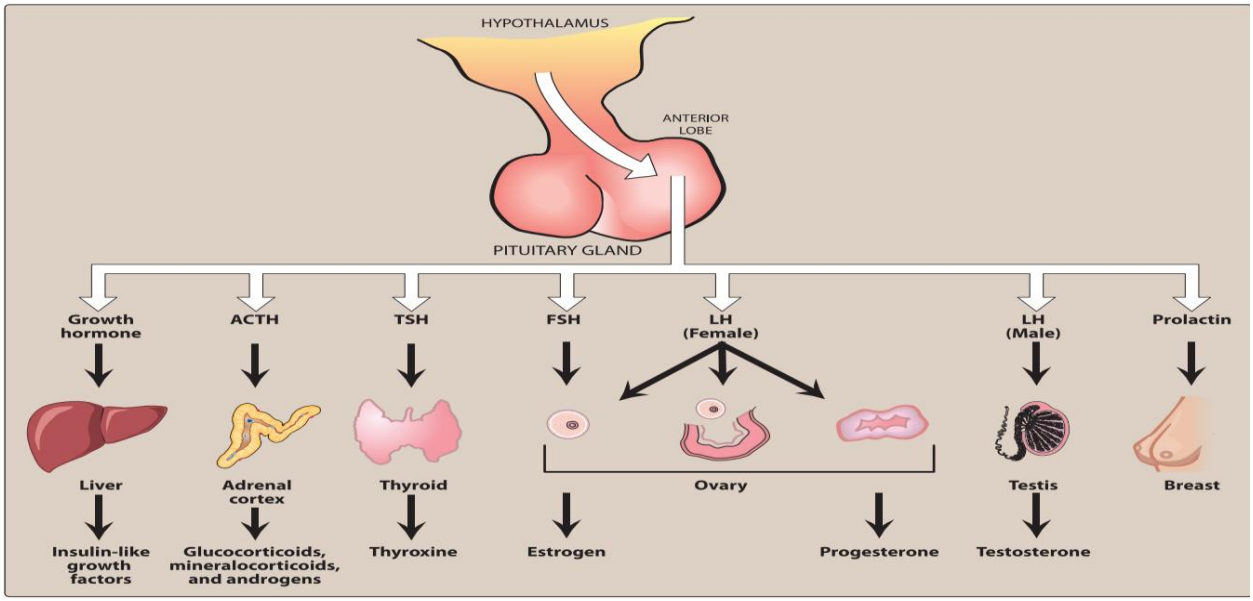
.....

Lec 6 Pitutary and thyroid hormones

The endocrine system releases hormones into the bloodstream, which carries chemical messengers to target cells throughout the body. Hormones have a much broader range of response time than do nerve impulses, requiring from seconds to days, or longer, to cause a response that may last for weeks or months. [Note: Nerve impulses generally act within milliseconds.] An important function of the hypothalamus is to connect the nervous system with the endocrine system via the pituitary gland.

HYPOTHALAMIC AND ANTERIOR PITUITARY HORMONES

The hormones secreted by the hypothalamus and the pituitary are peptides or glycoproteins that act by binding to specific receptor sites on target tissues. The hormones of the anterior pituitary are regulated by neuropeptides that are called either "releasing" or "inhibiting" factors or hormones. These are produced in the hypothalamus, and they reach the pituitary by the **hypophyseal portal system**.

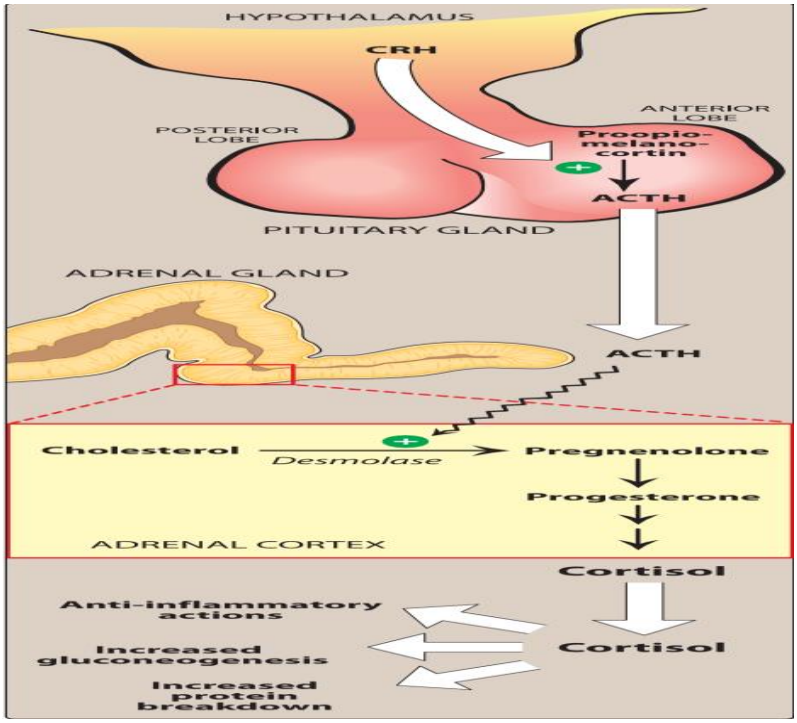


The interaction of the releasing hormones with receptors results in the activation of genes that promote the synthesis of protein precursors. The protein precursors then undergo posttranslational modification to produce hormones, which are released into the circulation. Each hypothalamic regulatory hormone controls the release of a specific hormone from the anterior pituitary.

Pituitary hormone preparations are currently used for specific hormonal deficiencies, although most of the agents have limited therapeutic applications. Hormones of the anterior pituitary are administered **intramuscularly (IM), subcutaneously, or intranasally** because their peptidyl nature makes them susceptible to destruction by proteolytic enzymes of the digestive tract.

A. Adrenocorticotropic hormone (corticotropin)

Corticotropin-releasing hormone (CRH) is responsible for the synthesis and release of the peptide proopiomelanocortin by the pituitary.



Adrenocorticotropic hormone (ACTH) or corticotropin is a product of the posttranslational processing of this precursor polypeptide. **[Note: CRH is used diagnostically to differentiate between Cushing syndrome and ectopic ACTH-producing cells.]** Normally, ACTH is released from the pituitary in pulses with an overriding diurnal rhythm, with the highest concentration occurring in early morning and the lowest in late evening. Stress stimulates its secretion, whereas cortisol acting via negative feedback suppresses its release

1. Mechanism of action: ACTH binds to receptors on the surface of the adrenal cortex, thereby activating G protein-coupled processes that ultimately stimulate the rate-limiting step in the adrenocorticosteroid synthetic pathway (cholesterol to pregnenolone). This pathway ends with the synthesis and release of adrenocorticosteroids and the adrenal androgens.

2. Therapeutic uses: The availability of synthetic adrenocorticosteroids with specific properties has limited the use of corticotropin mainly to serving as a diagnostic tool for differentiating between:

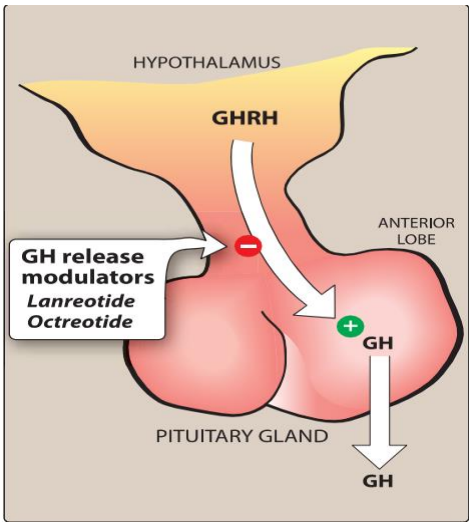
Primary adrenal insufficiency (Addison disease, associated with adrenal atrophy) and **secondary** adrenal insufficiency (caused by inadequate secretion of ACTH by the pituitary). Therapeutic corticotropin preparations are extracts from the anterior pituitaries of domestic animals or synthetic human ACTH. The latter, **cosyntropin**, is preferred for the diagnosis of adrenal insufficiency. ACTH is also used in the treatment of : infantile spasms and multiple sclerosis.

3. Adverse effects: Short-term use of ACTH for diagnostic purposes is usually well tolerated. With longer use, toxicities are similar to glucocorticoids and include

hypertension, peripheral edema, hypokalemia, emotional disturbances, and increased risk of infection.

B. Growth hormone (somatotropin)

Somatotropin is released by the anterior pituitary in response to growth hormone (GH)-releasing hormone.



Conversely, secretion of GH is inhibited by the hormone somatostatin. GH is released in a pulsatile manner, with the highest levels occurring during sleep.

With increasing age, GH secretion decreases, accompanied by a decrease in lean muscle mass. Somatotropin influences a wide variety of biochemical processes (for example, cell proliferation and bone growth). Synthetic human GH **(somatropin)** is produced using recombinant DNA technology.

Mechanism of action: Although many physiologic effects of GH are exerted directly at its targets, others are mediated through the somatomedins-insulin-like growth factors 1 and 2 (IGF-1 and IGF-2).

GH **is a large peptide**, the exogenous one, synthesized by gene technology and used as injection; the animal one is **ineffective** for human.

Over secretion of GH before puberty causes **Gigantism**

Over secretion of GH after puberty causes **Acromegaly**

Reduced secretion of GH causes **Dwarfism**.

GH has the following functions:

1- Glycogenolysis (catabolism of glycogen)→↑ blood sugar
2- Lipolysis (catabolism of lipid)
3- protein synthesis
4- Increase the no of cells and their density including bone and cartilage.

Therapeutic uses: Somatropin is used in the treatment of:

1- GH deficiency,
2- Growth failure in children,
3-treatment of HIV patients with cachexia, and
4-GH replacement in adults with confirmed deficiency.

The synthetic GH (somatrem has longer $t_{1/2}$ =25 min than natural GH, this drug is given to dwarf patients **before** puberty because after puberty the closure of long bones epiphysis occur, so administration of GH after puberty causes acromegaly, which characterized by thick skin & bone ,large nose and lower jaw and extremities specially fingers.

Adverse effects: Adverse effects of somatropin include pain at the injection site, edema, arthralgias, myalgias, nausea, and an increased risk of diabetes. Somatropin should not be used in pediatric patients with **closed epiphyses**, patients with **diabetic retinopathy**, or obese patients with **Prader-Willi syndrome**.

C. Somatostatin (growth hormone-inhibiting hormone)

In the pituitary, somatostatin binds to receptors that suppress GH and thyroid-stimulating hormone (TSH) release. Originally isolated from the hypothalamus, somatostatin is a small polypeptide found in neurons throughout the body as well as in the intestine, stomach, and pancreas. Somatostatin not only inhibits release of GH but also insulin, glucagon, and gastrin.

Octreotide and **lanreotide** are synthetic analogs of somatostatin with longer half-lives. Depot formulations of these agents allow for administration every 4 weeks. They have found use in the treatment of acromegaly and in severe diarrhea/flushing episodes associated with carcinoid tumors. An intravenous infusion of octreotide is also used for the treatment of bleeding esophageal varices. **Adverse effects** of octreotide include bradycardia, diarrhea, abdominal pain, flatulence, nausea, and steatorrhea. Gallbladder emptying is delayed, and asymptomatic cholesterol gallstones can occur with long-term treatment.

D. Gonadotropins

The gonadotropins (FSH and LH) are produced in the anterior pituitary. The regulation of gonadal steroid hormones depends on these agents. They used in the treatment of infertility. **Menotropins** (also known as human menopausal gonadotropins or hMG) are obtained from urine of postmenopausal women and marketed under trade name (pergonal ^{R}) and contain both FSH and LH.

Urofollitropin is FSH obtained from postmenopausal women and is devoid of LH. **Follitropin alfa** and **follitropin beta** are human FSH products manufactured using recombinant DNA technology.

Human chorionic gonadotropin (hCG) is a placental hormone that is excreted in urine of pregnant women isolated and marketed under trade name ^{R}(pregenyl).. The effects of hCG and **choriogonadotropin** alfa (made using recombinant DNA technology) are essentially identical to those of LH.

Both preparations administered as IM injection as follow:

For infertile women:

Give menotropin at 5-12 days of menstrual cycle (for growth and maturation of follicals) followed by HCG at day 13-15 from period for ovulation.

For infertile men:

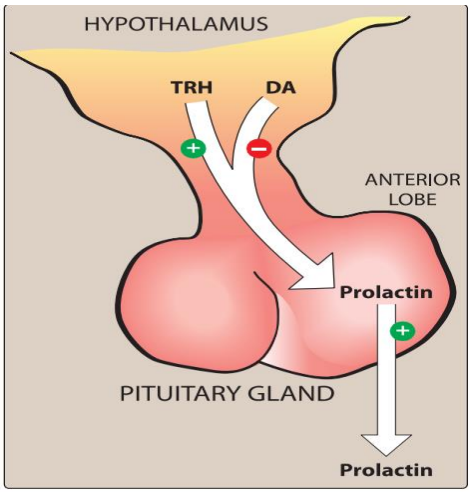
Give HCG for maturation of external sexual organs followed by menotropin for induction of spermatogenesis.

Adverse effects include ovarian enlargement and possible ovarian hyperstimulation syndrome, which may be life threatening. Multiple births can occur.

E. Prolactin

Prolactin is a peptide hormone secreted by the anterior pituitary. Its primary function is to stimulate and maintain lactation. In addition, it decreases sexual drive and reproductive function. Thyrotropinreleasing hormone stimulates the release of prolactin, and secretion is inhibited by dopamine acting at D_2 receptors.

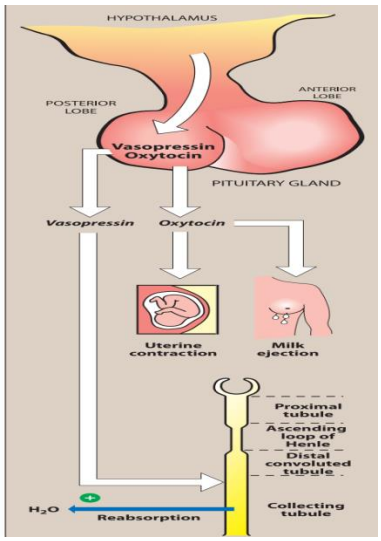
[Note: Drugs that act as dopamine antagonists (for example, **metoclopramide** and some **antipsychotics**) can increase the secretion of prolactin.]



Hyperprolactinemia, which is associated with galactorrhea and hypogonadism, is treated with D_2 receptor agonists, such as **bromocriptine** and **cabergoline**. Both of these agents also find use in the treatment of pituitary microadenomas. Bromocriptine is also indicated for treatment of type 2 diabetes. Among their adverse effects are nausea, headache and, less frequently, psychosis.

HORMONES OF THE POSTERIOR PITUITARY

In contrast to the hormones of the anterior lobe of the pituitary, those of the posterior lobe, **vasopressin** and **oxytocin**, are not regulated by releasing hormones. Instead, they are synthesized in the hypothalamus, transported to the posterior pituitary, and released in response to specific physiologic signals, such as high plasma osmolarity or parturition. Both hormones are administered intravenously and have very short half-lives.



A. Oxytocin Oxytocin is used in obstetrics to stimulate uterine contraction and induce labor. Oxytocin also causes milk ejection by contracting the myoepithelial cells around the mammary alveoli. Although toxicities are uncommon with proper drug use, hypertension, uterine rupture, water retention, and fetal death may occur. Its antidiuretic and pressor activities are much less than those of vasopressin.

B. Vasopressin

Vasopressin (antidiuretic hormone) is structurally related to oxytocin. Vasopressin has both antidiuretic and vasopressor effects.

In the kidney, it binds to the **V2 receptor** to increase water permeability and reabsorption in the collecting tubules. Thus, the major use of vasopressin is to treat diabetes insipidus. It also finds use in septic shock and in controlling bleeding due to esophageal varices. Other effects of vasopressin are mediated by the **V1 receptor,** which is found in the liver, vascular smooth muscle (where it causes constriction), and other tissues. The major toxicities of vasopressin are water

intoxication and hyponatremia. Abdominal pain, tremor, and vertigo can also occur.

Desmopressin, an analog of vasopressin, has minimal activity at the V1 receptor, making it largely free of pressor effects. This analog is longer acting than vasopressin and is preferred for the treatment of **diabetes insipidus and nocturnal enuresis.**

For these indications, desmopressin is administered intranasally or orally. [Note: The nasal spray should not be used for enuresis due to reports of seizures in children using this formulation.] Local irritation may occur with the nasal spray.

THYROID HORMONES

The thyroid gland facilitates normal growth and maturation by maintaining a level of metabolism in the tissues that is optimal for normal function. The two major thyroid hormones are **triiodothyronine** (T3; the most active form) and **thyroxine** (T4).

- Normal TH concentration called **Euthyroid**
- High TH concentration called **hyperthyroidism** or **Graves ' disease** or **thyrotoxicosis**.
- Low TH concentration called **cretinism** in children.
- Low TH concentration called **myxoedema** in adults.

NOTE: Hyper **or** hypothyroidism may **or** not associated with **goiter** formation.

