STEROIDS

**systemic glucocorticoids**
- ΔΔ beclomethasone (Beconase AQ #95)
- Δ cortisone (Celestone)
- Δ dexamethasone (Decadron)
- Δ dexamethasone acetate (Decadron-LA)
- ΔΔ hydrocortisone acetate (Anusol-HC #195)
- ΔΔ methylprednisolone (Medrol #192)
- ΔΔ prednisolone (Cortalone)
- ΔΔ prednisone (Deltasone #138)
- Δ triamcinolone (Azmacort #151)

**topical glucocorticoids**
- Δ fluocinolone (Fluonid)
- Δ flurandrenolide (Cordran)
- Δ triamcinolone (Aristocort)

**mineralocorticoids**
- Δ desoxycorticosterone (Doca Acetate)
- Δ fludrocortisone (Flurinef)

"Δ" indicates major drugs -- see table
"ΔΔ" indicates a Top 200 Drug in 1991 -- note ranking after trade name

**Background Information:**
Natural corticosteroids are hormones produced in the adrenal cortex and are classified by their biological activities:
- glucocorticoids affect carbohydrate and protein synthesis
- mineralocorticoids regulate electrolyte and water balance
Production of the natural corticosteroids is stimulated by trauma, infection, heat, cold, and mental stress. Corticotropic releasing hormone (CRH) is released from the hypothalamus which stimulates the secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland which in turn triggers the release of the corticosteroids from the adrenal cortex.
Indications for Use:

GLUCOCORTICOIDS:
- primarily used for inflammation, immunosuppression, replacement therapy in patients with adrenocortical insufficiency and suppression of adrenocortical hyperfunction in patients with adrenogenital syndrome
- their primary immunosuppressant application is treatment of hypersensitivity reactions by reducing inflammation. Specific indications are: rheumatoid arthritis, osteoarthritis, rheumatic fever, nephrotic syndrome, collagen diseases, asthma, chronic obstructive pulmonary disease, hay fever, bee stings, systemic and topical hypersensitivity reactions, prevention and treatment of transplant rejection, leukemias, lymphomas and myelomas

MINERALOCORTICOIDs:
- used in replacement therapy for patients with adrenocortical insufficiency and in the treatment of salt-losing congenital adrenogenital syndrome after the patient's electrolyte balance has been restored

Mechanism of Action:

GLUCOCORTICOIDs:
- controlling inflammation primarily by inhibiting the release of the arachadonic acid metabolites (the prostoglands and platelet activating factor); thereby decreasing platelet aggregation, chemotaxis, macrophage accumulation and histamine activity.

MINERALOCORTICOIDs:
- act on the distal renal tubule to enhance the reabsorption of sodium and secretion of potassium and hydrogen -- resulting in sodium retention

<table>
<thead>
<tr>
<th>major drugs</th>
<th>things to remember</th>
</tr>
</thead>
</table>
| beclomethasone | - used in inhalents for asthma sufferers  
- low dosage decreases risk of side effects |
| cortisone | - drug of choice for replacement therapy in adrenocortical insufficiency |
| dexamethasone | - for self-limiting allergic disorders and exacerbation of chronic allergies |
| dexamethasone acetate | - for chronic inflammations and cancer |
| hydrocortisone | - the prototype systemic glucocorticoid  
- for adrenocortical insufficiency and severe inflammation |
| methylprednisolone | - used for anti-inflammatory and immunosuppressive effects |
| prednisolone | - used for anti-inflammatory and immunosuppressive effects |
| prednisone | - oral glucocorticoid of choice for anti-inflammatory and immunosuppressive effects |
| triamcinolone | - used for anti-inflammatory and immunosuppressive effects |
TOPICAL GLUCOCORTICOSTEROIDS

- for acute and chronic inflammatory dermatoses, psoriasis, atopic eczema, pruritis ani, neurodermatitis, exfoliative dermatitis, seborrheic dermatitis, contact dermatitis

MINERALOCORTICOSTEROIDS

- the most potent mineralocorticoid to treat salt-losing adrenogenital syndrome
- given with cortisone to treat salt losing adrenogenital syndrome

Relative Potencies of Glucocorticoids:

The table below groups the glucocorticoids by their length of action and compares their anti-inflammatory potencies relative to hydrocortisone.

<table>
<thead>
<tr>
<th>Half-life</th>
<th>Generic Name</th>
<th>Oral Dose Equivalent</th>
<th>Rel. Anti-Inflamm. Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
<td>Cortisone</td>
<td>25 mg</td>
<td>0.8</td>
</tr>
<tr>
<td></td>
<td>Hydrocortisone</td>
<td>20 mg</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Prednisolone</td>
<td>5 mg</td>
<td>4</td>
</tr>
<tr>
<td>Acting</td>
<td>Prednisone</td>
<td>5 mg</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
<td>4 mg</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone</td>
<td>4 mg</td>
<td>5</td>
</tr>
<tr>
<td>Long-acting</td>
<td>Dexamethasone</td>
<td>0.75 mg</td>
<td>25-30</td>
</tr>
<tr>
<td></td>
<td>Betamethasone</td>
<td>0.60 mg</td>
<td>25</td>
</tr>
</tbody>
</table>

Adverse Reactions:

SYSTEMIC GLUCOCORTICOSTEROIDS:
- Adrenocortical insufficiency (decreased production of corticosteroids in the adrenal cortex, temporary or permanent) may occur in response to the introduction of exogenous steroids -- this affect is minimized by tapering dosages when ending therapy
- Severe muscle weakness
- Immunosuppression predisposes patients to infection
- Cushing's syndrome (abnormal fat distribution -- depleting fat from extremities and depositing it in face, abdomen and between shoulder blades)
- GI reactions: abdominal distension, pancreatitis, ulcerative esophagitis, gastric irritation, increased appetite, peptic ulcers
- Skin atrophy and thinning, acne, excessive diaphoresis, facial erythema, ecchymosis (easy bruising)
- CNS reactions: insomnia, headache, restlessness, seizures, severe mood swings
- May slow the growth of young children by interfering with DNA synthesis and cell division
- Others: electrolyte imbalances, increased red blood cell and hemoglobin levels, increased risk of emboli formation
TOPICAL GLUCOCORTICOIDS:
- local effects include: skin atrophy, muscle and fat wasting, rosacea eruptions
- absorption of topical glucocorticoids through the skin can cause the same adverse reactions as systemic glucocorticoids

MINERALOCORTICOIDS:
- fluid and electrolyte imbalances and these associated symptoms: edema, hypertension, congestive heart failure (CHF), hypernatremia, hypokalemia, hypocalcemia.

Ocular Adverse Reactions:
SYSTEMIC AND TOPICAL GLUCOCORTICOIDS:
- posterior subcapsular cataracts
- increased intraocular pressure
- exophthalmos
- secondary ocular infections due to immunosuppression

Contraindications and Precautions:
SYSTEMIC GLUCOCORTICOIDS:
- contraindicated in pregnant or breast feeding women
- cases of Cushing's syndrome, tuberculosis, severe infections, psychosis
- use caution in patients with diabetes mellitus, hypothyroidism, congestive heart failure, cardiac disease, hypertension, hepatic dysfunction, renal dysfunction, glaucoma, thromboembolic disorders, seizures

TOPICAL GLUCOCORTICOIDS:
- contraindicated in cases of skin infections
- use cautiously in ophthalmic applications in cases of glaucoma

MINERALOCORTICOIDS:
- contraindicated in cases of hypertension, congestive heart failure (CHF), or cardiac disease
- use cautiously in pregnant women, diabetics, and cases of Addison's disease
- use fludrocortisone cautiously in patients with GI ulceration, renal disease, hypertension, osteoporosis, varicella, vaccinia, exanthema, cushingoid symptoms, thromboembolic disorders
Drug Interactions:

SYSTEMIC GLUCOCORTICOIDS AND MINERALOCORTICOIDS:
- steroid action increased by: erythromycin, troleandomycin, estrogen
- steroid action decreased by: barbiturates, phenytoin, rifampin
- complications with: furosemide (hypokalemia), salicylates & NSAIDs (peptic ulcers), vaccines (decrease immune response), warfarin (steroids decrease its anticoagulant effect)

TOPICAL GLUCOCORTICOIDS:
- ethylenediamine, a stabilizing agent in some topical glucocorticoid agents interacts with systemic aminophylline, antazoline, antazoline hydrochloride ophthalmic solution, and edetate disodium, a preservative common in ophthalmic solutions -- these interactions can cause allergic contact dermatitis, urticaria, and systemic eczematous contact-type dermatitis
- parabens, another additive in glucocorticoid preparations can interact with other paraben-containing formulations such as toothpaste, cosmetics, and soaps, resulting in allergic contact dermatitis and urticaria
NONSTERoidal ANti-INFLAMMATORY AGENTS

carprofen (Rimadyl)
fenoprofen calcium (Nalfon)
\[Δ\] flurbiprofen (Ansaid #84)
\[ΔΔ\] ibuprofen (IBU #44, Motrin #69, Advil, Nuprin)
\[Δ\] indomethacin (Indocin)
\[ΔΔ\] ketoprofen (Orudis #107)
me clofenamate (Meclomen)
mefenamic acid (Ponstel)
mesalamine (Rowasa)
\[ΔΔ\] naproxen (Naprosyn #13)
\[ΔΔ\] naproxen sodium (Anaprox DS #65)
\[Δ\] phenylbutazone (Butazolidin)
\[ΔΔ\] piroxicam (Feldene #45)
\[ΔΔ\] sulindac (Clinoril #185)
\[Δ\] tolmetin sodium (Telectin)

"Δ" indicates major drugs -- see table
"ΔΔ" indicates a Top 200 Drug in 1991 -- note ranking after trade name

Indications for Use:
NSAIAs have a primary action of reducing inflammation, but also have analgesic (pain relieving) and antipyretic (fever reducing) properties. They are commonly used for such things as soft tissue athletic injuries, dental pain and dysmenorrhea (pain associated with menstruation), ankylosing spondylitis and arthritic disorders.

Individual responses to these drugs vary greatly. Therefore, it is often necessary to experiment with several drugs to find an effective therapy for each patient.

Mechanism of Action:
- reduces inflammation and pain by inhibiting prostaglandin activity
**Major Drugs** | **Things to Remember**
---|---
Flurbiprofen | for short or long term relief of rheumatoid arthritis and osteoarthritis
Ibuprofen | the only OTC NSAIA to relieve symptoms of osteoarthritis and rheumatoid arthritis, mild to moderate pain relief, dysmenorrhea
Indomethacin | for the pain and inflammation of rheumatoid arthritis and osteoarthritis in adults who do not respond to other treatments for acute gouty arthritis, bursitis, tendinitis, and ankylosing spondylitis
Ketoprofen | to relieve signs and symptoms of osteoarthritis and rheumatoid arthritis
Naproxen | for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, bursitis, tendinitis, acute gout, dysmenorrhea
Naproxen Sodium | same uses as naproxen but is absorbed more rapidly
Phenylbutazone | reserved for severe cases of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis that do not respond to other NSAIDAs
Piroxicam | for relief of osteoarthritis and rheumatoid arthritis reaches maximum effectiveness after 2 weeks of therapy
Sulindac | for acute or long term relief of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, bursitis, and acute gouty arthritis
Tolmetin | for relief of osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis

**Possible Adverse Reactions:**
- generally better tolerated than steroids and salicylates, all NSAIA produce similar, mild reactions
- GI: pain, bleeding, anemia, diarrhea, nausea, ulceration, hepatotoxicity
- CNS: depression, dizziness, drowsiness, headache, confusion, tinnitus
- renal: cystitis, hematuria, kidney necrosis
- hypersensitivity reactions: rash, urticaria, angioedema, hypotension and an asthma-like syndrome occur rarely

**Ocular Adverse Reactions:**
- blurred vision, diplopia, red-green color defects and faded colors, lid edema erythema and edema, optic neuritis, myopia, hallucinations, photophobia, central scotomas, toxic amblyopia, visual disturbances such as moving mosaic of colored lights and shooting streaks have been reported.
Contraindications and Precautions:
- contraindicated in patients with asthma
- contraindicated in cases of hypersensitivity
- use caution in cases of renal dysfunction and pregnancy

Drug Interactions:
- indomethacin:
  - corticosteroids increase risk of ulcers with indomethacin
  - captopril's antihypertensive effect is decreased by indomethacin
  - furosemide's antihypertensive and diuretic effects are decreased
  - oral anticoagulant's effects are increased
- sulindac:
  - oral anticoagulant's hypoprothrombinemic activity increases, causing bleeding
- piroxicam:
  - lithium carbonate's renal excretion is inhibited by piroxicam
- phenylbutazone:
  - anabolic steroids increase phenylbutazone levels and effects
  - oral anticoagulant's metabolism inhibited by phenylbutazone
  - oral hypoglycemic's effects increased
  - digitalis metabolism is increased, decreasing its effect
  - methotrexate's toxicity is increased
  - phenytoin's toxicity is increased
**NEUROTRANSMITTERS OF THE CNS**

Important Neurotransmitters of the CNS:
- acetylcholine (cholinergic)
- norepinephrine (adrenergic)
- dopamine
- serotonin
- enkephalins
- substance P
- GABA (gamma-aminobutyric acid)
- glycine
- glutamic acid
- histamine

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Things to Know for Boards</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetylcholine (Ach)</td>
<td>- major neurotransmitter (NT) of the motoneurons, autonomic preganglionic fibers, postganglionic cholinergic (parasympathetic) fibers*</td>
</tr>
<tr>
<td>(cholinergic)</td>
<td>- major NT of many neurons in the CNS (basal ganglia, motor cortex)</td>
</tr>
<tr>
<td></td>
<td>- synthesized from choline and acetyl-coenzyme A by the enzyme choline acetyltransferase (CAT)</td>
</tr>
<tr>
<td></td>
<td>- upon release, Ach stimulates cholinergic receptors of adjacent structures</td>
</tr>
<tr>
<td></td>
<td>- interaction terminated by hydrolysis of Ach to choline and acetate by acetylcholinesterase (ACE)</td>
</tr>
<tr>
<td></td>
<td>- levels of acetylcholine regulated by the activity of choline acetyltransferase and by choline re-uptake</td>
</tr>
<tr>
<td>norepinephrine (NE)</td>
<td>- one of the two major catecholamine NTs of many central neurons (locus ceruleus, hypothalamus)</td>
</tr>
<tr>
<td>(adrenergic)</td>
<td>- NT of most postganglionic sympathetic fibers and mediates emergency responses; acceleration of the heart, bronchi dilatation, blood pressure elevation</td>
</tr>
<tr>
<td></td>
<td>- NE synthesis starts with tyrosine &amp; is hydroxylated by dopamine-B - hydroxylase to form NE</td>
</tr>
<tr>
<td></td>
<td>- upon release, NE interacts with adrenergic receptors</td>
</tr>
<tr>
<td></td>
<td>- action terminated by the re-uptake of NE back into the prejunctional neurons</td>
</tr>
<tr>
<td></td>
<td>- intraneuronal NE levels regulated by MAO and tyrosine hydroxylase</td>
</tr>
<tr>
<td></td>
<td>- metabolism of NE occurs via MAO and catechol-0-methyltransferase</td>
</tr>
<tr>
<td>Neurotransmitter</td>
<td>Description</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------</td>
</tr>
</tbody>
</table>
| **dopamine (DA)** | - another catecholamine NT of many central neurons (substantia nigra, midbrain, hypothalamus)  
- tyrosine is converted by tyrosine hydroxylase to DOPA, decarboxylated by L-amino acid decarboxylase to dopamine and stored in vesicles  
- after release, DA interacts with dopaminergic receptors  
- pumped back by active processes (reuptake) into the prejunctional neurons  
- DA levels held constant by changes in tyrosine hydroxylase activity and the enzyme MAO  
- destruction of DA neurons in corpus striatum responsible for symptoms of Parkinson's disease  
- blockade of actions of dopamine in other brain regions accounts for therapeutic activities of antischizophrenic drugs |
| **serotonin (5-HT)** | - NT of many central neurons (raphe nucleus)  
- synthesized from tryptophan by tryptophan hydroxylase and decarboxylated by L-amino acid decarboxylase to serotonin  
- levels of serotonin are controlled by the uptake of tryptophan and intraneuronal MAO  
- changes in the activity of serotonin neurons are related to the actions of psychedelic drugs |
| **enkephalins** | - neurotransmitters discovered as normally occurring substances which act upon opiate receptors  
- can mimic the effects of opiates |
| **substance P** | - major transmitter of sensory neurons which convey pain sensation from the periphery into the spinal cord  
- opiates relieve pain in part by blocking the release of substance P |
| **GABA (gamma-aminobutyric acid)** | - major inhibitory NT in the CNS and found in many central neurons (basal ganglia, cerebellum)  
- NT at 25 to 40 percent of all synapses in the brain and, quantitatively, may be the predominant NT in the brain |
| **glycine** | - inhibitory NT in small neurons in the spinal cord and brain stem  
- NT at 30 to 40 percent of synapses in the spinal cord and brain stem |
| **glutamic acid** | - probably the principal excitatory NT in the brain  
- NT of major neuronal pathway connecting the cerebral cortex and the corpus striatum  
- NT of the granule cells, which are the most numerous neurons in the cerebellum |
| **histamine** | - acts as a NT in the brain; most highly concentrated in areas that regulate emotional behavior |
Non-Opioid Analgesic Agents