The $t_{1/2}$ of T3 is 2days, while the:

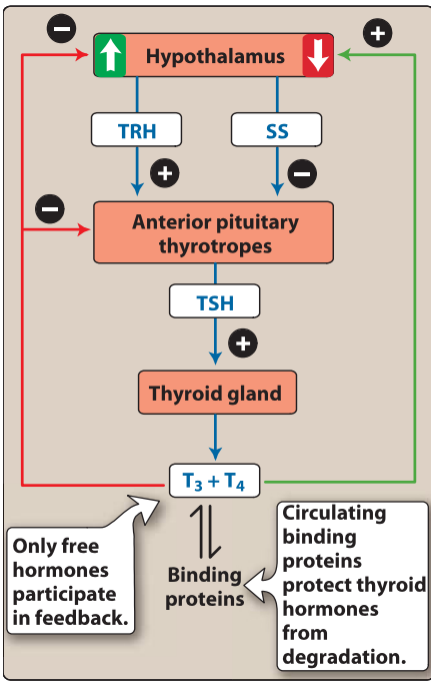
The $t_{1/2}$ of T4 in euthroid is 7 days

The $t_{1/2}$ of T4 in hyperthyroidism is 3 days

The $t_{1/2}$ of T4 in hypothyroidism is 14 days

A. Thyroid hormone synthesis and secretion

The thyroid gland is made up of multiple follicles that consist of a single layer of epithelial cells surrounding a lumen filled with thyroglobulin (the storage form of thyroid hormone). Thyroid function is controlled by TSH (thyrotropin), which is synthesized by the anterior pituitary.



[Note: The hypothalamic thyrotropin-releasing hormone (TRH) governs the generation of TSH.] TSH action is mediated by cAMP and leads to stimulation of iodide

Steps of TH synthesis:

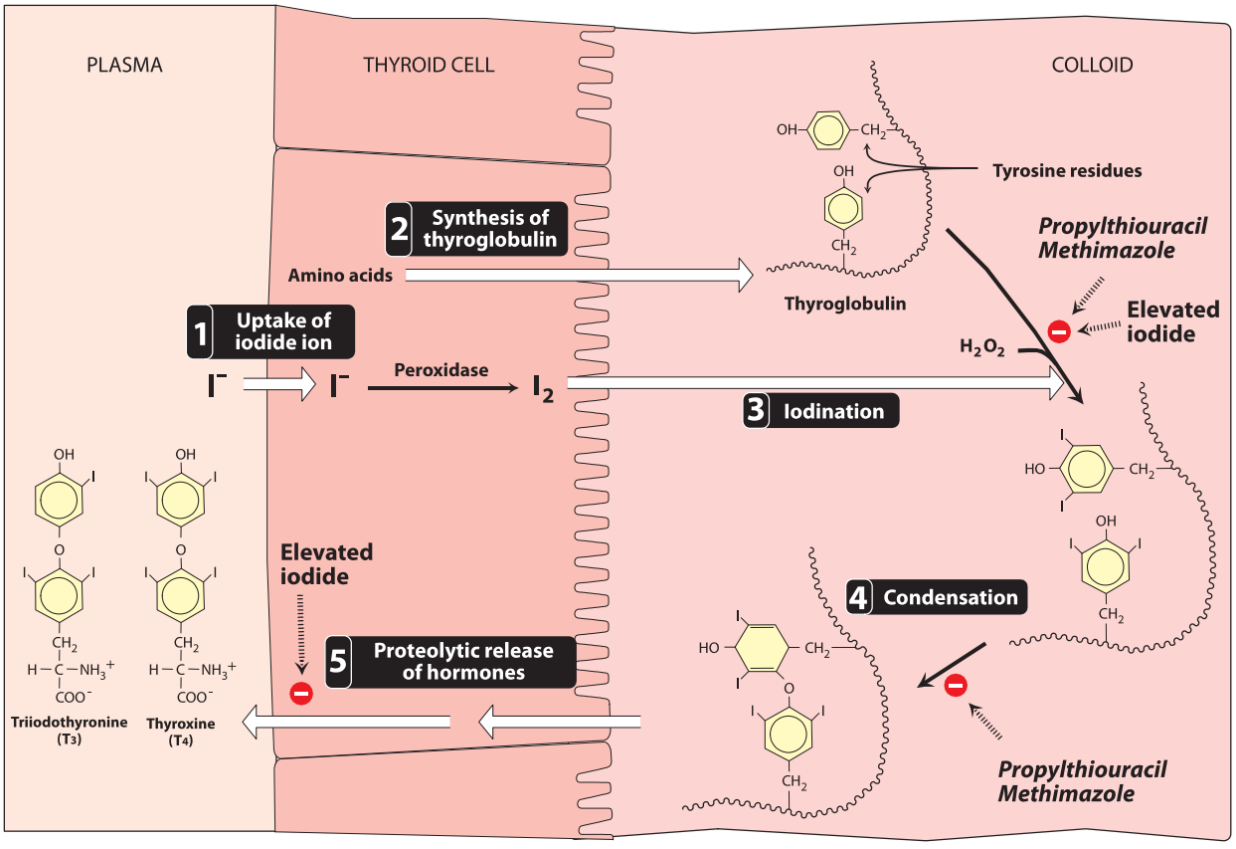
1-iodide trapping: active uptake of iodide from circulation into thyroid cells. The concentration of iodide in the thyroid gland is 25 times more than concentration in the blood.

2- Oxidation of iodide to iodine……. $2\ I^- = I^2$

3- Coupling of iodide with tyrosine (a.a) forming mono iodic tyrosine in the presence of peroxidase enzyme.

4- Condensation of 2 molecules of mono iodic tyrosine forming di-iodic tyrosine and then **tri iodic tyrosine** and **tetra-iodic tyrosine** in the presence of peroxidase enzyme.

- About 80% 0f T4 converted to T3 which is biologically 5 times more active than T4
- Both T3 and T4 are highly protein binding forming thyroglobulin (TG), especially T4.
- Both are metabolized by cytochrome p-450 in the liver so they affected by enzyme inducers and inhibitors……

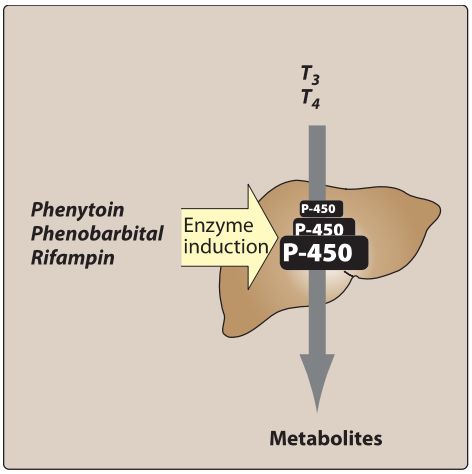


B. Mechanism of action Most circulating T3 and T4 is bound to thyroxine-binding globulin in the plasma. The hormones must dissociate from thyroxine-binding globulin prior to entry into cells. In the cell, T4 is enzymatically deiodinated toT3, which enters the nucleus and attaches to specific receptors. The activation of these receptors promotes the formation of RNA and subsequent protein synthesis, which is responsible for the effects of T4.

C. Pharmacokinetics Both T4 and T3 are absorbed after oral administration. Food, calcium preparations, iron salts, and aluminum-containing antacids can decrease the absorption of T4. Deiodination is the major route of metabolism of T4. T3 also undergoes sequential deiodination. The hormones are also metabolized via conjugation with glucuronides and sulfates and excreted into bile.

D. Treatment of hypothyroidism Hypothyroidism usually results from autoimmune destruction of the gland and is diagnosed by elevated TSH. **Levothyroxine (T4)** is **preferred** over **T3 (liothyronine)** or T3/T4 combination products (**liotrix**) for the treatment of hypothyroidism.

Levothyroxine is better tolerated than T3 preparations and has a longer half-life. It is dosed once daily, and steady state is achieved in 6 to 8 weeks. Toxicity is directly related to T4 levels and manifests as nervousness, palpitations and tachycardia, heat intolerance, and unexplained weight loss. Drugs that induce the cytochrome P-450 enzymes, such as phenytoin, rifampin, and phenobarbital, accelerate metabolism of thyroid hormones and may decrease the effectiveness.

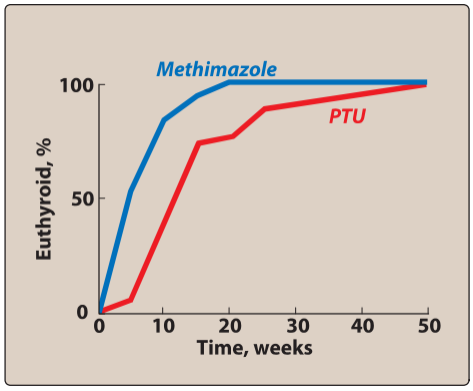


E. Treatment of hyperthyroidism (thyrotoxicosis) Graves' disease, an autoimmune disease that affects the thyroid, is the most common cause of hyperthyroidism. In these situations, TSH levels are low due to negative feedback. [Note: Feedback inhibition of TRH occurs with high levels of circulating thyroid hormone, which, in turn, decreases secretion of TSH.] The goal of therapy is to decrease synthesis and/or release of additional hormone. This can be accomplished by removing part or all of the thyroid gland, by inhibiting synthesis of the hormones, or by blocking release of hormones from the follicle.

1. Removal of the thyroid: This can be accomplished surgically or by destruction of the gland with radioactive iodine (^{131}I), which is selectively taken up by the thyroid follicular cells. Most patients become hypothyroid after radioactive iodine and require treatment with levothyroxine.

2. Inhibition of thyroid hormone synthesis: The thioamides, **propylthiouracil (PTU)** and **methimazole**, are concentrated in the thyroid, where they inhibit both the oxidative processes required for iodination of tyrosyl groups and the condensation (coupling) of iodotyrosines to form T3 and T4. PTU also blocks the peripheral conversion of T4 to T3. [Note: These drugs have no effect on

thyroglobulin already stored in the gland. Therefore, clinical effects may be delayed until thyroglobulin stores are depleted.



Methimazole is preferred over PTU because it has a longer half-life, allowing for once-daily dosing, and a lower incidence of adverse effects. However, PTU is recommended during the first trimester of pregnancy due to a greater risk of teratogenic effects with methimazole. PTU has been associated with hepatotoxicity and, rarely, agranulocytosis.

3. Blockade of hormone release: A pharmacologic dose of iodide inhibits the iodination of tyrosine **("Wolff-Chaikoff effect"),** but this effect lasts only a few days. More importantly, iodide inhibits the release of thyroid hormones from thyroglobulin by mechanisms not yet understood. Iodide is employed to treat thyroid storm or prior to surgery, because it decreases the vascularity of the thyroid gland. Iodide, administered orally, is not useful for long-term therapy; the thyroid ceases to respond to the drug after a few weeks. Adverse effects include sore mouth and throat, swelling of the tongue or larynx, rashes, ulcerations of mucous membranes, and metallic taste.

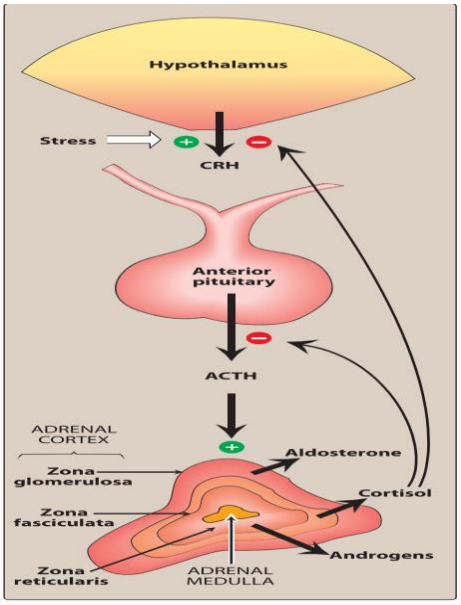
4. Thyroid storm: Thyroid storm presents with extreme symptoms of hyperthyroidism. The treatment of thyroid storm is the same as for

hyperthyroidism, except that the drugs are given in higher doses and more frequently.

β-blockers, such as metoprolol or propranolol, are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. but beta blockers can't be considered as anti- hyperthyroid drugs because:

1- B-Blockers don't change the lab-biochemical test results.
2- B-Blockers don't treat or block all metabolic effects of TH.
3- B-Blockers don't change the course of disease.

…….

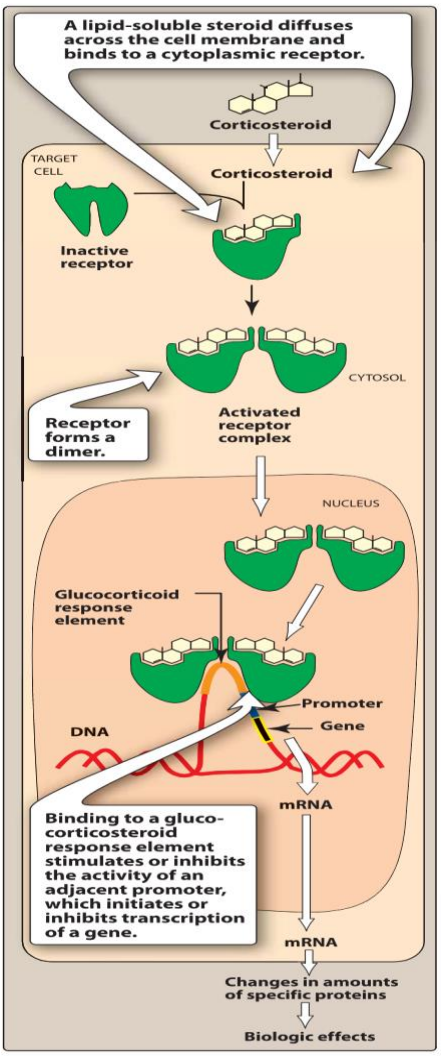


Lec 7 The adrenal hormones

The adrenal cortex secretes two types of corticosteroids **(glucocorticoids and mineralocorticoids) and the adrenal androgens**.

The adrenal cortex has three zones, and each zone synthesizes a different type of steroid hormone from cholesterol. The outer zona glomerulosa produces mineralocorticoids (for example, aldosterone) that are responsible for regulating salt and water metabolism. The middle zona fasciculata synthesizes glucocorticoids (for example, cortisol) that are involved with metabolism and response to stress. The inner zona reticularis secretes adrenal androgens. Secretion by the two inner zones and, to a lesser extent, the outer zone is controlled by pituitary adrenocorticotropic hormone (ACTH; also called corticotropin), which is released in response to hypothalamic corticotropin-

releasing hormone (CRH). Glucocorticoids serve as feedback inhibitors of ACTH and CRH secretion.



Corticosteroids

Corticosteroids differ in their metabolic (glucocorticoid) and electrolyteregulating (mineralocorticoid) activity. The corticosteroids bind to specific intracellular cytoplasmic receptors in target tissues. Glucocorticoid receptors are widely distributed throughout the body, whereas mineralocorticoid receptors are confined mainly to excretory organs, such as the kidney, colon, salivary glands, and sweat glands. Both types of receptors are found in the brain. After dimerizing, the receptor-hormone complex recruits coactivator (or corepressor) proteins and translocate into the nucleus, where it attaches to gene promoter elements. There it acts as a transcription factor to turn genes **on** (when complexed with coactivators) or **off** (when complexed with corepressors), depending on the tissue.

Because of this mechanism, some effects of corticosteroids take hours to days to occur.

This section describes normal actions and therapeutic uses of corticosteroids.

Glucocorticoids : **Cortisol** is the principal human glucocorticoid. Normally, its production is diurnal, with a peak in early morning followed by a decline and

then a secondary, smaller peak in late afternoon. Stress and levels of the circulating steroid influence secretion. The effects of cortisol are many and diverse. In general, all glucocorticoids:

1. Promote normal intermediary metabolism: Glucocorticoids stimulate hepatic glucose production by enhancing expression of enzymes involved in gluconeogenesis. They mobilize amino acids and stimulate lipolysis, thereby providing the building blocks and energy for glucose synthesis.

2. Increase resistance to stress: By raising plasma glucose levels, glucocorticoids provide the body with energy to combat stress caused by trauma, fright, infection, bleeding, or disease. [Note: Glucocorticoid insufficiency may result in hypoglycemia (for example, during stressful periods or fasting) .]

3. Alter blood cell levels in plasma:

Glucocorticoids cause: a**decrease** in eosinophils, basophils, monocytes, and lymphocytes by redistributing them from the circulation to lymphoid tissue.

Glucocorticoids **increase** hemoglobin, erythrocytes, platelets, and polymorphonuclear leukocytes.

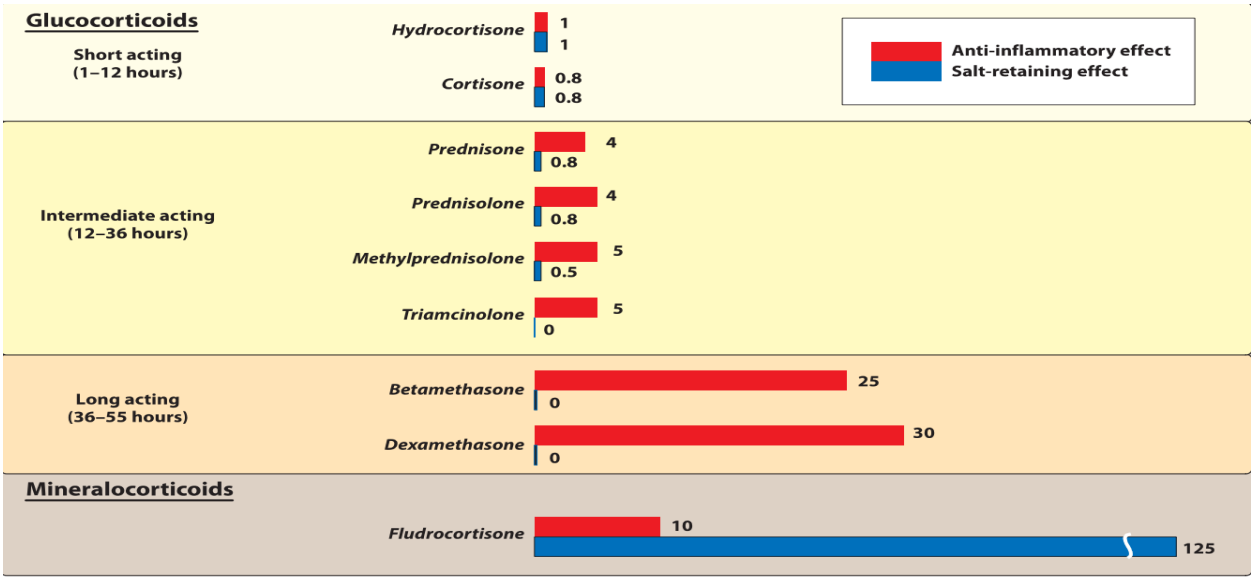
4. Possess anti-inflammatory action: Potent anti-inflammatory and immunosuppressive activities are the most important therapeutic properties of glucocorticoids. Glucocorticoids lower circulating lymphocytes and inhibit the ability of leukocytes and macrophages to respond to mitogens and antigens. Glucocorticoids also decrease the production and release of proinflammatory cytokines. They inhibit phospholipase A2, which blocks the release of arachidonic acid (the precursor of the prostaglandins and leukotriene) , resulting in anti-inflammatory actions. Lastly, these agents influence the inflammatory response by

stabilizing mast cell and basophil membranes, thereby decreasing histamine release.