**Salicylates**
- aspirin (Bayer)
- choline magnesium trisalicylate
- choline salicylate
- diflunisal (Dolobid) \#135 drug in 1991
- salsalate
- sodium salicylate

**Acetaminophen**
- acetaminophen (Tylenol)

**Nonsteroidal anti-Inflammatory Drugs**
- carprofen
- fenoprofen calcium
- ibuprofen (IBU, Motrin) \#44 & \#69 drugs in 1991
- indomethacin (Indocin)
  - mefenamic acid
  - mesalamine
- naproxen (Naprosyn, Anaprox DS) \#13 & \#65 drugs in 1991
  - naproxsodium
  - phenylbutazone
  - piroxicam
- sulindac (Clinoril) \#185 drug in 1991
- tolmetin sodium (Tolectin)

**Phenazopyridine**
- phenazopyridine hydrochloride

"\*\*\*\** indicates a top 200 drug in 1991 -- note ranking after trade name
"\*\* indicates major drugs -- see table

**Indications for Use:**
- salicylates -- primarily used to relieve pain (analgesic property) and reduce fever (antipyretic property)
- acetaminophen -- used to relieve pain, colds, and influenza; has no anti-inflammatory properties
- NSAIDs -- used to decrease inflammation and secondarily to relieve pain
- phenazopyridine -- produces a local analgesic effect on the urinary tract
acetaminophen - an alternative for patients who can’t tolerate aspirin and don’t need an analgesic with anti-inflammatory properties

ibuprofen (Advil, Nuprin) - only OTC NSAID, used to relieve mild to moderate pain, treat osteoarthritis and rheumatoid arthritis

indomethacin (Indocin) - used to control pain and inflammation of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute gouty arthritis, bursitis and tendinitis

naproxen (Anaprox) - used to relieve mild to moderate pain and treat osteoarthritis, rheumatoid arthritis, ankylosing spondylitis

tolmetin - used to relieve osteoarthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis

**SALICYLATES**

**Mechanism of Action:**
- produce analgesia primarily by inhibiting prostaglandin synthesis
- reduce fever through hypothalamic stimulation leading to vasodilation and increased diaphoresis (increased sweating)
- reduce inflammation by inhibition of prostaglandin synthesis and release during inflammation

**Adverse Reactions:**
- GI reactions -- gastric distress, nausea, vomiting
- respiratory alkalosis, metabolic acidosis, hearing problems

**Ocular Adverse Reactions:**
- conjunctivitis (nonspecific)
- allergic reactions or edema of eyelids or conjunctiva
- decreased vision
- color vision problems
  - red-green color vision defect
  - objects have a yellow tinge
- paralysis of extraocular muscle
- diplopia

**Contraindications:**
- in patients with hypertension or in patients on sodium restricted diets

**Drug Interactions:**
- salicylates may displace a large number of other protein-bound drugs from their binding sites to increase the the serum concentration level of the unbound active drug and increase its effect
- salicylates may also potentiate the effects of other drugs
ACETAMINOPHEN
Mechanism of Action:
- may act centrally by inhibiting prostaglandin synthesis
- antipyretic effect results from direct action on the heat-regulating center in the hypothalamus
Adverse Reactions:
- well tolerated; rarely causes gastric irritation
- chronic use of high doses can cause hypoglycemia, kidney damage, renal failure and other systemic complications
Ocular Adverse Reactions:
- decreased vision, allergic reactions and erythema of eyelids or conjunctiva, conjunctivitis (nonspecific), objects have yellow tinge
Contraindications:
- contraindicated in patients with anemia or hepatic disease
Drug Interactions:
- few significant interactions occur between acetaminophen and other drugs

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS
Mechanism of Action:
- decrease inflammation and pain by inhibiting prostaglandin activity
Adverse Reactions:
- can produce numerous adverse reactions
- GI tract (most common site) -- nausea, pain, bleeding, ulceration
- CNS effects -- dizziness, drowsiness, depression, headache, mental confusion
- renal system -- hematuria, kidney necrosis, cystitis
- ocular side effects -- blurred vision, corneal deposits, decreased acuity
Ocular Adverse Reactions:
- decreased vision, diplopia, red-green color vision defect, colors appear faded, erythema or edema to eyelids or conjunctiva, conjunctivitis (nonspecific), optic neuritis, myopia
Contraindications:
- contraindicated in patients with asthma
- contraindicated in patients hypersensitive to mesalamine (NSAID)
Drug Interactions:
- wide variety of drugs can interact with NSAIDs
- likely to interact with other protein-bound drugs, such as oral anticoagulants
- may interfere with antihypertensive drugs and decrease their antihypertensive effects

PHENAZOPYRIDINE
Mechanism of Action:
- produces a local analgesic effect on the urinary tract
- 35% metabolized in the liver with the remainder excreted unchanged in the urine
**Opioid Analgesic Agents**

**Narcotic Agonists**

- codeine
- fentanyl citrate
- hydrocodone bitartrate and acetaminophen
- hydromorphone hydrochloride (Dilaudid)
- levorphanol tartrate
- meperidine hydrochloride (Demerol)
- methadone hydrochloride
- morphine sulfate (Duramorph)
- oxycodone hydrochloride
- oxycodone hydrochloride and acetaminophen (Percocet-5)
  - #117 drug in 1991
- oxycodone hydrochloride and aspirin (Percodan)
- oxymorphone hydrochloride (Numorphan)
- propoxyphene hydrochloride (Darvon)
- propoxyphene and acetaminophen
  - (Darvocet-N, Propoxyphene w/apap, Propacet)
  - #35, #55, & #105 drugs in 1991

**Mixed Narcotic Agonist-Antagonists**

- butorphanol tartar (Stadol)
- buprenorphine hydrochloride
- nalbuphine hydrochloride (Nubain)
  - pentazocine hydrochloride and pentazocine lactate
  - pentazocine hydrochloride and aspirin

**Narcotic Antagonists**

- naloxone hydrochloride (Narcan)
- naltrexone hydrochloride (Trexan)

“ΔΔ” indicates a top 200 drug in 1991 -- note ranking after trade name
“Δ” indicates major drugs -- see table

**Indications for Use:**

- narcotic agonists (analgesics) -- can relieve or decrease pain without causing loss of consciousness
- mixed narcotic agonist-antagonists -- closely resemble those of morphine with some differences in onset of action and duration of action
  - used for relief of moderate to severe pain
- narcotic antagonists --
  - naloxone is drug of choice for managing a narcotic overdose
  - naltrexone used only as adjunct to counseling for patients who have been detoxified from narcotic drugs
nonnarcotic analgesics are measured best narcotic agonist for relief of severe pain

codeine - used for relief of mild to moderate pain and as an antitussive
- exhibits an analgesic ceiling effect

meperidine (Demerol) - synthetic narcotic agonist most commonly prescribed for postoperative pain
- for relief of visceral pain, for obstetric analgesia, and as a preoperative medication

propoxyphene (Darvon) weak synthetic narcotic agonist used for relief of mild pain

hydromorphone (Dilaudid) potent synthetic narcotic agonist used to relieve moderate to severe pain
- doesn't exhibit an analgesic ceiling effect

butophanol - for moderate to severe pain, for obstetric analgesia during labor, and for preoperative medication

nalbuphine - equianalgesic to morphine sulfate on a milligram-to-milligram basis
- relief of moderate to severe pain and preoperative and obstetric analgesia

naloxone (Narcan) - drug of choice for complete or partial reversal of respiratory depression caused by narcotic overdose

**NARCOTIC AGONISTS**

**Mechanism of Action:**
- act primarily at opiate receptor sites, bind to the receptors centrally and peripherally and activate the endogenous pain relief system
- the receptor-site binding produces the therapeutic effects of analgesia along with narcotic adverse reactions

**Adverse Reactions:**
- produce numerous adverse reactions that affect most body systems
- CNS reactions are most common and usually affect the respiratory and GI tracts
- decreased rate and depth of respiration
- dilation of peripheral arteries and veins leads to flushing and orthostatic hypotension
- GI adverse reactions -- nausea, vomiting, biliary colic, constipation
- ocular -- pupil (miosis), optic neuritis
NARCOTIC AGONISTS (cont)

Ocular Adverse Reactions:
- pupil miosis in acute and toxic states, pinpoint pupils in initial state and coma, decreased vision, myopia with codeine, edema and urticaria of eyelids or conjunctiva

Contraindications:
- use with extreme caution in patients with head injuries, brain tumors, increased intracranial pressure, or intracranial lesions
- these drugs can cause respiratory depression and may increase cerebrospinal fluid pressure

Drug Interactions:
- use of narcotic agonists with alcohol, sedatives, hypnotics, and anesthetics increases risk of severe respiratory depression
- concomitant therapy with tricyclic antidepressants, phenothiazines, or anticholinergics may cause severe constipation and urinary retention

MIXED NARCOTIC AGONIST-ANTAGONISTS

Mechanism of Action:
- occupy the same opiate receptor sites as the narcotic agonists but have few or no antitussive or GI effects
- exact mechanism of action has not been established

Adverse Reactions:
- adverse reactions occur less frequently than reactions to narcotic agonists and usually affect both the CNS and the GI tract
- nausea, vomiting, light-headedness, sedation, euphoria

Ocular Adverse Reactions:
- miosis, decreased vision, visual hallucinations, nystagmus, diplopia

Contraindications:
- use cautiously in patients with head injuries or intracranial lesions since these drugs may increase intracranial pressure
- contraindicated in patients with asthma, obstructive pulmonary disease
- butorphanol and pentazolone contraindicated in patients with angina since these drugs amy increase cardiac work load

Drug Interactions:
- patients dependent on narcotic agonist will often experience withdrawal symptoms if given mixed narcotic agonist-antagonists
- interact with other CNS depressants to increase CNS depression and cause an additive decrease in respiratory rate and depth
NARCOTIC ANTAGONISTS

Mechanism of Action:
- block the effects of narcotics by occupying the opiate receptor sites, displacing any narcotic molecules already present and blocking further narcotic binding at these sites

Adverse Reactions:
- naloxone may cause nausea, vomiting, and occasional hypertension and tachycardia
- naltrexone produces many adverse side effects affecting a number of body systems

Ocular Adverse Reactions:
- pupil mydriasis (may precipitate narrow-angle glaucoma if a prior narcotic has been given), decreased visual hallucinations, pseudoptosis

Contraindications:
- naltrexone is contraindicated in patients receiving narcotic drugs
- naloxone should be used cautiously in patients with cardiac irritability or narcotic addiction

Drug Interactions:
- no significant drug interactions except that withdrawal symptoms will be caused if naloxone or naltrexone are given to a narcotic addict or a patient receiving a narcotic agonist

narcotic. -- refers to any analgesic derived from active opium poppy alkaloids as well as to compounds chemically similar to the alkaloids.
SEDATIVE AND HYPNOTIC AGENTS

### Sedative Hypnotics

**Benzodiazepines**
- flurazepam
- lorazepam (Ativan, Lorazepam) #94 & #139 drugs in 1991
- temazepam (Restoril) #154 drug in 1991
- triazolam (Halcion) #38 drug in 1991

**Barbiturates**
- amobarbital
- aprobarbital
- mephobarbital
- pentobarbital (Nembutal)
- phenobarbital (Luminal)
- secobarbital (Seconal)

**Nonbenzodiazepines-nonbarbiturates**
- chloral hydrate (Noctec)
- ethchlorvynol
- glutethimide
- methyprylon
- paraldehyde

"△△" indicates a top 200 drug in 1991 -- note ranking after trade name
"△" indicates major drugs -- see table

**Indications for Use:**
depending on the dosage various sedative hypnotics are used as daytime sedatives for anxiety and tension, sedatives before surgery, hypnotics for insomnia, or as anticonvulsants

<table>
<thead>
<tr>
<th>Major Drugs</th>
<th>Things to Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>temazepam (Restoril)</td>
<td>- used as a hypnotic to relieve insomnia</td>
</tr>
<tr>
<td>triazolam (Halcion)</td>
<td>- used to treat insomnia -- very short acting with less tendency to cause morning drowsiness</td>
</tr>
<tr>
<td>pentobarbital (Nembutal)</td>
<td>- used as daytime sedative;as preoperative sedative; for short-term treatment of insomnia; for emergency control of convulsions</td>
</tr>
<tr>
<td>phenobarbital (Luminal)</td>
<td>- used as sedative for anxiety or tension; as a preoperative sedative; treatment for insomnia; as an anticonvulsant</td>
</tr>
<tr>
<td>secobarbital (Seconal)</td>
<td>- used as mild sedative; short-acting hypnotic for insomnia; treatment for acute convulsive disorders</td>
</tr>
<tr>
<td>chloral hydrate (Noctec)</td>
<td>- used as a daytime sedative; as a hypnotic to relieve insomnia</td>
</tr>
</tbody>
</table>
**BENZODIAZEPINES**

Mechanism of Action:
- sites and mechanisms of action have not been established but principal sites are believed to be the cerebral cortex and the limbic, thalamic, and hypothalamic levels of the CNS
- theorized that the drugs enhance the effects of the inhibitory neurotransmitter GABA

Adverse Reactions:
- daytime sedation and "hangover effect", rebound insomnia

Ocular Adverse Reactions:
- decreased vision, allergic reactions and erythema of eyelids or conjunctiva, decreased corneal reflex, jerky pursuit movements, decreased saccadic movements

Contraindications:
- acute narrow-angle glaucoma, liver disease, pregnant and lactating women

Drug Interactions:
- few drug interactions other than with other CNS depressant drugs

**BARSIBITURATES**

Mechanism of Action:
- sites and mechanisms of action have not been established but principal sites are believed to be the neuronal fibers and synapses that integrate the wake-sleep centers of the brain
- appear to act at the level of the thalamus where they inhibit the ascending conduction in the reticular formation, interfering with the transmission of impulses to the cortex

Adverse Reactions:
- drowsiness, lethargy, headache, mental depression, vertigo, and "hangover effect" Can cause severe CNS and respiratory depression

Ocular Adverse Reactions:
- conjunctivitis, Stevens-Johnson syndrome, ptosis, optic atrophy

Contraindications:
- history of porphyria, pulmonary insufficiency, severe cardiac or renal disease, pregnant or lactating women

Drug Interactions:
- many interactions with other drugs
NONBENZODIAZEPINES-NONBARBITURATES

Mechanism of Action:
- mechanisms of action are not completely known, but the drugs produce depressant effects similar to the barbiturates

Adverse Reactions:
- nausea, vomiting, and "hangover effect"

Ocular Adverse Reactions:
- decreased vision, pupil miosis, pupil mydriasis in toxic states, ptosis, decreased convergence, allergic reactions to eyelids or conjunctiva

Contraindications:
- markedly impaired renal and hepatic function, and other contraindications specific to the particular drug

Drug Interactions:
- when drugs are used with other CNS depressants, causing additive depression of the CNS
ANXIOLYTIC AGENTS

Anxiolytic Agents

**Benzodiazepines**
- ΔΔ alprazolam (Xanax) #5 drug in 1991
- Δ chlordiazepoxide (Librium)
- Δ clorazepate (Tranxene)
- ΔΔ diazepam (Valium) #57 drug in 1991
- Δ halazepam
- ΔΔ lorazepam (Ativan, Lorazepam) #94 & #139 drugs in 1991
- Δ oxazepam
- Δ prazepam

**Buspirone**
- ΔΔ Buspirone (Buspar) #93 drug in 1991

**Barbiturates**
- Δ pentobarbital
- Δ phenobarbital

**Other Antianxiety Agents**
- meprobamate
- beta blockers
- antihistamines

"ΔΔ" indicates a top 200 drug in 1991 -- note ranking after trade name
"Δ" indicates major drugs -- see table

**Indications for Use:**
- used primarily to treat anxiety orders
- include some of the most frequently prescribed drugs in the United States

<table>
<thead>
<tr>
<th>Major Drugs</th>
<th>Things to Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>clorazepate (Tranxene)</td>
<td>- used to treat anxiety and alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>- can be used as an adjunct in managing partial seizures</td>
</tr>
<tr>
<td>diazepam (Valium)</td>
<td>- used to treat anxiety, alcohol withdrawal, skeletal muscle spasms, and status epilepticus</td>
</tr>
<tr>
<td>chlordiazepoxide (Librium)</td>
<td>- used to treat anxiety and alcohol withdrawal</td>
</tr>
<tr>
<td>buspirone (Buspar)</td>
<td>- as effective as diazepam or clorazepate in relieving anxiety</td>
</tr>
<tr>
<td></td>
<td>- does not interact with alcohol</td>
</tr>
<tr>
<td>alprazolam (Xanax)</td>
<td>- #5 drug in 1991</td>
</tr>
<tr>
<td></td>
<td>- useful in treating anxiety associated with depression</td>
</tr>
<tr>
<td>phenobarbitol (Luminal)</td>
<td>- can be used as an antianxiety agent</td>
</tr>
</tbody>
</table>
Mechanism of Action:
- benzodiazepines --
  - work indirectly by enhancing gamma-aminobutyric acid (GABA) activity
- buspirone --
  - produces various effects in the midbrain and acts as a midbrain modulator
  - does not affect GABA receptors
- barbiturates -- in therapeutic concentrations, enhance the effects of GABA, but at higher concentrations they directly depress all neurons