5. Affect other systems: High levels of glucocorticoids provide negative feedback to reduce ACTH production and affect the endocrine system by suppressing synthesis of glucocorticoids and thyroid-stimulating hormone. In addition, adequate cortisol levels are essential for normal glomerular filtration. Corticosteroids may adversely affect other systems.

Mineralocorticoids: Mineralocorticoids help to control fluid status and concentration of electrolytes, especially sodium and potassium. Aldosterone acts on mineralocorticoid receptors in the distal tubules and collecting ducts in the kidney, causing **reabsorption** of sodium, bicarbonate, and water. Conversely, aldosterone **decreases** reabsorption of potassium, which, with H+, is lost in the urine. Enhancement of sodium reabsorption by aldosterone also occurs in gastrointestinal mucosa and in sweat and salivary glands. [Note: Elevated aldosterone levels may cause alkalosis and hypokalemia, retention of sodium and water, and increased blood volume and blood pressure. Hyperaldosteronism is treated with spironolactone.]

Therapeutic uses of the corticosteroids: Semisynthetic derivatives of corticosteroids vary in anti-inflammatory potency, mineralocorticoid activity, and duration of action. These agents are used in replacement therapy and in the treatment of severe allergic reactions, asthma, rheumatoid arthritis, other inflammatory disorders, and some cancers.



1. Replacement therapy for primary adrenocortical insufficiency (Addison disease): Addison disease is caused by adrenal cortex dysfunction (diagnosed by lack of response to ACTH administration). **Hydrocortisone**, which is identical to natural cortisol, is given to correct the deficiency. Failure to do so results in death. Two-thirds of the daily dosage of hydrocortisone is administered in the morning and one-third in the afternoon, mimicking the normal diurnal variation in cortisol levels. Administration of **fludrocortisone**, a potent synthetic mineralocorticoid, may also be necessary to correct mineralocorticoid deficiency.

2. Replacement therapy for secondary or tertiary adrenocortical insufficiency: These disorders are caused by a defect in CRH production by the hypothalamus or in ACTH production by the pituitary. **Hydrocortisone** is used for treatment of these deficiencies.

3. Diagnosis of Cushing syndrome : Cushing syndrome is caused by hypersecretion of glucocorticoids (hypercortisolism) that results from excessive release of ACTH by the anterior pituitary or an adrenal tumor. [Note: Chronic treatment with high doses of glucocorticoids is a frequent cause of iatrogenic Cushing syndrome.] Cortisol levels (urine, plasma, and saliva) and the **dexamethasone** suppression test are used to diagnose Cushing syndrome. The synthetic glucocorticoid dexamethasone suppresses cortisol release in normal individuals, but not those with Cushing syndrome.

4. Replacement therapy for congenital adrenal hyperplasia (CAH):

CAH is a group of diseases resulting from an enzyme defect in the synthesis of one or more of the adrenal steroid hormones. CAH may lead to virilization in females due to overproduction of adrenal androgens. Treatment requires administration of sufficient corticosteroids to suppress release of CRH and ACTH and normalize hormone levels. This decreases production of adrenal androgens. The choice of replacement hormone depends on the specific enzyme defect.

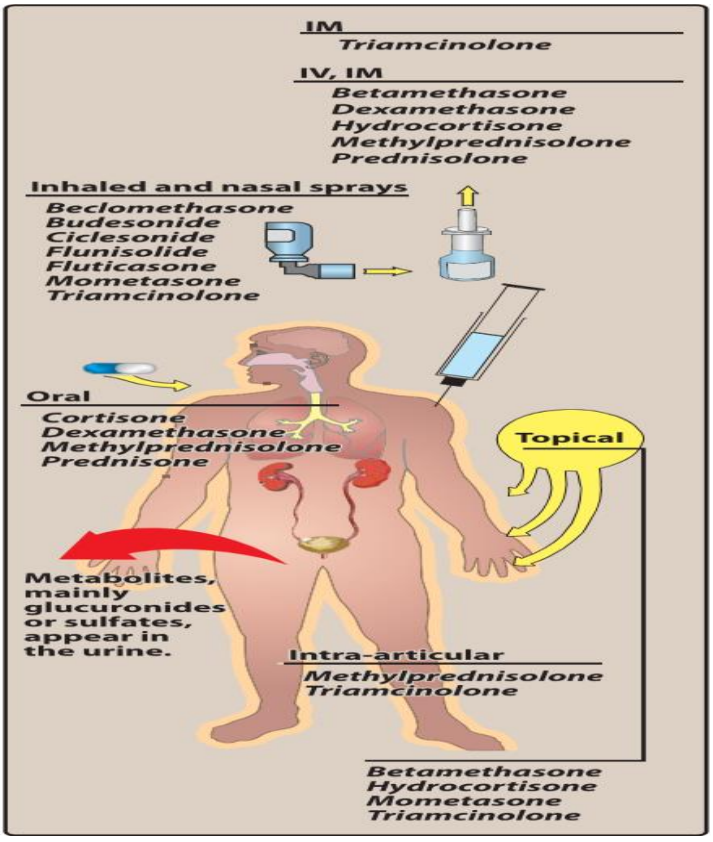
5. Relief of inflammatory symptoms:

Corticosteroids significantly reduce inflammation associated with rheumatoid arthritis and inflammatory skin conditions, including redness, swelling, heat, and tenderness. These agents are important for symptom control in persistent asthma, as well as treatment of exacerbations of asthma and inflammatory bowel disease. In osteoarthritis, intraarticular corticosteroids may be used for treatment of a disease flare. Corticosteroids are not curative in these disorders.

6. Treatment of allergies: Corticosteroids are beneficial in the treatment of allergic rhinitis, as well as drug, serum, and transfusion allergic reactions. In the treatment of allergic rhinitis and asthma, **fluticasone** and others are inhaled into the respiratory tract from a metered dose dispenser. This minimizes systemic effects, reducing or eliminating the use of oral corticosteroids.

7. Acceleration of lung maturation: Fetal cortisol is a regulator of lung maturation. Consequently, a regimen of **betamethasone or dexamethasone** administered intramuscularly to the mother within 48 hours proceeding premature delivery can accelerate lung maturation in the fetus and prevent respiratory distress syndrome.

Pharmacokinetics

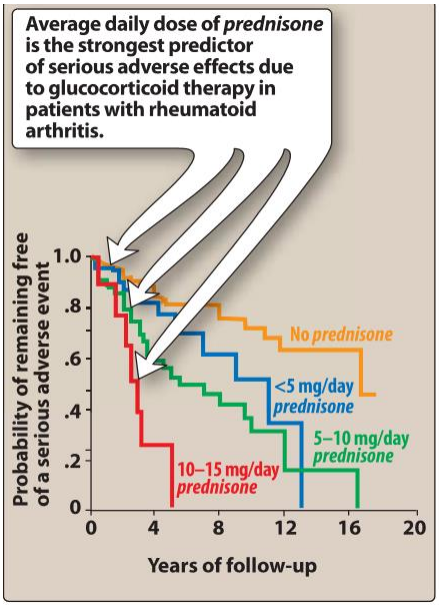


1-Absorption and fate: Corticosteroids are readily absorbed after oral administration. Selected compounds may be administered intravenously, intramuscularly, intra-articularly, topically, or via inhalation or intranasal delivery. All topical and inhaled glucocorticoids are absorbed to some extent and, therefore, have the potential to suppress the hypothalamic-pituitaryadrenal (HPA) axis. After absorption, glucocorticoids are greater than 90% bound to plasma proteins, mostly corticosteroid-binding globulin or albumin. Corticosteroids are metabolized by the liver microsomal oxidizing enzymes. The metabolites are conjugated to glucuronic acid or sulfate and excreted by the kidney.

[Note: The half-life of corticosteroids may increase substantially in hepatic dysfunction.] **Prednisone** is preferred in pregnancy because it minimizes steroid effects on the fetus. It is a prodrug that is not converted to the active compound, **prednisolone**, in the fetal liver. Any prednisolone formed in the mother is biotransformed to prednisone by placental enzymes.

2. Dosage: Factors that should be considered in determining the dosage of corticosteroids include glucocorticoid versus mineralocorticoid activity, duration of action, type of preparation, and time of day when the drug is administered. When large doses of corticosteroids are required for more than 2 weeks, suppression of the HPA axis occurs. Alternate-day administration of corticosteroids may prevent this adverse effect by allowing the HPA axis to recover/function on days the hormone is not taken.

Adverse effects: Common adverse effects of long-term corticosteroid therapy are often dose related. For example, in rheumatoid arthritis, the daily dose of prednisone was the strongest predictor of occurrence of adverse effects.



Osteoporosis is the most common adverse effect due to the ability of glucocorticoids to suppress intestinal Ca2 + absorption, inhibit bone formation, and decrease sex hormone synthesis. Patients are advised to take calcium and vitamin D supplements. **Bisphosphonates** may also be useful in the treatment of glucocorticoid-induced osteoporosis. [Note: Increased appetite is not necessarily an adverse effect. In fact, it is one of the reasons for the use of prednisone in cancer chemotherapy.] The classic Cushing-like syndrome (redistribution of body fat, puffy face, hirsutism, and increased appetite) is observed in excess corticosteroid replacement. Cataracts may also occur with long-term corticosteroid therapy. Hyperglycemia may develop and lead to diabetes mellitus. Diabetic patients should monitor blood glucose and adjust medications accordingly if taking corticosteroids. Topical therapy can cause skin atrophy, ecchymosis, and purple striae.

Other possible adverse effects of glucocorticosteroid include: Decrease growth in children, glaucoma, centripetal distribution of body fat, increase risk of infection, increase risk of diabetes, emotional disturbances, hypokalemia, hypertension and peripheral edema.

Discontinuation

Sudden discontinuation of these drugs can cause serious consequences if the patient has suppression of the HPA axis. In this case, abrupt removal of corticosteroids causes acute adrenal insufficiency that can be fatal. This risk, coupled with the possibility that withdrawal could exacerbate the disease, means that the dose must be tapered slowly according to individual tolerance. The patient must be monitored carefully.

Inhibitors of adrenocorticoid biosynthesis or function

Several substances are therapeutically useful as inhibitors of the synthesis or function of adrenal steroids: ketoconazole, spironolactone, and eplerenone.

1. Ketoconazole: Ketoconazole is an antifungal agent that strongly inhibits all gonadal and adrenal steroid hormone synthesis. It is used in the treatment of patients with Cushing syndrome.

2. Spironolactone: This antihypertensive drug competes for the mineralocorticoid receptor and, thus, inhibits sodium reabsorption in the kidney. Spironolactone also antagonizes aldosterone and testosterone synthesis. It is effective for hyperaldosteronism and hepatic cirrhosis, and is used with other standard therapies for treatment of heart failure with reduced ejection fraction. It is also useful in the management of hirsutism in women, probably due to antiandrogen activity on the hair follicle. Adverse effects include hyperkalemia, gynecomastia, menstrual irregularities, and skin rashes.

3. Eplerenone: Eplerenone specifically binds to the mineralocorticoid receptor, where it acts as an aldosterone antagonist. This specificity avoids the adverse effect of gynecomastia that is associated with spironolactone. It is approved for the treatment of hypertension and for heart failure with reduced ejection fraction.

……..

Lec 8

Estrogens and Androgens

Estrogens and androgens are sex hormones produced by the gonads. These hormones are necessary for conception, embryonic maturation, and development of primary and secondary sexual characteristics at puberty. The sex hormones are used therapeutically for 1-contraception, 2-management of menopausal symptoms, and 3- replacement therapy in hormone deficiency. Several antagonists are effective in the treatment or prevention of hormone-responsive cancers. Sex hormones are synthesized from the precursor, cholesterol, in a series of steps that includes shortening of the hydrocarbon side chain and hydroxylation of the steroid nucleus. Aromatization is the last step in estrogen synthesis.

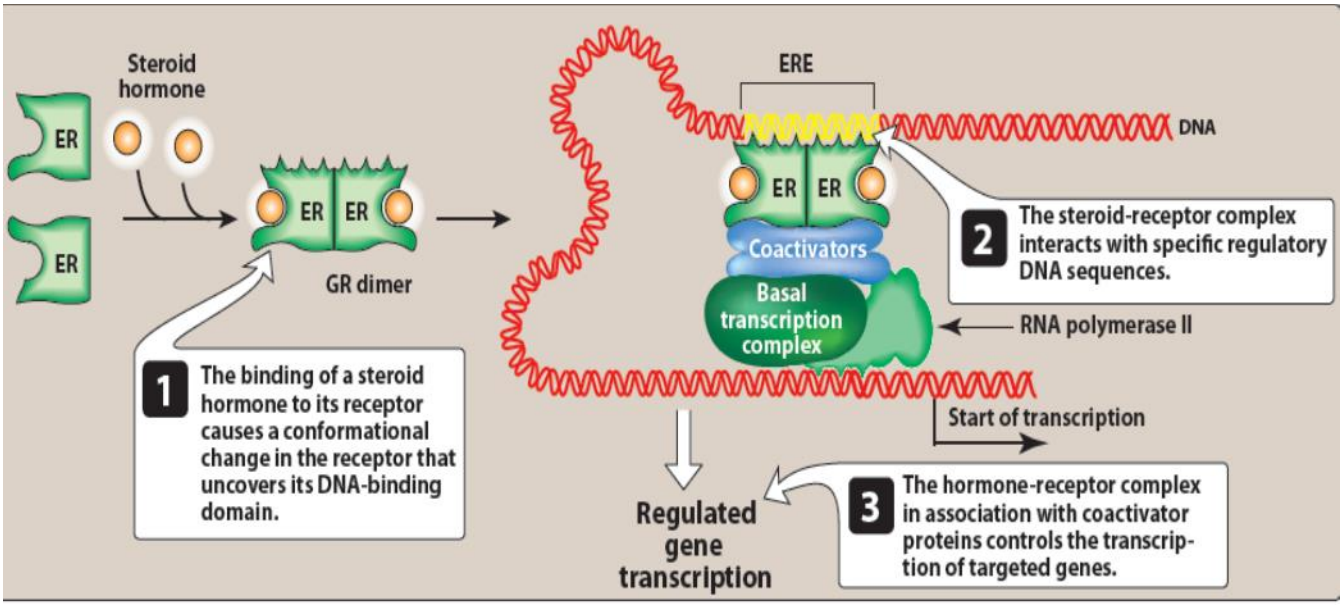
ESTROGENS

Estradiol is the most potent estrogen produced and secreted by the ovary. It is the principal estrogen in premenopausal women.

Estrone is a metabolite of estradiol that has approximately one-third the estrogenic potency of estradiol. Estrone is the primary circulating estrogen after menopause, and it is generated mainly from conversion of dehydroepiandrosterone [DHEA] in adipose tissue.

Estriol, another metabolite of estradiol, is significantly less potent than is estradiol. It is present in significant amounts during pregnancy, because it is synthesized by the placenta. Synthetic estrogens, such as **ethinyl estradiol**, undergo less first-pass metabolism than do naturally occurring hormones and, thus, are effective when administered orally at lower doses.

Mechanism of action: After dissociation from their binding sites on sex hormone-binding globulin or albumin in the plasma, steroid hormones (for example, estradiol) diffuse across the cell membrane and bind with high affinity to specific nuclear receptor proteins.



The activated steroid-receptor complex interacts with nuclear chromatin to initiate hormone-specific RNA synthesis. This results in the synthesis of specific proteins that mediate a number of physiologic functions.

Therapeutic uses Estrogens are most frequently used for contraception and postmenopausal hormone therapy (HT). In the past, estrogens were widely used for prevention of osteoporosis; however, due to risks associated with estrogen therapy, current guidelines recommend use of other therapies, such as **bisphosphonates**.

1. Postmenopausal HT:

The primary indication for estrogen therapy in postmenopausal women is menopausal symptoms, such as vasomotor instability (for example, "hot flashes" or

"hot flushes") and vaginal atrophy. **A common** oral preparation used for the treatment of menopausal symptoms is **conjugated equine estrogens** (obtained from urine of pregnant mares), which primarily contains sulfate esters of estrone and equilin. Other estrone-based oral preparations include esterified estrogens and **estropipate**. Transdermal preparations of estradiol are also effective in treating menopausal symptoms.

For women with an intact uterus, a progestogen is always included with the estrogen therapy, because the combination reduces the risk of endometrial carcinoma associated with unopposed estrogen. Women who have undergone a hysterectomy may use estrogen alone.

[Note: The potency of estrogen used in HT is substantially less than that of estrogens used in contraception. Thus, the adverse effects of estrogen replacement therapy are usually less pronounced than those seen in women taking estrogen for contraceptive purposes.] Use of HT has been associated with an increased risk of cardiovascular events and breast cancer. Thus, HT should be prescribed at the lowest effective dose for the shortest possible time to relieve menopausal symptoms. Women who only have urogenital symptoms, such as vaginal atrophy, should be treated with vaginal rather than systemic estrogen to minimize the risks of use.