Adverse Reactions:
- benzodiazepines --
  - sedation most common; may see impairment of motor coordination, reaction time, and cognitive reasoning
  - ocular side effects -- nystagmus
- buspirone --
  - dizziness, light-headedness, insomnia, and headache
- barbiturates --
  - sedation, lethargy, ataxia, headache, mental depression, impaired motor coordination, impaired reaction time, "hangover effect", and can cause severe CNS and respiratory depression

Ocular Adverse Reactions:
- conjunctivitis, Stevens-Johnson syndrome, ptosis, optic atrophy

Contraindications:
- benzodiazepines -- do not give to pregnant or breast-feeding women
- buspirone -- do not switch from long-term benzodiazepine therapy to buspirone without tapering to avoid withdrawal reaction
- barbiturates -- pulmonary insufficiency, severe cardiac or renal disease, use with caution in patient taking other CNS depressants, including alcohol

Drug Interactions:
- benzodiazepines -- major interactions occur with other CNS depressants, producing additive effects
- buspirone -- interacts with MAO inhibitors causing elevated blood pressure
- barbiturates -- produce additive depressant effects when administered with other CNS depressants
Important antipsychotics

**Phenothiazines**
- chlorpromazine (Thorazine)
- promazine
- triflupromazine
- acetophenazine
- fluphenazine
- perphenazine
- trifluoperazine
- mesoridazine
- thioridazine (Mellaril)

**Nonphenothiazines**
- droperidol
- haloperidol (Haldol)
- loxapine
- molindone
- pimozide (Orap)
- chlorprothixene
- thiothixene

<table>
<thead>
<tr>
<th>Drug</th>
<th>Things to Know for Boards</th>
</tr>
</thead>
<tbody>
<tr>
<td>chlorpromazine (Thorazine)</td>
<td>- prototype for all the phenothiazines&lt;br&gt;- used to treat schizophrenia, other psychoses, intractable hiccups, and nausea or vomiting</td>
</tr>
<tr>
<td>thioridazine (Mellaril)</td>
<td>- used to treat symptoms of psychoses&lt;br&gt;- an effective sedative and is used for dementia and depressive neurosis</td>
</tr>
<tr>
<td>haloperidol (Haldol)</td>
<td>- used to treat dyskinesia in Tourette's syndrome and symptoms of psychoses</td>
</tr>
<tr>
<td>pimozide (Orap)</td>
<td>- suppresses severe motor and phonic tics in patients with Tourette's syndrome when these symptoms do not respond to other treatments</td>
</tr>
</tbody>
</table>

**Indications for Use:**
Antipsychotic agents are used to treat schizophrenia, calm anxious or agitated patients, improve thought processes, and alleviate delusions and hallucinations. They may also be used to treat psychosis, autism, manic-depressive disorder, and major depression with psychosis.
Mechanism of Action: (same for both classes)
- cause a reduction of stimuli to the brain stem reticular activating system, which produces a sedative action
- block postsynaptic dopamine receptors in the limbic system and hypothalamus to produce an antipsychotic action
- may interfere with the transmitter function of dopamine in the extrapyramidal tract causing abnormal body movements

Adverse Reactions: (same for both classes)
reactions ranging from mild, such as dry mouth, to severe, such as tardive dyskinesia

Ocular Adverse Reactions:
- phenothiazines -- decreased vision, decrease or paralysis of accommodation, night blindness, red-green color vision defect, objects have yellow or brown tinge, colored haloes around lights, pigmentary deposits in cornea
- nonphenothiazines -- decreased vision, oculogyric crises, decrease or paralysis of accommodation

Contraindications:
- phenothiazines -- use cautiously in a patient with a seizure disorder, prostate disorder, liver disease, or cardiac disorder
- nonphenothiazines -- contraindicated in coma or CNS depression; use with caution in elderly patient or in one with a severe cardiovascular disorder, allergy, glaucoma, liver disease, or urine retention

Drug Interactions:
- phenothiazines
  - enhance effects of antihypertensives by increasing the alpha-adrenergic blocking action
  - may increase adverse reactions, such as dry mouth or blurred vision, when taken with anticholinergics, such as atropine
  - may enhance depressant effects when used with alcohol and CNS depressants, such as barbiturates and narcotics
- nonphenothiazines
  - interact with fewer drugs than phenothiazines
  - their dopamine-blocking activity can inhibit levodopa and may cause disorientation in patients receiving both medications
  - haloperidol may augment the effects of lithium, producing encephalopathy

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ANTIPARKINSONIANS

Important Antiparkinsonian Agents

**Anticholinergic Agents**
- benztropine
- biperiden
- procyclidine
- trihexphenidyl (Artane)
- ethopropazine
- diphenhydramine (Benadryl)
- orphenadrine

**Dopaminergic Agents**
- levodopa (Kopar)
- carbidopa-levodopa (Sinemet) #124 drug in 1991
- amantadine (Symmetrel)
- bromocriptine

"ΔΔ" indicates a top 200 drug in 1991 -- note ranking after trade name
"Δ" indicates major drugs -- see table

<table>
<thead>
<tr>
<th>Drug</th>
<th>Things to Know for Boards</th>
</tr>
</thead>
<tbody>
<tr>
<td>trihexphenidyl (Artane)</td>
<td>- most widely used anticholinergic for treatment of Parkinson's disease</td>
</tr>
<tr>
<td>diphenhydramine (Benadryl)</td>
<td>- this antihistamine's anticholinergic properties are responsible for its effectiveness in Parkinson's disease</td>
</tr>
<tr>
<td>levodopa (Dopar)</td>
<td>- most effective drug for parkinsonism</td>
</tr>
<tr>
<td>carbidopa-levodopa (Sinemet) #124 drug in 1991</td>
<td>- in this combination drug, carbidopa allows more levodopa to be converted to dopamine in the brain</td>
</tr>
</tbody>
</table>

Indications for Use of the Antiparkinsonians
- used to treat Parkinson's disease
- anticholinergics are most commonly used alone in the early stages of Parkinson's disease when symptoms are mild and do not have a major impact on the patient's life-style
- anticholinergics may be given with levodopa during the later stages to further relieve symptoms
- dopaminergic agents are used to treat patients with severe Parkinson's disease or who don't respond to anticholinergics alone
(ANTICHOLINERGIC AGENTS)

Mechanism of Action:
- anticholinergic agents counteract cholinergic activity believed to be present in Parkinson's disease in the brain
- these drugs prolong dopamine's action by blocking its reuptake into presynaptic neurons in the CNS and also suppress central cholinergic activity

Adverse Reactions:
- produce many adverse reactions
- CNS reactions -- drowsiness, dizziness, insomnia, confusion, restlessness, agitation, excitement
- GI reactions -- constipation, nausea, vomiting
- cardiovascular reactions -- tachycardia, palpitations

Ocular Adverse Reactions:
- mydriasis, blurred vision, photophobia, increased intraocular pressure

Contraindications:
- contraindicated in patients with narrow-angle glaucoma
- use cautiously in patients with tachycardia, cardiac dysrhythmias, hypotension, hypertension, hyperthyroidism, coronary artery disease, congestive heart failure

Drug Interactions:
- a few drugs produce clinically significant interactions with anticholinergics
  - include amantadine, levodopa, and the antipsychotics

(DOPAMINERGIC AGENTS)

Mechanism of Action:
- levodopa is pharmacologically inactive until it crosses the blood-brain barrier and is converted by enzymes in the brain to dopamine
- carbidopa enhances levodopa's effectiveness

Adverse Reactions:
- usually dose-dependent and reversible
- levodopa GI adverse effects -- nausea, vomiting, anorexia
- levodopa cardiovascular adverse effects -- hypotension, palpitations, tachycardia, dysrhythmias, flushing, hypertension
- levodopa has loss of effectiveness after 3 to 5 years
- amantadine -- few adverse reactions at usual dosages but long-term therapy produces GI and cardiovascular adverse effects similar to levodopa
- bromocriptine -- many adverse reactions which are an important factor limiting the use of bromocriptine
Dopaminergic Agents (continued)

Ocular Adverse Reactions:
- levodopa -- pupil mydriasis may precipitate narrow-angle glaucoma, widening of palpebral fissure, decreased vision, diplopia, blepharospasm, Horner's syndrome
- amantadine -- decreased vision, visual hallucinations, oculogyric crises, photosensitivity and purpura of eyelids or conjunctiva, mydriasis may precipitate narrow-angle glaucoma

Contraindications:
- levodopa is contraindicated in patients with narrow-angle glaucoma
  - use with caution in a patient with a history of peptic ulcer or psychosis, with bronchial asthma or emphysema, with severe cardiovascular, pulmonary, renal, hepatic, or endocrine disease
- amantadine -- use cautiously in patient with recurrent eczematoid dermatitis, seizure disorders, renal insufficiency, or recurrent psychosis
- bromocriptine -- use cautiously in patient with history of myocardial infarction with a residual dysrhythmia