2. Contraception: The combination of an estrogen and progestogen provides effective contraception via the oral, transdermal, or vaginal route.

3. Other uses:

Estrogen therapy mimicking the natural cyclic pattern, and usually in combination with a progestogen, is instituted to stimulate development of secondary sex

characteristics in young women with primary hypogonadism. Similarly, replacement therapy is used for women who have hormonal deficiencies due to surgical menopause or premature ovarian failure.

Pharmacokinetics

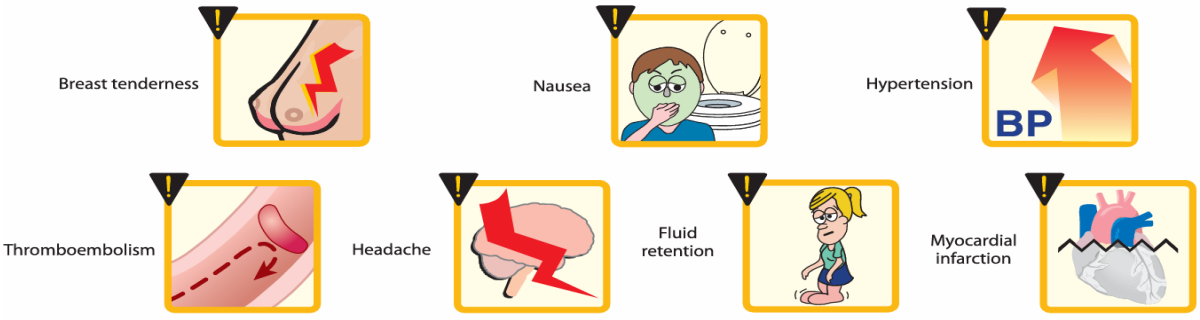
Naturally occurring estrogens: These agents and their esterified or conjugated derivatives are readily absorbed through the gastrointestinal tract, skin, and mucous membranes. Taken orally, estradiol is rapidly metabolized (and partially inactivated) by the microsomal enzymes of the liver. Micronized estradiol has better bioavailability. Although estradiol is subject to first-pass metabolism, it is still effective when taken orally.

Synthetic estrogens: These compounds, such as ethinyl estradiol and **estradiol valerate** are well absorbed after oral administration. Estradiol valerate is a prodrug of estradiol which is rapidly cleaved to estradiol and valeric acid. The synthetic estrogens are fat soluble, stored in adipose tissue, and slowly released. These compounds have a prolonged action and a higher potency compared to the natural estrogens.

Metabolism: Bioavailability of estradiol after oral administration is low due to first-pass metabolism. To reduce first-pass metabolism, estradiol may be administered via a transdermal patch, topical formulation (gel or spray), intravaginal preparation (tablet, cream, or ring), or injection. Following oral administration, estradiol is metabolized to estrone and estriol. Estrogens are transported in the blood bound to serum albumin or sex hormone-binding globulin.

Estradiol and its metabolites subsequently undergo glucuronide and sulfate conjugation.

Adverse effects: Nausea and breast tenderness are among the most common adverse effects of estrogen therapy. In addition, the risk of thromboembolic events, myocardial infarction, and breast and endometrial cancer is increased with the use of estrogen therapy. [Note: The increased risk of endometrial cancer can be offset by including a progestogen along with the estrogen therapy.] Other effects of estrogen therapy are shown in Figure below.



Selective estrogen receptor modulators

SEAMs are a class of estrogen-related compounds that display selective agonism or antagonism for estrogen receptors depending on the tissue type. This category includes **tamoxifen, raloxifene, bazedoxifene, clomiphene, and ospemifene.**

Mechanism of action **Tamoxifen** and **raloxifene** compete with estrogen for binding to the estrogen receptor in breast tissue. [Note: Normal breast growth is stimulated by estrogens. Therefore, some hormone-responsive breast tumors regress

following treatment with these agents.] In addition, raloxifene acts as an estrogen agonist in bone, leading to decreased bone resorption, increased bone density, and decreased vertebral fractures. Unlike estrogen and tamoxifen, raloxifene does not stimulate growth of the endometrium and, therefore, does not predispose to endometrial cancer. Raloxifene also lowers serum total cholesterol and low-density lipoprotein (LDL). Like raloxifene, **bazedoxifene** antagonizes the action of estrogen on the uterus. The drug reduces the risk of endometrial hyperplasia with estrogen use.

Clomiphene (Clomid^{R}) acts as a partial estrogen agonist and interferes with the negative feedback of estrogens on the hypothalamus. This effect increases the secretion of gonadotropin-releasing hormone and gonadotropins, thereby leading to stimulation of ovulation.

Therapeutic uses:

Tamoxifen is currently used in the treatment of metastatic **breast cancer**, or as adjuvant therapy following mastectomy or radiation for breast cancer. Both tamoxifen and raloxifene can be used as prophylactic therapy to reduce the risk of breast cancer in high-risk patients.

Raloxifene is also approved for the prevention and treatment of **osteoporosis** in postmenopausal women.

Clomiphene is used in the treatment of **infertility**. Ospemifene is indicated for the treatment of dyspareunia (painful sexual intercourse) related to menopause. **Bazedoxifene** is available in a combination product with conjugated estrogens. The combination is indicated for the treatment of **menopausal symptoms** in women with an intact uterus.

Pharmacokinetics: The SEAMs are rapidly absorbed after oral administration. Tamoxifen is extensively metabolized by cytochrome P450 system, including the formation of active metabolites. [Note: Patients with a genetic polymorphism in CYP2D6 may produce less active metabolite, resulting in diminished activity of tamoxifen.] Raloxifene is rapidly converted to glucuronide conjugates through first-pass metabolism. These agents undergo enterohepatic cycling, and the primary route of excretion is through the bile into feces.

Adverse effects: The most frequent adverse effects of tamoxifen are hot flashes and nausea. Due to its estrogenic activity in the endometrium, endometrial hyperplasia and malignancies have been reported with tamoxifen therapy. This has led to recommendations for limiting the length of time on the drug for some indications. Because it is metabolized by various CYP450 isoenzymes, tamoxifen is subject to many drug interactions. **[Note:** Tamoxifen is also an inhibitor of P-glycoprotein.]

Some CYP450 inhibitors may prevent the formation of active metabolites of tamoxifen and possibly reduce the efficacy (for example, amiodarone, haloperidol, paroxetine). Hot flashes and leg cramps are common adverse effects with raloxifene. ln addition, there is an increased risk of deep vein thrombosis and pulmonary embolism. Women who have a past or active history of venous thromboembolic events should not take the drug.

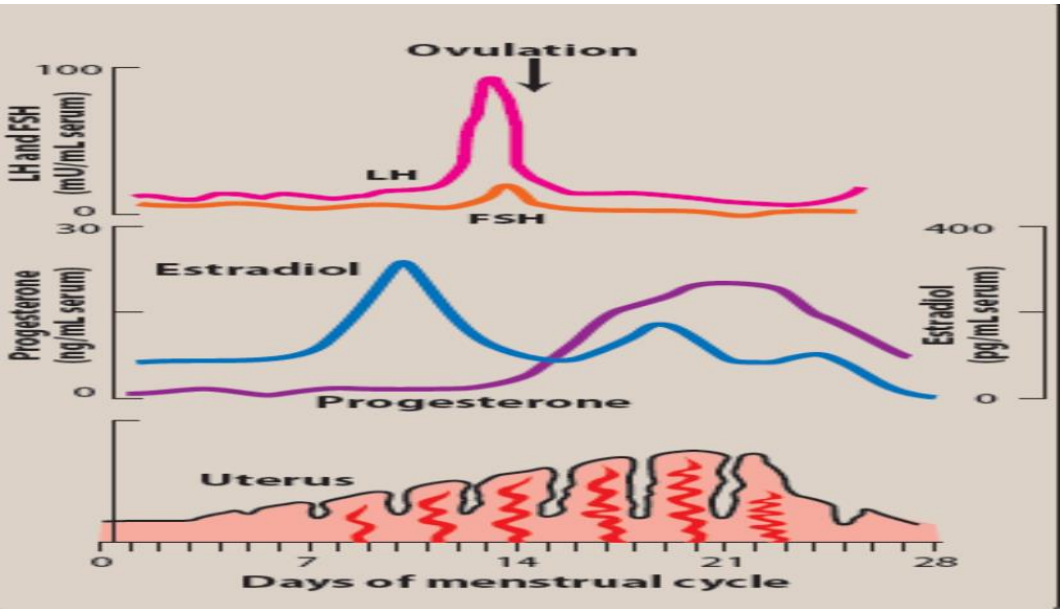
Adverse effects of clomiphene are dose-related and include headache, nausea, vasomotor flushes, visual disturbances, and ovarian enlargement. Use of clomiphene increases the risk of multiple gestation, usually twins.

Ospemifene may stimulate endometrial growth, and addition of a progestogen in women with an intact uterus should be considered.

PROGESTOGENS

Progesterone, the natural progestogen, is produced in response to luteinizing hormone (LH) by both females (secreted by the corpus luteum, primarily during the second half of the menstrual cycle, and by the placenta) and by males (secreted by the testes). It is also synthesized by the adrenal cortex in both sex

Mechanism of action: Progestogens exerts their effects in a manner analogous to that of the other steroid hormones. In females, progesterone promotes the development of a secretory endometrium that can accommodate implantation of a newly forming embryo. The high levels of progesterone that are released during the second half of the menstrual cycle (the luteal phase) inhibit the production of gonadotropin and, therefore, prevent further ovulation. If conception takes place, progesterone continues to be secreted, maintaining the endometrium in a favorable state for the continuation of the pregnancy and reducing uterine contractions. If conception does not take place, the release of progesterone from the corpus luteum ceases abruptly. The decline in progesterone stimulates the onset of menstruation.



Therapeutic uses: The major clinical uses of progestogens are for contraception or hormone replacement therapy. For both contraception and HT, progestogens are often used in combination with estrogens. Progesterone is not used as a contraceptive therapy because of its rapid metabolism, resulting in low bioavailability. Synthetic progestogens (like, progestins) used for contraception are more stable to first-pass metabolism, allowing lower doses when administered orally. These agents include **desogestrel, dienogest, levonorgestrel, norethindrone, norethindrone acetate, norgestimate, and norgestrel**.

Medroxyprogesterone acetate is an injectable contraceptive, and the oral form is a common progestin component of postmenopausal HT. Progestogens are also used for the control of dysfunctional uterine bleeding, treatment of dysmenorrhea, and management of endometriosis and infertility.

Pharmacokinetics A micronized preparation of progesterone is rapidly absorbed after oral administration. It has a short half-life in the plasma and is

metabolized by the liver to pregnanediol and glucuronide and sulfate conjugates. The metabolites are excreted primarily in the urine.

Synthetic progestins are less rapidly metabolized. Oral medroxyprogesterone acetate has a half-life of **30** hours. When injected intramuscularly or subcutaneously, the drug has a half-life of about **40 to 50** days and provides contraception for approximately 3 months. The other progestins have half-lives of **7 to 30** hours, allowing for once-daily dosing.

Adverse effects The major adverse effects associated with the use of progestins are headache, depression, weight gain, and changes in libido. Progestins that are derived from 19-nortestosterone (for example, norethindrone, norethindrone acetate, norgestrel, levonorgestrel) possess some androgenic activity because of their structural similarity to testosterone and can cause acne and hirsutism.

Less androgenic progestins, such as norgestimate and drospirenone may be preferred in women with acne. Drospirenone may raise serum potassium due to ant mineralocorticoid effects, and concurrent use with other drugs that increase potassium (for example, angiotensin converting enzyme inhibitors) may increase the risk of hyperkalemia.

Antiprogestin : **Mifepristone** (also designated as RU-486) is a progesterone antagonist. Administration of this drug results in termination of pregnancy due to interference with the progesterone needed to maintain pregnancy. Mifepristone is often combined with the prostaglandin analog misoprostol to induce uterine contractions. The major adverse effects are abdominal pain, uterine bleeding, and the possibility of an incomplete abortion.

CONTRACEPTIVES

Contraceptives may be hormonal or nonhormonal {for example, condom, diaphragm, contraceptive sponge, and copper intrauterine device). Figure 25.8 outlines the frequency of use for various hormonal and nonhormonal methods of contraception. An overview of the hormonal methods of contraception is provided below. A. Types of hormonal contraceptives

1. Combination oral contraceptives: A combination of estrogen and progestin is the most common type of oral contraceptive. [Note: The most **common** estrogen in combination pills is **ethinyl estradiol.**

The most **common** progestins are norethindrone, **norethindrone** acetate, levonorgestrel, desogestrel, norgestimate, and drospirenone.] These preparations are highly effective in achieving contraception {Figure 25.9). Monophasic combination pills contain a constant dose of estrogen and progestin given over 21 to 24 days.

Triphasic oral contraceptive products attempt to mimic the natural female cycle and usually contain a constant dose of estrogen with increasing doses of progestin given over 21 days. With most oral contraceptives, active pills are taken for 21 to 24 days, followed by 4 to 7 days of placebo, for a total regimen of 28 days. Withdrawal bleeding occurs during the hormone-free (placebo) interval. Use of extended-cycle contraception (84 active pills followed by 7 days of placebo) results in less frequent withdrawal bleeding. A continuous oral contraceptive product (active pills taken every day) is also available.

2. Transdermal patch: The contraceptive transdermal patch contains ethinyl estradiol and the progestin norelgestromin. During the 28-day cycle, one patch is applied each week for 3 weeks to the abdomen, upper torso, or buttock. No patch is worn during the 4th week, and withdrawal bleeding occurs. The transdermal patch

has efficacy comparable to that of the oral contraceptives, but it is less effective in women weighing greater than 90 kg. Total estrogen exposure with the transdermal patch may be significantly greater than that seen with oral contraceptives.

3. Vaginal ring: The contraceptive vaginal ring contains ethinyl estradiol and etonogestrel. The ring is inserted into the vagina and left in place for 3 weeks. After 3 weeks, the ring is removed, and withdrawal bleeding occurs during the 4th week.

4. Progestin-only pills: Progestin-only pills (the "mini-pill") contain a progestin, usually norethindrone, and are administered daily to deliver a low, continuous dosage of drug. These preparations are less effective than combination oral contraceptives, and irregular menstrual cycles may be more frequent.

Progestin only pills may be used in patients who are **breast-feeding** (unlike estrogen, progestins do not have an effect on milk production) or who have intolerance or contraindications to estrogen-containing products.

5. InJectable progestin: Medroxyprogesterone acetate is a contraceptive that is administered via intramuscular or subcutaneous injection every 3 months. This product provides high sustained levels of progestin, and many women experience amenorrhea with medroxyprogesterone acetate. In addition, return to fertility may be delayed for several months after discontinuation. Weight gain is a common adverse effect. **Medroxyprogesterone acetate** may contribute to **bone loss** and predispose patients to osteoporosis and/or fractures. Therefore, the drug should not be continued for more than 2 years unless the patient is unable to tolerate other contraceptive options.

6. Progestin implants: After subdermal placement in the upper arm, the etonogestrel implant offers contraception for up to 3 years. The implant is as

reliable as sterilization, and the contraceptive effect is reversible when removed. [Note: Progestin implants and intrauterine devices are known as long-acting reversible contraceptives (LARC).] Adverse effects include irregular menstrual bleeding and headaches. The etonogestrel implant has not been studied in women who weigh more than 130% of ideal body weight and may be less effective in this population.

7. Progestin intrauterine device: Various levonorgestrel-releasing intrauterine devices offer a highly effective method of contraception for 3 to 5 years. This is a suitable method of contraception for women who desire long-term contraception. It should be avoided in patients with pelvic inflammatory disease or a history of ectopic pregnancy. The /evonorgestre/intrauterine device is a highly effective treatment for heavy menstrual bleeding.

[Note: The nonhormonal copper intrauterine device provides contraception for up to 10 years.] 8. Postcoital contraception: Postcoital or emergency contraception reduces the probability of pregnancy after intercourse without effective contraception (Figure 25.10) to between 0.2% and 3%. The most common method of emergency contraception uses a single high dose of /evonorgestrel. For maximum effectiveness, emergency contraception should be taken as soon as possible after unprotected intercourse and preferably within 72 hours. The /evonorgestrel emergency contraceptive regimens are generally better tolerated than the estrogen-progestin combination regimens. An alternative emergency contraceptive is the progesterone agonist/antagonist u/ipristal [ue-li-PRIS-tal]. It is indicated for emergency contraception within 5 days of unprotected intercourse. B. Mechanism of action Exogenously administered estrogen in contraceptives provides negative feedback which blunts release of follicle-stimulating hormone (FSH) by the pituitary gland and progestin inhibits LH secretion, thus preventing

ovulation. Progestin also thickens the cervical mucus, thus hampering the transport of sperm. Withdrawal of the progestin stimulates menstrual bleeding during the placebo week.

Adverse effects: The incidence of adverse effects with contraceptives is determined by the specific compounds and combinations used.

The most common adverse effects with:

Estrogens are **breast fullness, fluid retention, headache, and nausea. Increased blood pressure** may also occur. **Progestins** may be associated with **depression, changes in libido, hirsutism, and acne. Although rare, thromboembolism, thrombophlebitis, myocardial infarction, and stroke** may occur with use of estrogen-containing contraceptives. These severe adverse effects are most common among women who are over age 35 and smoke, and estrogen-containing contraceptives should be avoided in this population. Progestin-only products are preferred in older women who are smokers, due to a lower risk of severe adverse effects. The incidence of cervical cancer may be increased with hormonal contraceptives, because women are less likely to use barrier methods of contraception that reduce exposure to human papillomavirus, the primary risk factor for cervical cancer. [Note: Oral contraceptives are associated with a decreased risk of endometrial and ovarian cancer.] Oral contraceptives are contraindicated in the presence of cerebrovascular and thromboembolic disease,. .