Drug Interactions:
- levodopa combined with monamine oxidase (MAO) inhibitors can produce hypertensive crisis
- interactions between dopaminergics and other drugs usually decrease the effectiveness of the dopaminergic agent
Important antidepressant and antimanic agents

**MAO Inhibitors**
- isocarboxazid
- phenelzine (Nardil)
- tranylcypromine

**Tricyclic Antidepressants**
- amitriptyline (Elavil, Amitriptyline) #171 & #186 drugs in 1991
desipramine
- doxepin (Sinequan)
imipramine
- nortriptyline (Pamelor) #59 drug in 1991
protriptyline
- trimipramine

**Second-generation antidepressants**
- amoxapine
- maprotiline
- trazodone (Desyrel)
- fluoxetine (Prozac) #18 drug in 1991

**Lithium**
- Lithium (Lithium)

"ΔΔ" indicates a top 200 drug in 1991 -- note ranking after trade name
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<table>
<thead>
<tr>
<th>Things to Know for Boards</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenelzine (Nardil)</td>
</tr>
<tr>
<td>- less potent than other MAO inhibitors</td>
</tr>
<tr>
<td>- less likely to produce hypertensive crisis</td>
</tr>
<tr>
<td>amitriptyline (Elavil, Amitriptyline) #171 &amp; #186 drugs in 1991</td>
</tr>
<tr>
<td>- used to treat depression</td>
</tr>
<tr>
<td>- produces greater sedative and anticholinergic effects than other tricyclics</td>
</tr>
<tr>
<td>trazodone (Desyrel)</td>
</tr>
<tr>
<td>- used to treat depression</td>
</tr>
<tr>
<td>- may produce additive effects when combined with other drugs</td>
</tr>
<tr>
<td>lithium</td>
</tr>
<tr>
<td>- drug of choice to prevent or treat mania</td>
</tr>
</tbody>
</table>

**Indications for Use:**
- antidepressant and antimanic agents are used to treat affective disorders
- MAO inhibitors, tricyclic antidepressants, and second-generation antidepressants are used to treat unipolar disorders, characterized by periods of clinical depression
- lithium is used to treat bipolar disorders, characterized by alternating periods of manic behavior and clinical depression
(MAO INHIBITORS)
Mechanism of Action:
- inhibit monoamine oxidase, the enzyme that normally metabolizes the neurotransmitters thereby making more norepinephrine and serotonin available to the receptors and relieving the symptoms of depression

Adverse Reactions:
- most common adverse reaction is orthostatic hypotension which can lead to syncope; impotence and edema may also occur

Ocular Adverse Reactions:
- decreased vision, mydriasis, miosis, anisocoria; extraocular muscles affected to produce diplopia or nystagmus, or strabismus; photophobia

Contraindications:
- do not discontinue use of MAO inhibitor abruptly; therapy should be tapered to avoid withdrawal reactions

Drug Interactions:
- most serious reactions involve tyramine-rich foods and sympathomimetic agents

(TRICYCLIC ANTIDEPRESSANTS)
Mechanism of Action:
- theorized to increase the amount of norepinephrine, serotonin, or both, normalizing the hyposensitive receptor site associated with depression

Adverse Reactions:
- elevation of intraocular pressure
- orthostatic hypotension
- conduction delay which can exacerbate congestive heart failure or an existing bundle branch block
- anticholinergic reactions such as blurred vision, urine retention, dry mouth, and constipation

Ocular Adverse Reactions:
- decreased vision, decrease or paralysis of accommodation, pupil mydriasis may precipitate narrow-angle glaucoma, diplopia, photophobia, visual hallucinations, oculogyric crises, jerky pursuit movements

Contraindications:
- avoid abrupt withdrawal from long-term use since may produce nausea, headache, and malaise

Drug Interactions:
- interact with numerous drugs
- with MAO inhibitors to cause hyperpyrexia, excitation, seizures
- with sympathomimetics -- increase catecholamine effects, leading to hypertension
(SECOND-GENERATION ANTIDEPRESSANTS)

Mechanism of Action:
- action similar to the tricyclic antidepressants
- inhibit reuptake of the neurotransmitters norepinephrine, serotonin, or both

Adverse Reactions:
- produce fewer adverse reactions than tricyclic antidepressants
- seizures may occur at high doses
- trazodone may produce sedation and dizziness
- Amoxapine and maprotiline may cause anticholinergic effects, orthostatic hypotension, and tachycardia
- fluoxetine produces nausea, nervousness, headache, and insomnia more frequently than tricyclic antidepressants

Ocular Adverse Reactions:
- amoxapine -- decreased vision, pupil mydriasis, decrease or paralysis of accommodation, photosensitivity and erythema of eyelids or conjunctiva, nystagmus, oculogyric crises
- trazodone -- decreased vision, visual hallucinations, hyperemia, photophobia, allergic reactions of eyelids or conjunctiva, diplopia

Contraindications:
- avoid abrupt withdrawal of therapy

Drug Interactions:
- patients receiving drugs that interact with tricyclic antidepressants should be observed for similar interactions
- trazodone may produce additive effects when combined with other drugs

(LITHIUM)

Mechanism of Action:
- normalizes the catecholamine receptors to reduce the swings of excessive catecholamine stimulation of mania and the diminished catecholamine stimulation of depression

Adverse Reactions:
- GI complaints most frequent during the initial phase of therapy and after dosage adjustments
- polyuria accompanied by polydipsia may occur
- toxicity may occur, producing confusion, lethargy, slurred speech, hyperreflexia, and convulsions

Ocular Adverse Reactions:
- decreased vision, nystagmus, scotomas, oculogyric crises, conjunctivitis, lacrimation, photophobia
Lithium (continued)

Contraindications:
- patient on severe salt restricted diet is susceptible to lithium toxicity

Drug Interactions:
- serious interactions with other drugs can occur because of lithium's narrow therapeutic range
- the interactions may occur at the receptor site, where potentiation takes place or may occur in the kidneys
**Anticonvulsants**

**Important Anticonvulsants**

**Hydantoins**
- Phenytin (Dilantin) #29 drug in 1991
- Mephentoin
- Ethotoin

**Barbiturates**
- Phenobarbital (Luminal)
- Mephobarbital
- Primidone

**Limonstilbenes**
- Carbamazepine (Tegretol) #80 drug in 1991

**Benzodiazepines**
- Clonazepam (Klonopin) #101 drug in 1991
- Diazepam (Valium) #57 drug in 1991

**Succinimides**
- Ethosuximide (Zarotin)
- Methsuximide
- Phensuximide

**Valproic Acid**
- Valproate sodium

**Other Anticonvulsants**
- Acetazolamide (Diamox)
- Trimethadione
- Paramethadione
- Magnesium sulfate

"ΔΔ" indicates a top 200 drug in 1991 — note ranking after trade name
"Δ" indicates major drugs — see table

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<tr>
<th>Drug</th>
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</table>
| Phenytoin (Dilantin)          | - Most commonly prescribed anticonvulsant
|                               | - Drug of choice to treat complex partial and tonic-clonic seizures                      |
| Phenobarbital (Luminal)       | - One of the most widely employed anticonvulsants                                         |
|                               | - Used in long-term treatment of epilepsy                                                 |
| Carbamazepine (Tegretol)      | - Anticonvulsant with chemical structure similar to the tricyclic antidepressants so it can produce many of the same adverse reactions |
| Clonazepam (Klonopin)         | - Only benzodiazepine recommended for long-term treatment of epilepsy                    |
| Diazepam (Valium)             | Restricted to the acute treatment of status epilepticus                                   |
| Ethosuximide (Zarotin)        | - Used to treat absence seizures                                                         |
|                               | - Among the succinimides, the drug of choice                                             |
Indications for Use of Anticonvulsants
used for long-term management of chronic epilepsy and for short-term management of acute isolated seizures not caused by epilepsy

(HYDANTOINS)
Mechanism of Action:
- primary site of action appears to be the motor cortex where the drugs inhibit the spread of seizure activity
- alters ion movement across cell membranes

Adverse Reactions:
- slurred speech, confusion, insomnia, twitching, drowsiness, headache, blurred vision, mydriasis, hyperactive tendon reflexes, and hallucinations

Ocular Adverse Reactions:
- nystagmus, diplopia, decreased vision, pupil mydriasis, decreased accommodation

Contraindications:
- in patients who experience hypersensitivity to any hydantoin product
- use cautiously in patients with impaired renal or hepatic function, alcoholism, hypotension, myocardial insufficiency, or pancreatic disorders
- birth defects and fetal hydantoin syndrome have occurred with phenytoin use