ANDROGENS

The androgens are a group of steroids that have anabolic and/or masculinizing effects in both males and females. Testosterone [tess-TOSS-terone], the most

important androgen in humans, is synthesized by Leydig cells in the testes and, in smaller amounts, by thecal cells in the ovaries and by the adrenal gland in both sexes. Other androgens secreted by the testes are Sa-dihydrotestosterone (DHT), androstenedione, and DHEA in small amounts.

In adult males, testosterone secretion by Leydig cells is controlled by gonadotropin-releasing hormone from the hypothalamus, which stimulates the anterior pituitary gland to secrete FSH and LH. Testosterone or its active metabolite, DHT, inhibits production of these specific trophic hormones through a negative feedback loop and, thus, regulates testosterone production (Figure 25.11). The androgens are required for

1) Normal maturation in the male,

2) Sperm production,

3) Increased synthesis of muscle proteins and hemoglobin, and

4) Decreased bone resorption.

Synthetic modifications of the androgen structure modify solubility and susceptibility to metabolism (thus prolonging the half-life of the hormone), and separate anabolic and androgenic effects.

Mechanism of action Like the estrogens and progestins, androgens bind to a specific nuclear receptor in a target cell. Although testosterone itself is the active ligand in muscle and liver, in other tissues, it must be metabolized to derivatives, such as DHT. For example, after diffusing into the cells of the prostate, seminal vesicles, epididymis, and skin, testosterone is converted by Sa-reductase to DHT, which binds to the receptor.

Therapeutic uses Androgenic steroids are used for males with primary hypogonadism (caused by testicular dysfunction) or secondary hypogonadism (due to failure of the hypothalamus or pituitary).

[Note: Testosterone replacement should only be used for males with hypogonadism related to medical conditions and not low testosterone associated with aging.]

Anabolic steroids can be used to treat chronic wasting associated with human immunodeficiency virus or cancer. An unapproved use of anabolic steroids is to increase lean body mass, muscle strength, and endurance in athletes and body builders'. Formulations of testosterone or its derivatives (for example, methyltestosterone) may be used in combination with estrogen for women with menopausal symptoms unresponsive to estrogen alone.

Danazol: a weak androgen is used in the treatment of endometriosis and fibrocystic breast disease. [Note: Danazol also possesses antiestrogenic activity.] Weight gain, acne, decreased breast size; deepening voice, increased libido, and increased hair growth are among the adverse effect.

Pharmacokinetics : Testosterone: This agent is ineffective orally because of inactivation by first-pass metabolism. Therefore, testosterone is administered via a transdermal patch, topical gel or solution, buccal tablet, or implantable pellet. Esters of testosterone (for example, testosterone cypionate or enanthate) are administered intramuscularly. The esterified formulations are more lipid soluble and have an increased duration of action up to several weeks.

Inactive metabolites are excreted primarily in the urine. Testosterone and its esters demonstrate a 1:1 relative ratio of androgenic to anabolic activity. 2. Testosterone derivatives: Alkylation of the 17a position of testosterone is associated with less

hepatic metabolism and allows oral administration of the hormone. Methyltestosterone and fluoxymesterone [are examples of orally administered testosterone derivatives. Oxandrolone and oxymetholone are orally active 17a-alkylated derivatives of DHT. Oxandrolone has anabolic activity 3 to 13 times that of testosterone.

Adverse effects. **In females:** Androgens can cause masculinization, acne, growth of facial hair, deepening of the voice, male pattern baldness, and excessive muscle development. Menstrual irregularities may also occur. Testosterone should not be used by pregnant women because of possible virilization of the female fetus.

In males: Excess androgen can cause priapism, impotence, decreased spermatogenesis, gynecomastia, and cosmetic changes such as those described for females. Androgens can also stimulate growth of the prostate.

In children: Androgens can cause abnormal sexual maturation and growth disturbances resulting from premature closing of the epiphyseal plates.

General effects: Androgens can increase serum LDL and lower serum high-density lipoprotein levels. They may also cause fluid retention and peripheral edema. Testosterone replacement therapy has been associated with a possible increased risk of myocardial infarction and stroke. Hepatic adverse effects have been associated with the 17a-alkylated androgens. Local skin irritation is a common adverse effect with topical formulations.

In athletes: Use of anabolic steroids (for example, DHEA) by athletes can cause premature closing of the epiphysis of the long bones, which stunts growth and interrupts development. High doses taken by young athletes may result in reduction of testicular size, hepatic abnormalities, increased aggression ("reid rage"), major mood disorders, and other adverse effects described above .

Anti- androgens

Counter male hormonal action by interfering with the synthesis of androgens or by blocking their receptors. Antiandrogens, such as flutamide , bicalutamide , enzalutamide and nilutamide act as competitive inhibitors of androgens at the target cell and are effective orally for the treatment of prostate cancer

Finasteride and dutasteride inhibit Sa-reductase, resulting in decreased formation of dihydrotestosterone. These agents are used for the treatment of benign prostatic hyperpy.

Lec 10 Cancer Chemotherapy

Principles of Cancer Chemotherapy

Cancer chemotherapy aims to cause a lethal cytotoxic event or apoptosis in the cancer cell that can arrest tumor progression. The attack is generally directed toward DNA or against metabolic sites essential to cell replication. Ideally, these anticancer drugs should interfere only with cellular processes that are **unique** to malignant cells. Indeed, most anticancer drugs **do not** specifically recognize neoplastic cells and affect **all** kinds of proliferating cells including the normal cells. Therefore, almost all antitumor agents have a steep dose–response curve for both therapeutic and toxic effects. Newer agents are being developed that take a different approach to cancer treatment by blocking checkpoints and allowing the patient's own immune system to attack cancer cells.. Chemotherapeutic agents also used in non-cancer diseases, e.g. methotrexate in rheumatoid arthritis and psoriasis, azathioprine in organ transplantation, and hydroxyurea in sickle cell anemia.

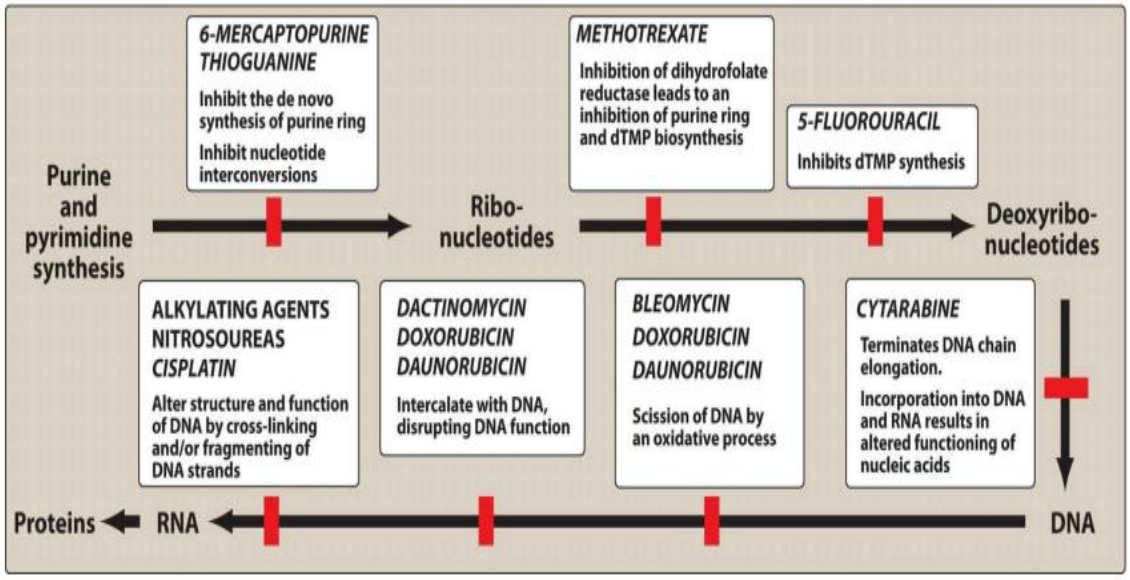


Figure. Examples of chemotherapeutic agents affecting RNA and DNA. dTMP = deoxythymidine monophosphate.

Treatment strategies

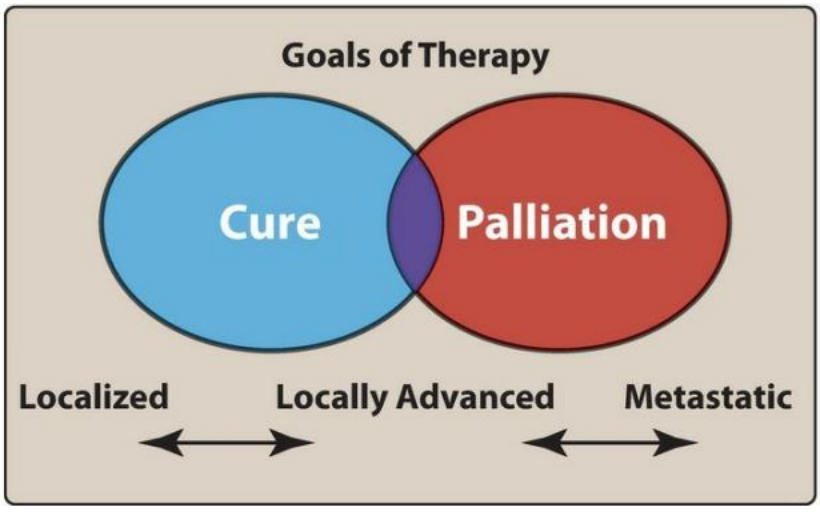
Goals of treatment: Chemotherapy reduces neoplastic cell burden to maintain "normal" existence of the disease with the patient as a chronic disease, accordingly three goals intended depending upon complicated factors mainly the type and stage of cancer:

First fundamental goal of cancer chemotherapy is to cure the disease. Cure means long-term disease-free survival. True cure requires the eradication of every neoplastic cell.

Second goal becomes control of the disease by stopping the cancer from enlarging and spreading to extend survival and maintain the "best quality" of life. In advanced stages of cancer, controlling the disease **is not possible**.

Third goal is palliation. Palliation means alleviation of symptoms and avoidance of life threatening toxicity. This means that chemotherapeutic drugs may be used to relieve symptoms caused by the cancer and improve the quality of life, even

though the drugs may not extend survival. The goal of treatment should always be kept in mind, as it often influences treatment decisions.



Indications for treatment:

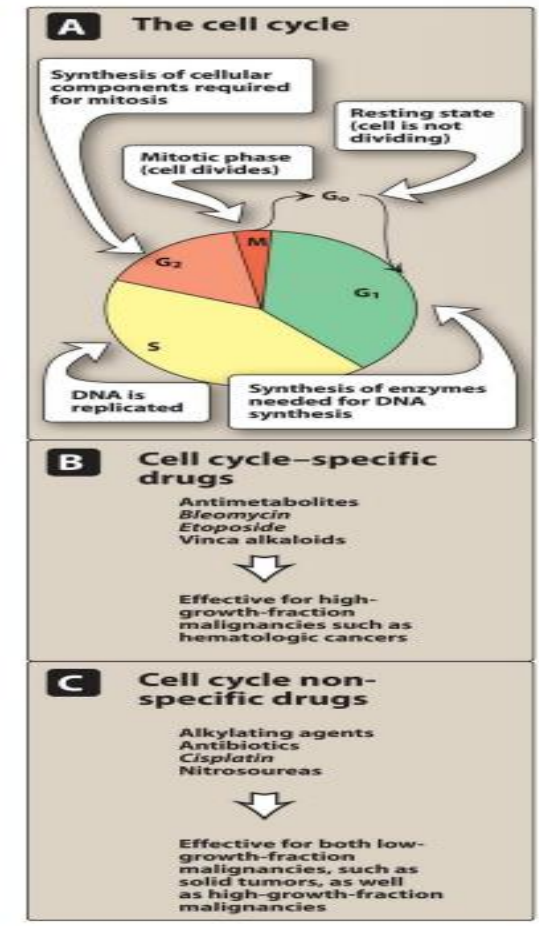
Chemotherapy is indicated in the following cases:

a) Initial chemotherapy: indicated when the neoplasm is disseminated and are not suitable to surgery, e.g esophageal, head and neck cancers, and leukemia.

b) Adjuvant chemotherapy: is indicated as supplemental treatment to attack micro metastases following surgery or radiation, e.g in breast and colorectal cancers.

c) Neo-adjuvant chemotherapy: given prior to surgery in an attempt to shrink the cancer in solid tumors.

d) Maintenance chemotherapy: given in low doses to cancer patients to assist in prolonging remission.



Treatment regimens and scheduling

Drug dosages are usually calculated on the basis of body surface area, in an effort to tailor the dosage to each patient.

Destruction of cancer cells by chemotherapeutic agents follows **first-order** kinetics (that is, a given dose of drug destroys a constant fraction of cells).

Combination chemotherapy is more successful than single-drug treatment in most cancers for which chemotherapy is effective. Cytotoxic agents with different toxicities, and with different molecular sites and mechanisms of action, are usually combined **at full doses.** This results in higher response rates, due to additive and/or

potentiated cytotoxic effects, and nonoverlapping host toxicities. In contrast, agents with similar dose-limiting toxicities, such as myelosuppression, nephrotoxicity, or cardiotoxicity, can be combined safely only by reducing the doses of each.

The advantages of combination chemotherapy are that it

1) Provides maximal cell killing within the range of tolerated toxicity,

2) Is effective against a broader range of cell lines in the heterogeneous tumor population, and 3) may delay or prevent the development of resistant cell lines.

Treatment protocols: Many cancer treatment protocols have been developed, and each is applicable to a particular neoplastic state. They are usually identified by an acronym. For example, a common regimen called R-CHOP, used for the treatment of non-Hodgkin lymphoma, consists of rituximab, cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and prednisone. Therapy is scheduled intermittently to allow recovery or rescue of the immune system, which is also affected by the chemotherapeutic agents, thus reducing the risk of serious infection.

Resistance and toxicity with chemotherapy

Resistance one of the major difficulties in cancer therapy is the development of resistance to cancer chemotherapy. Resistance could be categorized into two forms:

1- **Inherited** or primary resistance: were some types of neoplasms are inherently resistant to some anticancer drug (e.g. melanoma) even when the chemotherapy treatment used for the first time.

2- **Acquired** resistance: were the tumor cells that previously sensitive will develop resistance during treatment with chemotherapy. This type of resistance developed by modulations made by the tumor cells to overcome the lethal effect of the drug. including **decreased** accumulation of drug (e.g. P-glycoprotein), insufficient activation of the drug (e.g. 5- FU, mercaptopurine), **decreased** taking up the drug (e.g. methotrexate), **increased** the concentration of target enzyme (e.g. methotrexate), utilization of alternative metabolic pathway (e.g. antimetabolites), increased repair of drug-induced lesions (e.g. alkylating agents), and **mutations** in various genes that giving rise to resistant target site (e.g. overexpression of antiapoptotic genes).

Resistance to chemotherapy commonly developed with:

* Long-term, continuous,
* Suboptimal doses and
* Single drug regimens. Therefore, to minimize resistance, it is advised to use short-term, intermittent, and intensive and drug combination regimens.

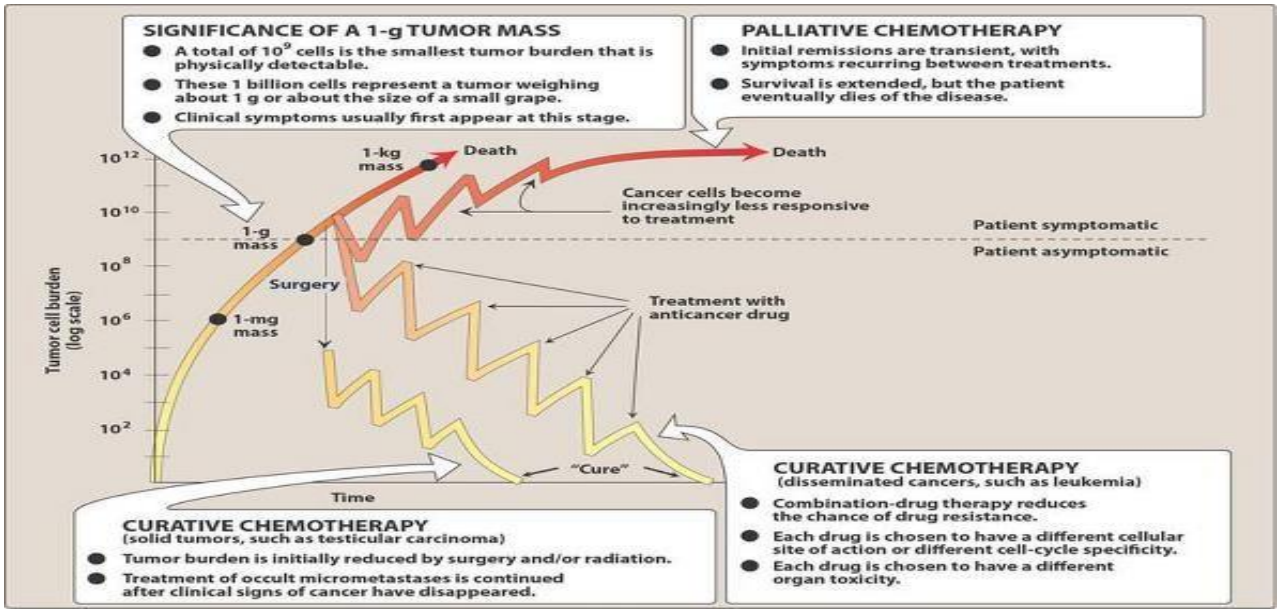
Toxicity

Therapy aimed at killing rapidly dividing cancer cells also affects normal cells undergoing rapid proliferation (for example, cells of the buccal mucosa, bone marrow, gastrointestinal [GI] mucosa, and hair follicles), contributing to the toxic manifestations of chemotherapy.