Drug Interaction
- interact with a number of other drugs and the activities of either or both may be altered

(BARBITURATES)
Mechanism of Action:
- limit seizure activity by increasing the threshold for motor cortex stimuli
- the threshold increase may be due to increased inhibitory action of the neurotransmitter gamma-aminobutyric acid

Adverse Reactions:
- CNS reactions -- drowsiness, lethargy, dizziness, nystagmus, confusion
- GI adverse reactions -- nausea, vomiting

Ocular Adverse Reactions:
- ptosis, blepharoclonus, mydriasis, decreased reaction to light, diplopia, decreased convergence, nystagmus
Barbiturates (continued)

Contraindications:
- in patients with sensitivity to barbiturates or manifest porphyria
- use cautiously in patients with severe respiratory, cardiac, or renal disease or with impaired hepatic function or severe anemia
- use cautiously in depressed patients or those with suicidal tendencies

Drug Interactions:
- most of the clinically significant interactions from barbiturates occur with phenobarbital
- primidone is converted to phenobarbital in the body so concurrent administration of both may result in excessive phenobarbital serum levels

(IMINOSTILBENES)

Mechanism of Action:
- anticonvulsants effect similar to that of the hydantoins
- anticonvulsant action may occur because of the drug's ability to inhibit the spread of seizure activity or neuromuscular transmission in general
- increases the discharge of noradrenergic neurons

Adverse Reactions:
- drowsiness, diplopia, ataxia, vertigo, nystagmus, headaches, tremor, and dry mouth
- related to tricyclics so can produce many similar adverse reactions - including heart failure, hypertension or hypotension, syncope, dysrhythmia, and myocardial infarction

Ocular Adverse Reactions:
- extracocular muscle paralysis, diplopia, decreased vision, allergic reactions of eyelids or conjunctiva, conjunctivitis, mydriasis, decreased accommodation

Contraindications:
- in patients with hypersensitivity to carbamazepine or to tricyclic compounds
- may be contraindicated with MAO inhibitors because the concomitant use of MAO inhibitors and tricyclic antidepressants results in hyperpyretic crises or severe convulsions

Drug Interactions:
- carbamazepine possesses enzyme-inducing properties and generally decreases the steady-state levels of other drugs
(BENZIDIAZEPINES)
Mechanism of Action:
- may involve availability of the inhibitory neurotransmitter gamma-aminobutyric acid to brain neurons

Adverse Reactions:
- primarily neurologic and include drowsiness, confusion, ataxia, weakness, dizziness, nystagmus, vertigo, syncope, dysarthria, headache, tremor, and a glassy-eyed appearance

Ocular Adverse Reactions:
- decreased vision, allergic reactions of eyelids or conjunctiva, conjunctivitis, photosensitivity, decreased corneal reflex, oculogyric crises, decreased accommodation, diplopia

Contraindications:
- in patients with known hypersensitivity to a benzodiazepine compound
- in patients with liver disease, acute narrow-angle glaucoma, or in pregnant and lactating women

Drug Interactions:
- occur with CNS depressants and alcohol

(SUCCINIMIDIES)
Mechanism of Action:
- reduce frequency of absence seizures in children and adults by depressing nerve transmission in the motor cortex and increasing the seizure threshold for stimulus

Adverse Reactions:
- involving GI tract -- nausea, vomiting, weight loss, abdominal pain, constipation, diarrhea
- neurologic complaints -- ataxia, dizziness, drowsiness, headache, euphoria, restlessness, irritability, lethargy, confusion
- hypersensitivity reactions -- Stevens-Johnson syndrome, pruritic skin eruptions, exfoliative dermatitis, and systemic lupus erythematosus
- methsuximide can produce renal and hepatic damage

Ocular Adverse Reactions:
- decreased vision, diplopia, photophobia, myopia, periorbital edema or hyperemia, subconjunctival or retinal hemorrhages secondary to drug-induced anemia, allergic reactions of eyelids or conjunctiva

Contraindications:
- use cautiously in patients with severe hepatic or renal disease

Drug Interactions:
- the succinimides may inhibit the metabolism of hydatoin anticonvulsant
(VALPROIC ACID)

Mechanism of Action:
- mechanism of action remains unknown
- may be related to increased availability of the inhibitory neurotransmitter
  GABA to brain neurons due to inhibition of GABA transaminase by
  valproic acid

Adverse Reactions:
- GI reactions -- nausea, vomiting, appetite changes, diarrhea, constipation
- CNS reactions -- sedation, drowsiness, dizziness, ataxia, headache,
  decreased alertness, muscle weakness
- hematologic adverse reactions -- inhibited platelet aggregation and
  prolonged bleeding time

Ocular Adverse Reactions:
- diplopia, nystagmus, visual hallucinations

Contraindications:
- should not be prescribed for patients with liver dysfunction - fatal
  hepatotoxicity has been reported

Drug Interactions:
- prolonged bleeding time in patients also receiving anticoagulants
- inhibition of the hepatic metabolism of phenobarbital
Important Skeletal Muscle Relaxing Agents:

**Centrally Acting Skeletal Muscle Relaxants**
- carisoprodol (Soma)
- chlorphenesin
- chlorzoxazone
- cyclobenzaprine hydrochloride
- metaxalone
- methocarbamol

**Peripherally Acting Skeletal Muscle Relaxants**
- dantrolene sodium (Dantrium)

**Other Skeletal Muscle Relaxants**
- baclofen (Lioresal)
- diazepam (Valium) #57 drug in 1991

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<tr>
<td>carisoprodol (Soma)</td>
<td>used to treat acute, painful muscle spasms</td>
</tr>
<tr>
<td>dantrolene (Dantrium)</td>
<td>helps manage all types of spasticity, regardless of the lesion location</td>
</tr>
<tr>
<td></td>
<td>most effective when the lesion is cerebral</td>
</tr>
<tr>
<td>diazepam (Valium) #57 drug in 1991</td>
<td>primarily an antianxiety agent but also useful to treat acute muscle spasms and spasticity</td>
</tr>
<tr>
<td>baclofen (Lioresal)</td>
<td>drug of choice to treat spasticity for some physicians</td>
</tr>
<tr>
<td></td>
<td>produces less sedation than diazepam and less peripheral muscle weakness than dantrolene</td>
</tr>
</tbody>
</table>

**Indications for Use:**
- used to treat acute, painful musculoskeletal conditions and the muscle spasticity associated with multiple sclerosis, cerebral palsy, cerebrovascular accident, and spinal cord injuries
- centrally acting skeletal muscle relaxants -- used to alleviate acute muscle spasms
  - ineffective in treating spasticity associated with chronic neurologic disease
- peripherally acting skeletal muscle relaxants -- most effective for spasticity of cerebral origin
(CENTRALLY ACTING SKELETAL MUSCLE RELAXANTS)

Mechanism of Action:
- the precise mechanism of action of these drugs is not known
- the skeletal muscle relaxant effects of the centrally acting agents are minimal and probably related to their sedative effects

Adverse Reactions:
- drowsiness and dizziness are the most common adverse reactions to drugs in this class
- occasionally, nausea, vomiting, heartburn, ataxia, diarrhea, constipation

Ocular Adverse Reactions:
- carisoprodol -- decreased accommodation, decreased vision, diplopia, paralysis of extraocular muscles, decreased corneal reflex, constriction of visual fields, allergic reactions of eyelids or conjunctiva

Contraindications:
- these drugs contraindicated in pregnant or lactating women
- carisoprodol -- contraindicated in patients with acute intermittent porphyria because it may increase porphyria synthesis
- cyclobenzaprine and orphenadrine -- contraindicated in patients with narrow-angle glaucoma or myasthenia gravis
- parenteral methocarbamol -- contraindicated in patients who have convulsive disorders because it may precipitate seizures

Drug Interactions:
- interact with few drugs
- all interact with other CNS depressants causing additive depression of the CNS

(PERIPHERALLY ACTING SKELETAL MUSCLE RELAXANTS)

Mechanism of Action:
- may act by inhibiting calcium release from the sarcoplasmic reticulum in muscle cells to prevent the triggering of muscle contraction

Adverse Reactions:
- muscle weakness
- drowsiness, dizziness, lightheadedness, nausea, malaise, fatigue
- neurological adverse effects -- may include visual and speech disturbances, headache, depression, confusion, hallucinations, nervousness, insomnia
Peripherally Acting Skeletal Muscle Relaxants (continued)

**Ocular Adverse Reactions:**
- decreased vision, photosensitivity and urticaria of eyelids or conjunctiva, diplopia, licrimation, visual hallucinations

**Contraindications:**
- in women who are or may become pregnant or who are lactating
- in patients who must use spasticity to maintain posture and balance
- in patients with active hepatic disease such as hepatitis or cirrhosis