Common adverse effects

Most chemotherapeutic agents have a **narrow** therapeutic index. Severe vomiting, stomatitis, bone marrow suppression, and alopecia occur to varying extents during therapy with most antineoplastic agents. Vomiting is often controlled by administration of antiemetic drugs. Some toxicities, such as myelosuppression that predisposes to infection, are common to many chemotherapeutic agents, whereas

other adverse reactions are confined to specific agents, such as bladder toxicity with cyclophosphamide, cardiotoxicity with doxorubicin, and pulmonary fibrosis with bleomycin. The duration of the adverse effects varies widely. For example, alopecia is transient, but the cardiac, pulmonary, and bladder toxicities can be irreversible.



Cancer cell burden with/without treatment

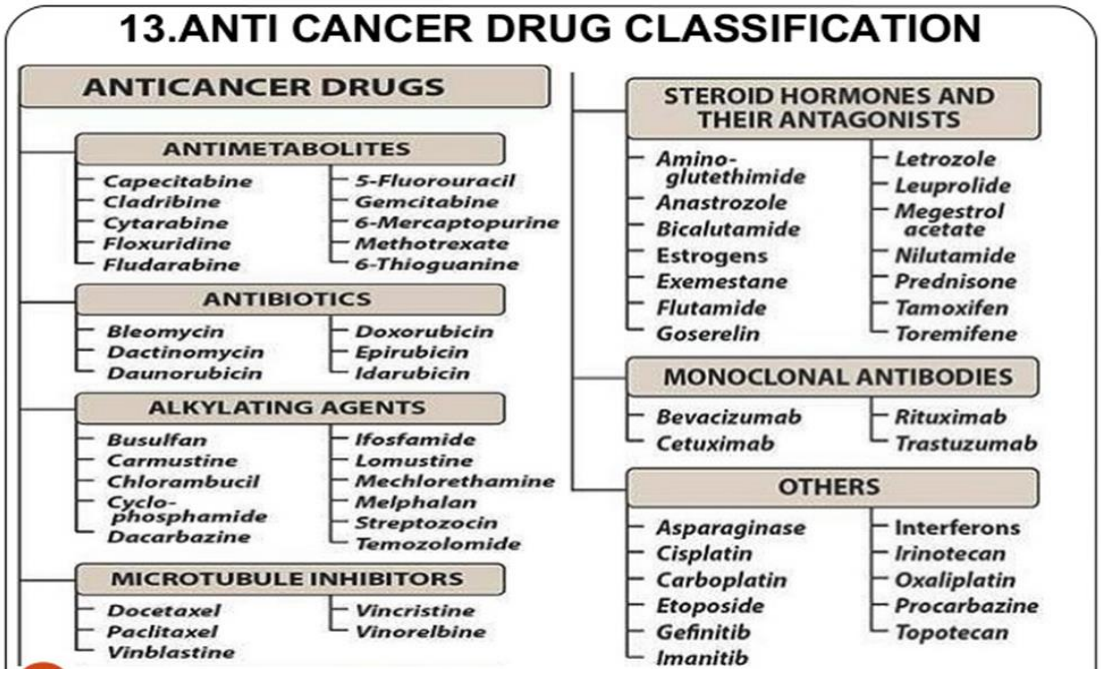


Figure 1 Classification of anticancer drug.

Antimetabolites

Antimetabolites are structurally related to normal compounds that exist within the cell. They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis. Their maximal cytotoxic effects are in S phase and are, therefore, cell cycle specific.

Methotrexate, pemetrexed, and pralatrexate

The vitamin folic acid plays a central role in a variety of metabolic reactions involving the transfer of one-carbon units and is essential for cell replication. Folic acid is obtained mainly from dietary sources and from that produced by intestinal flora. Methotrexate, pemetrexed, and pralatrexate are antifolate agents.

Mechanism of action

MTX is structurally related to folic acid and acts as an antagonist of the vitamin by inhibiting mammalian dihydrofolate reductase (DHFR), the enzyme that converts folic acid to its active, coenzyme form, tetrahydrofolic acid (FH4). The inhibition of DHFR can only be reversed by a 1000-fold excess of the natural substrate, dihydrofolate (FH2), or by administration of leucovorin, which bypasses the blocked enzyme and replenishes the folate pool.

Folinic acid (leucovorin) could restore MTX inhibition by replenishing THF pool as it bypasses the MTX inhibition sites.

Pemetrexed is an antimetabolite similar in mechanism to methotrexate. However, in addition to inhibiting DHFR, it also inhibits thymidylate synthase and other enzymes involved in folate metabolism and DNA synthesis. Pralatrexate is an antimetabolite that also inhibits DHFR.

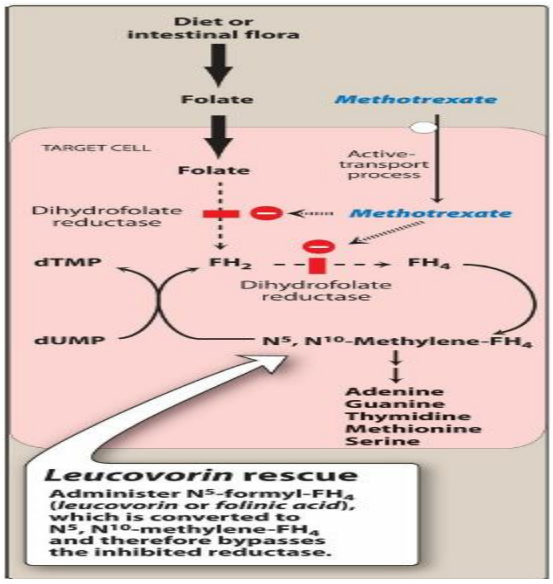


Figure 2 Mechanism of action of methotrexate and the effect of administration of leucovorin.

Therapeutic uses

MTX, usually in combination with other drugs, is effective against acute lymphocytic leukemia, Burkitt lymphoma in children, breast cancer, bladder

cancer, and head and neck carcinomas. In addition, low-dose MTX is effective as a single agent against certain inflammatory diseases, such as severe psoriasis and rheumatoid arthritis, as well as Crohn disease. Pemetrexed is primarily used in non–small cell lung cancer. Pralatrexate is used in relapsed or refractory T-cell lymphoma.

Pharmacokinetics

MTX is variably absorbed orally at low doses from the GI tract, it can also be administered by intramuscular, intravenous (IV), and intrathecal routes.

Small amounts of MTX undergo hydroxylation at the 7th position to form 7-hydroxymethotrexate. This derivative is less water soluble than MTX and may lead to crystalluria. Therefore, it is important to keep the urine alkaline and the patient well hydrated to avoid renal toxicity. Excretion of the parent drug and the 7-OH metabolite occurs primarily via urine.

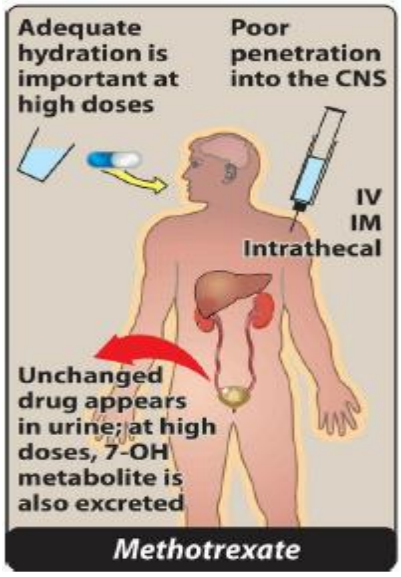


Figure 3 Administration and fate of methotrexate.

Adverse effects: MTX, Pemetrexed and pralatrexate should be given with folic acid and vitamin B12 supplements to reduce hematologic and GI toxicities.

Pretreatment with corticosteroids to prevent cutaneous reactions is recommended with pemetrexed.

However, it may cause ocular toxicity, including irreversible retinal damage and corneal deposits, CNS disturbances, GI upset, and skin discoloration and eruptions.

Purine analogs

Drugs belong to this category are guanine analogs (6-mercaptopurine, 6-thioguanine), and adenosine analogs (fludarabine, and cladribine).

Some drugs in this category dose **not used** in cancer chemotherapy but as immunosuppressant (e.g. azathioprine), antiviral (e.g. acyclovir, zidovudine) and hypouricemic agent (allopurinol).

6-Mercaptopurine

6-Mercaptopurine (6-MP), a purine antimetabolite, is the thiol analog of hypoxanthine. 6-MP and 6-thioguanine were the first purine analogs to prove beneficial for treating neoplastic disease. [Note: Azathioprine, an immunosuppressant, exerts its cytotoxic effects after conversion to 6-MP.] 6-MP is used principally in the maintenance of remission in acute lymphoblastic leukemia. 6-MP and its analog, azathioprine, are also beneficial in the treatment of Crohn's disease.

Adenosine analogs

Fludarabine and Cladribine. Both agents are adenosine analogs used in leukemia's and lymphomas. Fludarabine is the 5′-phosphate of 2-fluoroadenine arabinoside, a purine nucleotide analog. It is useful in the treatment of chronic lymphocytic leukemia, hairy cell leukemia, and indolent non-Hodgkin lymphoma. Fludarabine is a prodrug, and the phosphate is removed in the plasma to form 2-F-araA, which is taken up into cells and again phosphorylated (initially by

deoxycytidine kinase). Although the exact cytotoxic mechanism is uncertain, the triphosphate is incorporated into both DNA and RNA. This decreases their synthesis in the S phase and affects their function.

Resistance is associated with reduced uptake into cells, lack of deoxycytidine kinase, and decreased affinity for DNA polymerase, as well as other mechanisms. Fludarabine is administered IV rather than orally, because intestinal bacteria split off the sugar to yield the very toxic metabolite, fluoroadenine.

Pyrimidine analogs

This category of chemotherapeutic agents designed as a false metabolite to inhibit pyrimidine nucleotide synthesis, thus inhibit DNA synthesis, and to lesser extent inhibit RNA synthesis. Pyrimidine analogs could be divided into two groups according to the nucleotide target: thymidine and cytosine inhibitors. Thymidine inhibitors include 5-fluorouracil (5-FU), capecitabine; while the cytosine inhibitors include cytarabine, 5-azacytidine and gemcitabine.

1-(5-Fluorouracil)

5-Fluorouracil (5-FU), a pyrimidine analog, has a stable fluorine atom in place of a hydrogen atom at position 5 of the uracil ring. The fluorine interferes with the conversion of deoxyuridylic acid to thymidylic acid, thus depriving the cell of thymidine, one of the essential precursors for DNA synthesis. 5-FU is employed primarily in the treatment of slow-growing solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas). When applied topically, 5-FU is also effective for the treatment of superficial basal cell carcinomas.

Mechanism of action : 5-FU itself is devoid of antineoplastic activity. It enters the cell through a carrier-mediated transport system and is converted to the corresponding deoxynucleotide (5-fluorodeoxyuridine monophosphate [5-FdUMP]), which competes with deoxyuridine monophosphate for thymidylate synthase, thus inhibiting its action. DNA synthesis decreases due to lack of thymidine, leading to imbalanced cell growth and "thymidine-less death" of rapidly dividing cells. [Note: Leucovorin is administered with 5-FU, because the reduced folate coenzyme is required in the thymidylate synthase inhibition]. 5-FU is also incorporated into RNA, and low levels have been detected in DNA. In the latter case, a glycosylase excises the 5-FU, damaging the DNA. 5-FU produces the anticancer effect in the S phase of the cell cycle.

Pharmacokinetics

Because of severe toxicity to the GI tract, 5-FU is administered IV or, in the case of skin cancer, topically. The drug penetrates well into all tissues, including the CNS. 5-FU is rapidly metabolized in the liver, lung, and kidney. It is eventually converted to fluoro-β-alanine, which is removed in the urine.

Elevated levels of dihydropyrimidine dehydrogenase (DPD) can increase the rate of 5-FU catabolism and decrease its bioavailability. Patients with DPD deficiency may experience severe toxicity manifested by pancytopenia, mucositis, and life-threatening diarrhea. Knowledge of DPD activity in an individual should allow more appropriate dosing of 5-FU.

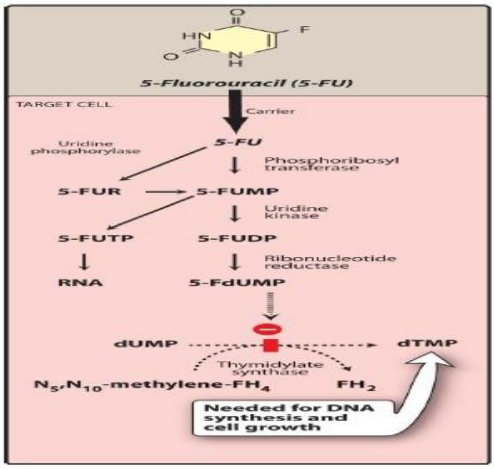


Figure Mechanism of the cytotoxic action of 5-FU.

2. Capecitabine

Capecitabine is a fluoropyrimidine carbamate. It is used in the treatment of colorectal and metastatic breast cancer. Capecitabine is well absorbed following oral administration. After being absorbed, capecitabine, which is itself nontoxic, undergoes a series of enzymatic reactions, the last of which is hydrolysis to 5-FU. This step is catalyzed by thymidine phosphorylase, an enzyme that is concentrated primarily in tumors. Thus, the cytotoxic activity of capecitabine is the same as that of 5-FU and is tumor specific. The most important enzyme inhibited by 5-FU (and, thus, capecitabine) is thymidylate synthase.

Cytidine analogs

These pyrimidine inhibitors are cytidine analogs with antineoplastic action include cytarabine, 5-azacytidine and gemcitabine.

1- Cytarabine

Cytarabine : is an analog of 2′-deoxycytidine in which the natural ribose residue is replaced by D-arabinose. Cytarabine acts as a pyrimidine antagonist. The major clinical use of cytarabine is in acute nonlymphocytic (myelogenous) leukemia (AML). Cytarabine enters the cell by a carrier-mediated process and, like the other

purine and pyrimidine antagonists, must be sequentially phosphorylated by deoxycytidine kinase and other nucleotide kinases to the nucleotide form (cytosine arabinoside triphosphate or ara- CTP) to be cytotoxic. Ara-CTP is an effective inhibitor of DNA polymerase. The nucleotide is also incorporated into nuclear DNA and can terminate chain elongation. It is, therefore, S phase (and, hence, cell cycle) specific.

Pharmacokinetics

Cytarabine is **not** effective when given orally, because of deamination to the noncytotoxic ara-U by cytidine deaminase in the intestinal mucosa and liver. Given IV, it distributes throughout the body but does not penetrate the CNS in sufficient amounts. Therefore, it may also be injected intrathecally. Cytarabine undergoes extensive oxidative deamination in the body to ara-U, a pharmacologically inactive metabolite. Both cytarabine and ara-U are excreted in urine.

2- Azacitidine

Azacitidine is a pyrimidine nucleoside analog of cytidine. It is used for the treatment of myelodysplastic syndromes and AML. Azacitidine undergoes activation to the nucleotide metabolite azacitidine triphosphate and gets incorporated into RNA to inhibit RNA processing and function. It is S-phase cell cycle specific.

3-Gemcitabine

Gemcitabine is an analog of the nucleoside deoxycytidine. It is used most commonly for pancreatic cancer and non–small cell lung cancer. Gemcitabine is a substrate for deoxycytidine kinase, which phosphorylates the drug to 2′,2′-difluorodeoxycytidine triphosphate. Gemcitabine is administered by IV infusion. It is deaminated to difluorodeoxyuridine, which is not cytotoxic, and is excreted in urine.

Lec 11 Antibiotics (antitumor)

The antitumor antibiotics owe their cytotoxic action primarily to their interactions with DNA, leading to disruption of DNA function. In addition to intercalation, their abilities to inhibit topoisomerases (I and II) and produce free radicals also play a major role in their cytotoxic effect. They are cell cycle nonspecific, with bleomycin as an exception.

A. Anthracyclines: Doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone

Doxorubicin and daunorubicin are classified as anthracycline antibiotics. Doxorubicin is the hydroxylated analog of daunorubicin. Idarubicin, the 4-demethoxy analog of daunorubicin, epirubicin, and mitoxantrone are also available.

Therapeutic uses for these agents differ despite their structural similarity and apparently similar mechanisms of action.

Doxorubicin used in combination with other agents for treatment of sarcomas and a variety of carcinomas, including breast cancer, as well as for treatment of acute lymphocytic leukemia and lymphomas. Daunorubicin and idarubicin are used in the treatment of acute leukemias, and mitoxantrone is used in prostate cancer.

Mechanism of action

Doxorubicin and other anthracyclines induce cytotoxicity through several different mechanisms. For example, doxorubicin-derived free radicals can induce membrane lipid peroxidation, DNA strand scission, and direct oxidation of purine or pyrimidine bases, thiols, and amines.

Pharmacokinetics

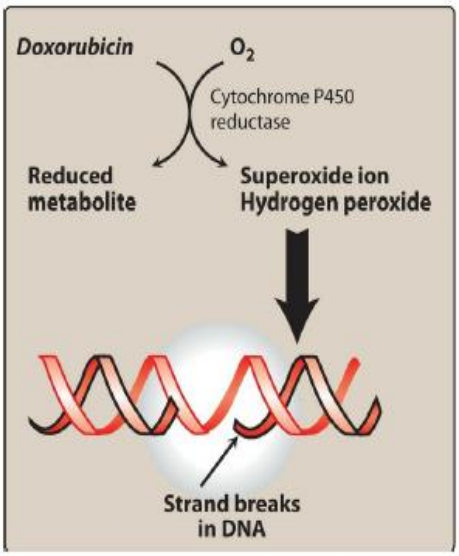
These agents must be administered intravenously, because they are inactivated in the GI tract. Extravasation is a serious problem that can lead to tissue necrosis.

The anthracycline antibiotics bind to plasma proteins as well as to other tissue components, where they are widely distributed. They **do not** penetrate the blood–brain barrier or the testes.

These agents undergo extensive hepatic metabolism, and dosage adjustments are needed in patients with impaired hepatic function.

Biliary excretion is the major route of elimination. .

Because of the dark red color of the anthracycline drugs, the veins may become visible surrounding the site of infusion, and red discoloration of urine may occur.



Adverse effects

Irreversible, dose-dependent **cardiotoxicity** is the most serious adverse reaction and is more common with daunorubicin and doxorubicin than with idarubicin and

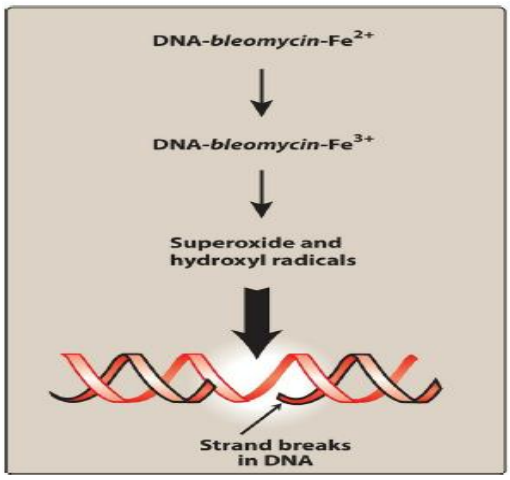
epirubicin. There has been some success with the iron chelator dexrazoxane in protecting against the cardiotoxicity of doxorubicin. The liposomal-encapsulated doxorubicin is reported to be less cardiotoxic than the standard formulation.

B. Bleomycin: Bleomycin is a mixture of different copper-chelating glycopeptides that, like the anthracycline antibiotics, cause scission of DNA by an oxidative process.

Bleomycin is cell cycle specific and causes cells to accumulate in the G2 phase.
It is primarily used in the treatment of testicular cancers and Hodgkin lymphoma.

Mechanism of action

A DNA–bleomycin–Fe2+ complex appears to undergo oxidation to bleomycin–Fe3+. The liberated electrons react with oxygen to form superoxide or hydroxyl radicals, which, in turn, attack the phosphodiester bonds of DNA, resulting istrand breakage and chromosomal aberrations.



Pharmacokinetics

Bleomycin is administered by a number of routes.

The bleomycin-inactivating enzyme (a hydrolase) is high in a number of tissues (for example, liver and spleen) but is low in the lung and absent in the skin, accounting for toxicity in those tissues. Most of the parent drug is excreted unchanged in the urine, necessitating dose adjustment in patients with renal failure.

Adverse effects

Pulmonary toxicity is the most serious adverse effect, progressing from rales, cough, and infiltrate to potentially fatal fibrosis. The pulmonary fibrosis that is caused by bleomycin is often referred as "bleomycin lung."
Hypertrophic skin changes and hyperpigmentation of the hands are prevalent.
Bleomycin is unusual in that myelosuppression is rare.

Alkylating Agents

Alkylating agents exert their cytotoxic effects by covalently binding to nucleophilic groups on various cell constituents. Alkylation of DNA is probably the crucial cytotoxic reaction that is lethal to the tumor cells. Alkylating agents do not discriminate between cycling and resting cells, even though they are **most** toxic for rapidly dividing cells. They are used in combination with other agents to treat a wide variety of lymphatic and solid cancers. In addition to being cytotoxic, **all** are mutagenic and carcinogenic and can lead to secondary malignancies such as acute leukemia.

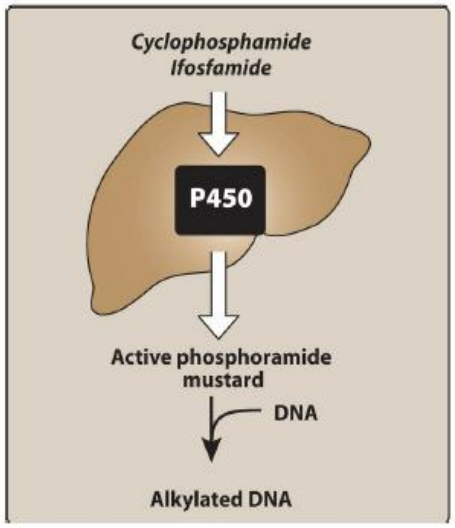
A. Cyclophosphamide and ifosfamide

These drugs are very closely related mustard agents that share most of the same primary mechanisms and toxicities. These agents have a broad clinical spectrum and are used as single agents or in combinations in the treatment of a wide variety

of neoplastic diseases, such as non-Hodgkin lymphoma, sarcoma, and breast cancer.

Mechanism of action

Cyclophosphamide is the most commonly used alkylating agent. Both cyclophosphamide and ifosfamide are first biotransformed to hydroxylated intermediates primarily in the liver by the CYP450 system. The hydroxylated intermediates then undergo metabolism to form the active compounds, phosphoramide mustard and acrolein. Reaction of the phosphoramide mustard with DNA is considered to be the cytotoxic step.



Pharmacokinetics

Cyclophosphamide is available in oral and IV preparations, whereas ifosfamide is IV only. Cyclophosphamide is metabolized in the liver to active and inactive metabolites, and minimal amounts are excreted in the urine as unchanged drug.

Ifosfamide is metabolized primarily by CYP450 3A4 and 2B6 isoenzymes. It is mainly renally excreted.

Adverse effects : A unique toxicity of both drugs is **hemorrhagic cystitis**, which can lead to fibrosis of the bladder. Bladder toxicity has been attributed to acrolein in the urine in the case of cyclophosphamide and to toxic metabolites of ifosfamide.

Adequate hydration as well as IV injection of mesna (sodium 2-mercaptoethane sulfonate), which neutralizes the toxic metabolites, can minimize this problem. Neurotoxicity has been reported in patients on high-dose ifosfamide, probably due to the metabolite, chloroacetaldehyde.

B. Nitrosoureas

Carmustine and lomustine are closely related nitrosoureas. Because of their ability to penetrate the CNS, the nitrosoureas are primarily employed in the treatment of brain tumors.

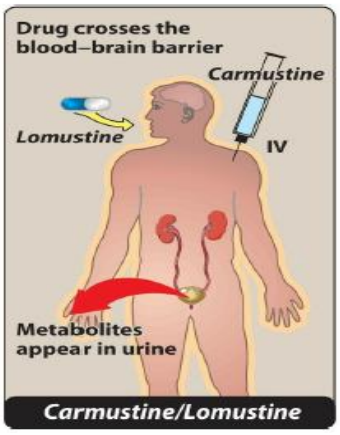
Mechanism of action

The nitrosoureas exert cytotoxic effects by an alkylation that inhibits replication and, eventually, RNA and protein synthesis. Although they alkylate DNA in resting cells, cytotoxicity is expressed primarily in cells that are actively dividing. Therefore, nondividing cells can escape death if DNA repair occurs. Nitrosoureas also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins in the targeted cells.

Pharmacokinetics

Carmustine is administered IV and as chemotherapy wafer implants, whereas lomustine is given orally. Because of their lipophilicity, these agents distribute

widely in the body and readily penetrate the CNS. The drugs undergo extensive metabolism. Lomustine is metabolized to active products. The kidney is the major excretory route for the nitrosoureas.



C. Dacarbazine and temozolomide

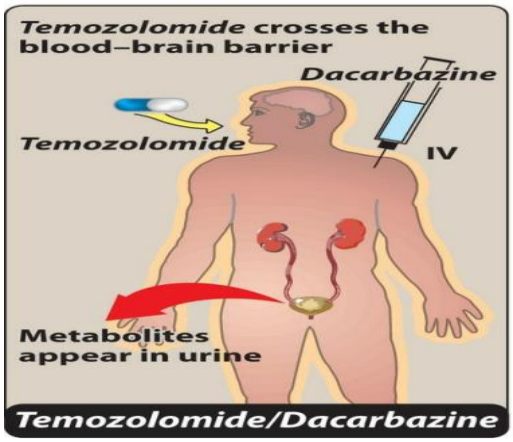
Dacarbazine is an alkylating agent that must undergo biotransformation to an active metabolite, methyltriazenoimidazole carboxamide (MTIC). The metabolite is responsible for the alkylating activity of this agent by forming methyl carbonium ions that attack the nucleophilic groups in the DNA molecule.

The cytotoxic action of dacarbazine has been attributed to the ability of its metabolite to methylate DNA on the O-6 position of guanine. Dacarbazine has found use in the treatment of melanoma and Hodgkin lymphoma.

Temozolomide is related to dacarbazine, because both must undergo biotransformation to an active metabolite, MTIC, which is likely responsible for the methylation of DNA on the O-6 and N-7 position of guanine. Unlike dacarbazine, temozolomide does not require the CYP450 system for metabolic transformation, and it undergoes chemical transformation at normal physiological

pH. Temozolomide also inhibits the repair enzyme, O-6-guanine-DNA alkyltransferase.

Temozolomide differs from dacarbazine in that it crosses the blood brain barrier and, therefore, is used in the treatment of brain tumors such as glioblastomas and astrocytomas. It is also used in metastatic melanoma. Temozolomide is administered **intravenously or orally** and has excellent bioavailability after oral administration. The parent drug and metabolites are excreted in urine.



D. Other alkylating agents

Mechlorethamine was developed as a vesicant (nitrogen mustard) during World War I. Its ability to cause lymphocytopenia led to its use in **lymphatic** cancers.

Melphalan, a phenylalanine derivative of nitrogen mustard, is used in the treatment of **multiple myeloma**. This is a bifunctional alkylating agent that can be given orally, although the plasma concentration differs from patient to patient due to variation in intestinal absorption and metabolism. The dose of melphalan is carefully adjusted by monitoring the platelet and white blood cell counts.

Chlorambucil is another bifunctional alkylating agent that is used in the treatment of chronic lymphocytic leukemia.

Busulfan is an alkylating agent that is effective against chronic myelogenous leukemia. This agent can cause pulmonary fibrosis ("busulfan lung"). Like other alkylating agents, all of these agents are leukemogenic.

Microtubule Inhibitors

The mitotic spindle is part of a larger, intracellular skeleton (cytoskeleton) that is essential for the movements of structures occurring in the cytoplasm of all eukaryotic cells. The mitotic spindle is essential for the equal partitioning of DNA into the two daughter cells that are formed when a eukaryotic cell divides.

Several plant-derived substances used as anticancer drugs disrupt this process by affecting the equilibrium between the polymerized and depolymerized forms of the microtubules, thereby causing cytotoxicity.

A. Vincristine and vinblastine

Vincristine (VX) and vinblastine (VBL) are structurally related compounds derived from the periwinkle plant, Vinca rosea. They are, therefore, referred to as the Vinca alkaloids. A less neurotoxic agent is vinorelbine (VRB). Although the Vinca alkaloids are structurally similar, their therapeutic indications are different. They are generally administered in combination with other drugs.

VX is used in the treatment of acute lymphoblastic leukemia in children, Wilms tumor, Ewing soft tissue sarcoma, and Hodgkin and non-Hodgkin lymphomas, as well as some other rapidly proliferating neoplasms. VBL is administered with bleomycin and cisplatin for the treatment of metastatic testicular carcinoma. It is

also used in the treatment of systemic Hodgkin and non-Hodgkin lymphomas. VRB is beneficial in the treatment of advanced non–small cell lung cancer, either as a single agent or with cisplatin.

Mechanism of action: These agents are cell cycle specific and **phase specific**, because they block mitosis in metaphase (M phase). Their binding to the microtubular protein, tubulin, blocks the ability of tubulin to polymerize to form microtubules. Instead, paracrystalline aggregates consisting of tubulin dimers and the alkaloid drug are formed. The resulting dysfunctional spindle apparatus, frozen in metaphase, prevents chromosomal segregation and cell proliferation.

Pharmacokinetics

IV injection of these agents leads to rapid cytotoxic effects and cell destruction. This, in turn, can cause hyperuricemia due to the oxidation of purines that are released from fragmenting DNA molecules.

The Vinca alkaloids are concentrated and metabolized in the liver by the CYP450 pathway and eliminated in bile and feces. Dosage adjustment is required in patients with impaired hepatic function or biliary obstruction.

Adverse effects: VX and VBL are both associated with phlebitis or cellulitis if extravasation occurs during injection, as well as nausea, vomiting, diarrhea, and alopecia. VBL is a potent myelosuppressant, whereas peripheral neuropathy (paresthesias, loss of reflexes, foot drop, and ataxia) and constipation are more common with VX. These agents should not be administered intrathecally. This potential drug error can result in death, and special precautions should be in place for administration.

B- Paclitaxel and docetaxel

Paclitaxel was the first member of the taxane family to be used in cancer chemotherapy. Substitution of a side chain resulted in docetaxel, which is the more potent of the two drugs. Paclitaxel has good activity against advanced ovarian cancer and metastatic breast cancer, as well as non–small cell lung cancer when administered with cisplatin. Docetaxel is commonly used in prostate, breast, GI, and non–small cell lung cancers.

Mechanism of action

Both drugs are active in the G2/M phase of the cell cycle, but unlike the Vinca alkaloids, they promote polymerization and stabilization of the polymer rather than disassembly, leading to the accumulation of microtubules (Figure 3). The microtubules formed are overly stable and nonfunctional, and chromosome desegregation does not occur. This results in cell death.

Pharmacokinetics These agents undergo hepatic metabolism by the CYP450 system and are excreted via the biliary system. Dosages should be reduced in patients with hepatic dysfunction.

Adverse effects: The dose-limiting toxicities of paclitaxel and docetaxel are neutropenia and leukopenia. Peripheral neuropathy is also a common adverse effect with the taxanes.

[Note: Because of serious hypersensitivity reactions (including dyspnea, urticaria, and hypotension), patients who are treated with paclitaxel should be premedicated with dexamethasone and diphenhydramine, as well as with an H2 receptor antagonist.]

Lec 12 Steroid Hormones and Their Antagonists (antitumor)

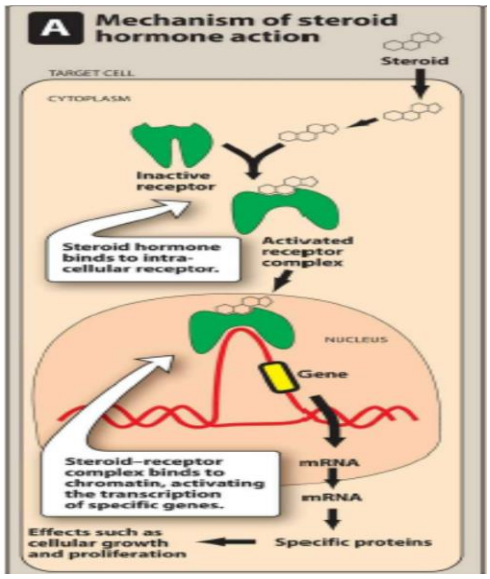
Tumors that are sensitive to steroid hormones may be either

1-hormone responsive, in which the tumor regresses following treatment with a specific hormone; or

2-hormone dependent, in which removal of a hormonal stimulus causes tumor regression; or

3- Both.

Removal of hormonal stimuli from hormone-dependent tumors can be accomplished by surgery (for example, in the case of orchiectomy—surgical removal of one or both testes—for patients with advanced prostate cancer) or by drugs (for example, in breast cancer treatment with the antiestrogen tamoxifen prevents estrogen stimulation of breast cancer cells). For a steroid hormone to influence a cell, that cell must have intracellular (cytosolic) receptors that are specific for that hormone.



A. Tamoxifen

Tamoxifen is a selective estrogen modulator (SERM).

It is an estrogen antagonist in breast tissue and an agonist in other tissues, such as bone and the endometrium.Tamoxifen is used for first-line therapy in the treatment of estrogen receptor–positive **breast cancer**. It is also used for prevention of breast cancer in high-risk women.

Mechanism of action

Tamoxifen competes with estrogen for binding to estrogen receptors in the breast tissue, and inhibits estrogen induced growth of breast cancer.

The result is

- depletion (down-regulation) of estrogen receptors, and the
- growth-promoting effects of the natural hormone and other growth factors are suppressed.

Pharmacokinetics

Tamoxifen is effective after oral administration. It is partially metabolized by the liver. Some metabolites possess estrogen antagonist activity, whereas others have agonist activity.

Unchanged drug and metabolites are excreted predominantly through the bile into the feces. Tamoxifen is an inhibitor of CYP3A4 and P-glycoprotein.

Adverse effects

Adverse effects caused by tamoxifen include : Hot flashes, nausea, vomiting, skin rash, and vaginal bleeding and discharge (due to estrogenic activity of the drug and some of its metabolites in the endometrial tissue).Tamoxifen has the potential to cause endometrial cancer, thromboembolism and effects on vision.

B. Fulvestrant and raloxifene

Fulvestrant is an estrogen receptor antagonist that is given via IM injection to patients with hormone receptor–positive metastatic breast cancer. This agent binds to and causes estrogen receptor down regulation on tumors and other targets.

Raloxifene is an oral SERM that blocks estrogen effects in the uterine and breast tissues, while promoting effects in the bone to inhibit resorption. This agent reduces the risk of estrogen receptor–positive invasive breast cancer in postmenopausal women. Both drugs are known to cause hot flashes, arthralgias, and myalgias.

C. Aromatase inhibitors

The aromatase reaction is responsible for extra-adrenal synthesis of estrogen from androstenedione, which takes place in liver, fat, muscle, skin, and breast tissues, including breast malignancies.

Peripheral aromatization is an important source of estrogen in postmenopausal women. Aromatase inhibitors decrease the production of estrogen in these women.

1. Anastrozole and letrozole

Anastrozole and letrozole are nonsteroidal aromatase inhibitors.
These agents are considered **first**-line drugs for the treatment of **breast cancer** in postmenopausal women. They are orally active and cause almost a total suppression of estrogen synthesis.
Anastrozole and letrozole do not predispose patients to endometrial cancer.
Both drugs are extensively metabolized in the liver, and metabolites and parent drug are excreted primarily in the urine.

2. Exemestane

A steroidal, irreversible inhibitor of aromatase,

Exemestane, is well absorbed after oral administration and widely distributed.

Hepatic metabolism occurs via the CYP3A4 isoenzyme. Because the metabolites are excreted in urine, doses of the drug must be adjusted in patients with renal failure.

Major toxicities are nausea, fatigue, and hot flashes. Alopecia and dermatitis have also been noted.

D. Leuprolide, goserelin, and triptorelin

Gonadotropin-releasing hormone (GnRH) is normally secreted by the hypothalamus and stimulates the anterior pituitary to secrete the gonadotropic hormones:

1-Luteinizing hormone (LH), the primary stimulus for the secretion of testosterone by the testes, and

2-Follicle-stimulating hormone (FSH), which stimulates the secretion of estrogen.

Leuprolide, goserelin, and triptorelin are synthetic analogs of GnRH.

As GnRH analogs, they occupy the GnRH receptor in the pituitary, which leads to its desensitization and, consequently, inhibition of release of FSH and LH. Thus, both androgen and estrogen synthesis are reduced. Response to leuprolide in prostatic cancer is equivalent to that of orchiectomy with regression of tumor and relief of bone pain.

These drugs have some benefit in **pre**menopausal women with advanced breast cancer and have largely replaced estrogens in therapy for prostate cancer.

Leuprolide is available as:

1) A subcutaneous daily injection,

2) A subcutaneous depot injection, or

3) An intramuscular depot injection to treat metastatic carcinoma of the prostate.

Goserelin acetate is a subcutaneous implant, and triptorelin pamoate is injected intramuscularly. Levels of androgen in prostate cancer patients may initially rise, but then fall to castration levels.

The **adverse effects** of these drugs, including

Impotence, hot flashes, and tumor flare, are minimal compared to those experienced with estrogen treatment.

E. Antiandrogens

Flutamide, nilutamide, bicalutamide, and enzalutamide are oral antiandrogens used in the treatment of prostate cancer. They compete with the natural hormone for binding to the androgen receptor and prevent its action in the prostate

Adverse effects include : gynecomastia, constipation, nausea, and abdominal pain.

Rarely, liver failure has occurred with flutamide. Nilutamide can cause visual problems.

Platinum Coordination Complexes

A. Cisplatin, carboplatin, and oxaliplatin

Cisplatin was the first member of the platinum coordination complex class of anticancer drugs, but because of severe toxicity, carboplatin was developed.
Cisplatin has **synergistic** cytotoxicity with radiation and other chemotherapeutic agents. It has found wide application in the treatment of solid tumors, such as metastatic testicular carcinoma in combination with VBL and bleomycin, ovarian carcinoma in combination with cyclophosphamide, or alone for bladder carcinoma.
Carboplatin is used when patients cannot be vigorously hydrated, as is required for cisplatin treatment, or if they suffer from kidney dysfunction or are prone to neuro- or ototoxicity.

Oxaliplatin is a closely related analog of carboplatin used in the setting of colorectal cancer.

Mechanism of action

The mechanism of action of these agents is similar to that of the alkylating agents. In the high-chloride milieu of the plasma, cisplatin persists as the neutral species, which enters the cell and loses chloride in the low-chloride milieu. It then binds to guanine in DNA, forming inter- and intrastrand cross-links. The resulting cytotoxic lesion inhibits both polymerases for DNA replication and RNA synthesis.

Cytotoxicity can occur at any stage of the cell cycle, but cells are most vulnerable to the actions of these drugs in the G1 and S phases.

Pharmacokinetics

These agents are administered via IV infusion. Cisplatin and carboplatin can also be given intraperitoneally for ovarian cancer and intra-arterially to perfuse other organs. The highest concentrations of the drugs are found in the liver, kidney, and intestinal, testicular, and ovarian cells, but little penetrates into the cerebrospinal fluid (CSF). The renal route is the main pathway of excretion.

Adverse effects

Severe nausea and vomiting occurs in most patients after administration of cisplatin and may continue for as long as 5 days. Premedication with antiemetic agents is required. The **major** limiting toxicity is dose-related **nephrotoxicity,** involving the distal convoluted tubule and collecting ducts. This can be prevented by aggressive hydration. Other toxicities include ototoxicity with high-frequency hearing loss and tinnitus. Unlike cisplatin, **carboplatin** causes only mild nausea and vomiting, and it is rarely nephro-, neuro-, or ototoxic. The dose-limiting toxicity is myelosuppression. **Oxaliplatin** has a distinct adverse effect of cold-induced peripheral neuropathy that usually resolves within 72 hours of administration. It also causes myelosuppression and cumulative peripheral

neuropathy. Hepatotoxicity has also been reported. These agents may cause hypersensitivity reactions ranging from skin rashes to anaphylaxis.

Topoisomerase Inhibitors

These agents exert their mechanism of action via inhibition of topoisomerase enzymes, a class of enzymes that reduce supercoiling of DNA.

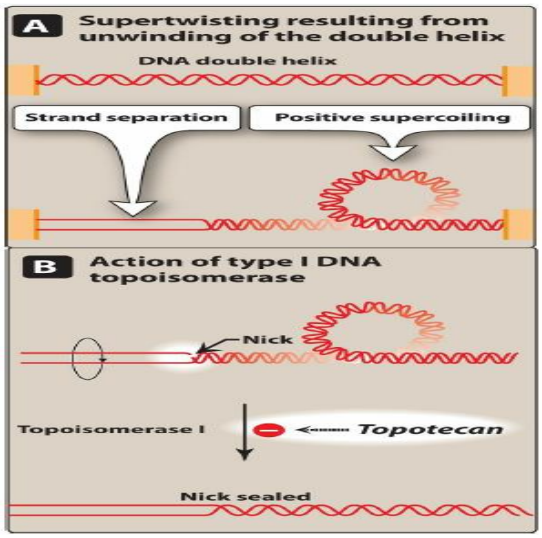
A. Camptothecins

Camptothecins are **plant** alkaloids originally isolated from the Chinese tree Camptotheca. **Irinotecan and topotecan** are **semisynthetic** derivatives of camptothecin.

Topotecan is used in metastatic ovarian cancer when primary therapy has failed and also in the treatment of small cell lung cancer. Irinotecan is used with 5-FU and leucovorin for the treatment of colorectal carcinoma.

Mechanism of action

These drugs are S-phase specific and inhibit topoisomerase I, which is essential for the replication of DNA in human cells. SN-38 (the active metabolite of irinotecan) is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I. The topoisomerases relieve torsional strain in DNA by causing reversible, singlestrand breaks.



Adverse effects: Bone marrow suppression, particularly neutropenia, is the dose-limiting toxicity for topotecan. Frequent blood counts should be performed in patients receiving this drug. Myelosuppression is also seen with irinotecan. Acute and delayed diarrhea with irinotecan may be severe and require treatment with atropine during the infusion or high doses of loperamide in the days following the infusion.

B. Etoposide

Etoposide is a semisynthetic derivative of the plant alkaloid, podophyllotoxin.

This agent blocks cells in the late S to G2 phase of the cell cycle, and the major target is topoisomerase II. Binding of the drug to the enzyme–DNA complex results in persistence of the transient, cleavable form of the complex and, thus, renders it susceptible to irreversible double-strand breaks.

Etoposide finds its major clinical use in the treatment of lung cancer and in combination with bleomycin and cisplatin for testicular carcinoma. Etoposide may

be administered either IV or orally. Dose-limiting myelosuppression (primarily leukopenia) is the major toxicity.

Monoclonal antibodies

Monoclonal antibodies are an active area of drug development for anticancer therapy and other nonneoplastic diseases, because they are directed at specific targets and often have different adverse effect profiles as compared to traditional chemotherapy agents. **All** of these agents are administered intravenously, and infusion-related reactions are common.

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS	MONITORING PARAMETERS	NOTES
Bevacizumab	Binds VEGF and prevents binding of VEGF to its receptors on endothelial cells Inhibits vascularization of the tumor	Hypertension, GI perforation, proteinuria, wound healing problems, bleeding	BP, urine protein, signs and symptoms of bleeding	Hold for recent or upcoming surgical procedures
Cetuximab	Binds to EGFR and competitively inhibits the binding of epidermal growth factor and other ligands Inhibits tumor cell growth and increases apoptosis	Skin rash, electrolyte wasting, infusion reaction, diarrhea	Electrolytes, vital signs during infusion	Premedication with antihistamine required before infusion; rash equated with increased response
Daratumumab	Binds to the transmembrane protein CD38 on multiple myeloma cells and causes cell lysis	Infusion reactions, diarrhea, fatigue, pyrexia	CBC with differential, vital signs during infusion	Can bind CD38 on red blood cells Type and screen patients before starting therapy Premedication with antihistamines, antipyretics, and corticosteroids required
Ramucirumab	Binds VEGF receptor 2 and blocks binding of VEGF receptor ligands	Proteinuria, hypertension, wound healing problems, bleeding	BP, urine protein, signs and symptoms of bleeding	Hold for recent or upcoming surgical procedures
Rituximab	Targets the CD20 antigen expressed on the surface of pre-B lymphocytes and mature B lymphocytes	Fatal infusion reaction, TLS, mucocutaneous reactions, PML	Vital signs during infusion, TLS labs	Fatal reactivation of hepatitis B Premedication with antihistamine and acetaminophen required Increased risk of nephrotoxicity when given with *cisplatin*
Trastuzumab	Inhibits the proliferation of human tumor cells that overexpress HER2	Cardiomyopathy, infusion-related fever and chills, pulmonary toxicity, headache, nausea/vomiting	LVEF, CBC, pulmonary toxicity due to infusion reaction	Embryo-fetal toxicity Neutropenia in combination with chemotherapy Premedication with antihistamine and *acetaminophen* required

Tyrosine Kinase Inhibitors

The tyrosine kinases are a family of enzymes that are involved in several important processes within a cell, including signal transduction and cell division. The

tyrosine kinase inhibitors are administered orally, and these agents have a wide variety of applications in the treatment of cancer.

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS	NOTABLE DRUG INTERACTIONS	MONITORING PARAMETERS	NOTES
Afatinib	Inhibits EGFR tyrosine kinase	Diarrhea, rash, stomatitis, paronychia, nausea, vomiting, pruritus	P-gp inhibitors and inducers	CBC, CMP	Administer on an empty stomach Reduce dose for significant diarrhea Use effective contraception for female patients
Dabrafenib	Inhibits mutated BRAF kinases	Pyrexia, rash, arthralgia, cough, embryo-fetal toxicity	CYP3A4 inhibitors and substrates; CYP2C8 inhibitors and substrates; substrates of CYP2C9, CYP2C19, or CYP2B6	Glucose, symptoms of heart failure or bleeding, CBC, BMP, INR (if *warfarin*)	Use effective contraception for female patients Administer on empty stomach May cause new primary malignancies
Dasatinib	Inhibits BCR-ABL tyrosine kinase	Myelosuppression, fluid retention, diarrhea	CYP3A4 substrates, acid-reducing agents	CBC, BCR-ABL, electrolytes	QT prolongation
Erlotinib	Inhibits EGFR tyrosine kinase	Rash, ILD, hepatoxicity	CYP3A4 substrates, acid-reducing agents, *warfarin*	CMP	Rash equated with increased response
Ibrutinib	Inhibits Bruton tyrosine kinase	Neutropenia, thombocytopenia, diarrhea, anemia, pain, rash, nausea, bruising, fatigue, hemorrhage, pyrexia	CYP3A inhibitors and inducers	CBC, CMP, atrial fibrillation, BP, tumor lysis syndrome	Avoid grapefruit juice and Seville oranges Can cause hepatitis B reactivation Use effective contraceptive
Idelalisib	Inhibits phosphatidylinositol 3-kinase	Diarrhea, fatigue, nausea, cough, pyrexia, abdominal pain, pneumonia, rash, neutropenia, infection	CYP3A inducers and substrates	CBC, LFTs, pulmonary symptoms, infection	Use effective contraception for female patients
Imatinib	Inhibits BCR-ABL tyrosine kinase	Myelosuppression, fluid retention, CHF	CYP3A4 substrates, *warfarin*	CBC, BCR-ABL	Monitor for development of heart failure
Nilotinib	Inhibits BCR-ABL tyrosine kinase	Myelosuppression, QT prolongation, hepatotoxicity	CYP3A4 substrates, acid-reducing agents	CBC, BCR-ABL, electrolytes	QT prolongation Administer on empty stomach
Osimertinib	Inhibits EGFR tyrosine kinase	Diarrhea, rash, dry skin, nail toxicity, fatigue	Strong CYP3A inducers	CBC, ECG, electrolytes	Use effective contraceptive for female patients
Pazopanib	Multi–tyrosine kinase inhibitor	Diarrhea, hypertension, hair color changes, nausea, anorexia, vomiting	CYP3A4 inhibitors, inducers, and substrates; CYP2D6 or CYP2C8 substrates; *simvastatin*; drugs that reduce gastric pH	ECG, electrolytes, thyroid function tests, LFTs, UA, CBC, BP	Use effective contraceptive for female patients
Sorafenib	Inhibits multiple intracellular and cell surface kinases	Hypertension, hand-foot syndrome, rash, diarrhea, fatigue	CYP3A4 inducers, *warfarin*	BP, CMP	Wound healing complications, cardiac events
Sunitinib	Multi–tyrosine kinase inhibitor	Hypertension, hand-foot syndrome, rash, diarrhea, fatigue, hepatotoxicity, hypothyroidism	CYP3A4 substrates	BP, CMP, TSH	Monitor for development of heart failure
Trametinib	Reversible inhibitor of mitogen-activated extracellular kinases	Pyrexia, rash, diarrhea, vomiting, lymphedema	CYP2C8 substrates, P-gp	Fever, new cutaneous malignancies, serum glucose, LVEF, CBC, CMP	Used in combination with *dabrafenib* Administer on empty stomach
Vemurafenib	Inhibits mutated BRAF serine-threonine kinase	Arthralgia, rash, alopecia, fatigue, photosensitivity, pruritus, skin papilloma	CYP3A4 inhibitors and inducers, CYP1A2 substrates	ECG, electrolytes, CMP, uveitis	May cause new primary cutaneous malignancies Use effective contraception in female patients

Immunotherapy

Immunotherapy with intravenous immune checkpoint inhibitors is a rapidly evolving option for cancer treatment. The goal of immune checkpoint inhibitors is

to block the checkpoint molecules, such as the programmed death (PD-1) receptor, that normally help to keep the immune system in check. By blocking these molecules, the immune system is better able to attack the tumor and cause destruction. The two most commonly used checkpoint inhibitors are **pembrolizumab and nivolumab.** The adverse reaction profiles of these agents consist of potentially severe and even fatal immune-mediated adverse events. This is because turning off the immune checkpoints allows attack of the tumor, but can also lead to unchecked autoimmune response to normal tissues.

Adverse events include diarrhea, colitis, pneumonitis, hepatitis, nephritis, neurotoxicity, dermatologic toxicity in the form of severe skin rashes, and endocrinopathies such as hypo- or hyperthyroidism. Patients should be closely monitored for the potential development of signs and symptoms of toxicity and promptly treated with corticosteroids if necessary.

Miscellaneous Agents

Abiraterone acetate

Abiraterone acetate is an oral agent used in the treatment of metastatic castration–resistant prostate cancer. Abiraterone acetate is used in conjunction with prednisone to inhibit the CYP17 enzyme (an enzyme required for androgen synthesis), resulting in reduced testosterone production. Coadministration with prednisone is required to help lessen the effects of mineralocorticoid excess resulting from CYP17 inhibition.

Hepatotoxicity may occur, and patients should be closely monitored for hypertension, hypokalemia, and fluid retention. Joint and muscle discomfort, hot flushes, and diarrhea are common adverse effects with this agent.

Immuno-modulating agents

Thalidomide, lenalidomide, and pomalidomide are oral agents used in the treatment of multiple myeloma. Their exact mechanism of action is not clear, but they possess antimyeloma properties including antiangiogenic, immune-modulation, anti-inflammatory and antiproliferative effects. These agents are often combined with dexamethasone or other chemotherapeutic agents.

Adverse effects include thromboembolism, myelosuppression fatigue, rash, and constipation. Thalidomide was previously given to pregnant women to prevent morning sickness. However, severe birth defects were prevalent in children born to mothers who used thalidomide. Because of their structurally similarities to thalidomide, lenalidomide and pomalidomide are contraindicated in pregnancy.

Proteasome inhibitors

Bortezomib, Ixazomib, and Carfilzomib are proteasome inhibitors commonly used as the backbone therapy in the treatment of multiple myeloma. These agents work by inhibiting proteasomes, which in turn prevents the degradation of proapoptotic factors, thus leading to a promotion in programmed cell death (apoptosis).

Malignant cells readily depend on suppression of the apoptotic pathway; therefore, proteasome inhibition works well in multiple myeloma.

Bortezomib can be administered IV, but the subcutaneous route is preferred because it is associated with less neuropathy. Other adverse effects include myelosuppression, diarrhea, nausea, fatigue, and herpes zoster reactivation. Patients should receive antiviral prophylaxis if they are receiving therapy with bortezomib.

Ixazomib is an oral agent with an adverse effect profile similar to bortezomib. **Carfilzomib** is administered intravenously, and common adverse effects include myelosuppression, fatigue, nausea, diarrhea, and fever.