**Drug Interactions:**
- CNS depressants combined with dantrolene increase CNS depression -- may lead to sedation, motor skill impairment, and respiratory depression

**(OTHER SKELETAL MUSCLE RELAXANTS) baclofen and diazepam**

**(BACLOFEN)**

**Mechanism of Action:**
- baclofen is an analogue of the neurotransmitter GABA and probably acts in the spinal cord
- biochemically, baclofen resembles an inhibitory neurotransmitter

**Adverse Reactions:**
- few adverse reactions when administered appropriately to patients with spinal lesions
- general CNS depression produces the most problems
- transient drowsiness is most common
- less frequent reactions include fatigue, nausea, vertigo, muscle weakness, depression, and headache

**Ocular Adverse Reactions:**
- decreased vision, decreased accommodation, diplopia, visual hallucinations, pupil mydriasis may precipitate narrow-angle glaucoma, nystagmus, strabismus

**Contraindications:**
- contraindicated in pregnant or lactating women
- patients with impaired renal function may require a reduced dosage because baclofen is excreted primarily unchanged in the urine

**Drug Interactions:**
- few drug interactions are reported with baclofen
- most significant -- CNS depression when baclofen administered with other CNS depressants
(DIAZEPAM) Valium

Mechanism of Action:
- works indirectly by enhancing GABA activity

Adverse Reactions:
- sedation most common; may see impairment of motor coordination, reaction time, and cognitive reasoning

Ocular Adverse Reactions:
- decreased vision, allergic reactions and erythema or eyelids or conjunctiva, conjunctivitis (nonspecific), decreased corneal reflex, oculogyric crises, abnormal conjugate deviations, jerky pursuit movements, decreased accommodation, diplopia

Contraindications:
- contraindicated in pregnant or lactating women

Drug Interactions:
- major interactions occur with other CNS depressants, producing additive effects
Hallucinogens and Drugs of Abuse:

Hallucinogens
- LSD (Lysergic acid diethylamide)
- MDA (methylene dioxyamphetamine)
- MDMA (Ecstasy)
- Mescaline
- peyote
- psilocybin
- Marijuana
- THC (tetrahydrocannabinol) active constituent of marijuana

Stimulants
- Amphetamine
- Methamphetamine
- dextoamphetamine (Dexedrine)
- Cocaine

CNS Depressant
- heroin
- morphine
- opium
- hydromorphone (Dilaudid)
- methadone
- meperidine (Demerol)
- oxycodone (Percodan)
- oxymorphone (Numorphan)
- methaqualone (Quaalude)
- amobarbital (Amytal)
- pentobarbital (Nembutal)
- secobarbital (Seconal)
- glutethimide
- methyprylon
- ethchlorvynol (Placidyl)
- alcohol

Minor Tranquilizers
- meprobamate (Miltown)
- benzodiazepines
(HALLUCINOGENS)

Mechanism of Action:
- all major psychedelic drugs bear a close chemical resemblance to the neurotransmitters serotonin, norepinephrine, and dopamine
- LSD --
  -- postulated to directly affect neurons involved in sensory perception which communicate to accelerate firing of norepinephrine neurons of the locus coeruleus
  -- firing of the norepinephrine neurons provoke a powerful patterned release of norepinephrine from nerve terminals throughout the brain
- the locus coeruleus is a funneling mechanism that integrates all sensory input -- from sights, sounds, tactile pressures, smells, tastes -- into a generalized excitation system within the brain, so stimulation of the locus coeruleus may cause the drug user to feel that sensations are crossing the boundaries between different modalities, an effect known as synesthesia
- other research has revealed that psychedelic agents exert potent effects on a serotonin receptor subtype, designated $S_2$. At $S_2$ receptors, psychedelic drugs mimic the effects of serotonin. The relative strengths with which psychedelic drugs influence $S_2$ receptors parallel the drugs' relative psychedelic potencies in humans

Possible Side Effects:
- cannabis --
  - dose-dependent hypothermia, decrease in aggressive behavior, sedation
  - dreamy state of consciousness; ideas seem disconnected, uncontrollable, and freely flowing
  - time, color and spatial perceptions are distorted and enhanced
  - feeling of well-being, exaltation, excitement
- LSD and other hallucinogens --
  - pupillary dilatation, increased blood pressure, tachycardia, tremor, nausea
  - synesthesias -- the overflow of from one sensory modality to another may occur; colors are heard and sounds may be seen
  - sense of time is markedly distorted; hours may seem to take years
  - sense of space is altered; space expands and distances seem increased

Contraindications:
- contraindicated in jet pilots
(STIMULANTS)
Mechanism of Action:
- cocaine and amphetamines may each act in the same manner.
- amphetamines closely resemble dopamine and norepinephrine, two major neurotransmitters contained in brain pathways that regulate emotional behavior. Norepinephrine neurons in the brain have their origin in the locus coeruleus.
- the amphetamine or cocaine molecules diffuse into the nerve ending where dopamine and norepinephrine are stored and displace those neurotransmitters from their storage sites. The neurotransmitters are pushed out into the synaptic cleft, where they stimulate appropriate receptors.
- the alerting, stimulating effects of cocaine and amphetamines are produced by an enhancement of norepinephrine activity in the cerebral cortex. The euphoria brought on by these drugs probably involves the limbic system.

Possible Side Effects:
- cardiovascular -- palpitations, tachycardia, elevation of blood pressure
- CNS -- overstimulation restlessness, dizziness, insomnia, euphoria, tremor, changes in libido
- GI -- dry mouth, unpleasant taste, diarrhea, constipation

(CNS DEPRESSANTS AND MINOR TRANQUILIZERS)
Mechanism of Action:
- for these drugs of abuse see the mechanisms of action for the specific drugs listed under sections -- SEDATIVE AND HYPNOTIC AGENTS -- Benzodiazepines, Barbiturates, Nonbenzodiazepines-nonbarbiturates -- or under OPIOID AND NON-OPIOID ANALGESICS -- Narcotic Antagonists

Possible Side Effects:
- for side effects of these drugs of abuse see the same sections which were listed above in the mechanisms of action section
- additional side effects include the high potential for physical and psychological dependence
injectable local anesthetics

- bupivacaine (Marcaine)
- chloroprocaine (Nesacaine)
- dibucaine
- etidocaine
- lidocaine (Lignocaine)
- mepivacaine
- prilocaine
- procaine (Novacain)
- propoxycaine
- tetracaine

topical local anesthetics

- benoxinate (Fluress)
- benzocaine (Americaine, Anbesol, Ora Jel, Solarcaine)
  - benzyl alcohol
  - butacaine
  - butamben picrate
  - clove oil
  - cocaine hydrochloride
- dibucaine (Nupercainal)
  - dichlorotetrafluoroethane
  - dyclonine
- ethyl chloride
- lidocaine (Xylocaine)
  - menthol
  - pramoxine
- proparacaine (Alcaine, Ophthaine)
- tetracaine (Pontocaine)

"Δ" indicates major drugs -- see table.
Injectable Local Anesthetics

Indications for Use:
- Injectable local anesthetics are used to interrupt the transmission of pain and reflex impulses from peripheral nerves by causing a temporary loss of sensation in a limited area of the body.
- For severe pain from a medical procedure, injury, or disease.

Mechanism of Action:
Act on sodium channels to prevent action potentials in all nerves within a localized area.

<table>
<thead>
<tr>
<th>major drugs</th>
<th>things to remember</th>
</tr>
</thead>
<tbody>
<tr>
<td>bupivacaine</td>
<td>- an amide</td>
</tr>
<tr>
<td></td>
<td>- for infiltration (direct injection into targeted tissue), spinal, caudal, lumbar, peripheral and retrobulbar anesthesia</td>
</tr>
<tr>
<td>chloroprocaine</td>
<td>- an ester of PABA</td>
</tr>
<tr>
<td></td>
<td>- for infiltration, peripheral, caudal and sympathetic anesthesia</td>
</tr>
<tr>
<td>lidocaine</td>
<td>- an amide</td>
</tr>
<tr>
<td></td>
<td>- for infiltration, peripheral, sympathetic, epidural, caudal and spinal anesthesia</td>
</tr>
<tr>
<td>procaine</td>
<td>- an ester of PABA</td>
</tr>
<tr>
<td></td>
<td>- for infiltration, spinal, peripheral, sympathetic anesthesia</td>
</tr>
<tr>
<td></td>
<td>- drug of choice for dental surgery</td>
</tr>
</tbody>
</table>

Adverse Reactions:
- Usually results from overdose, hypersensitivity or improper injection technique.
- CNS: Anxiety, apprehension, restlessness, nervousness, confusion, nausea, vomiting, chills.
- Bradycardia, cardiac dysrhythmias, hypotension, cardiac arrest.
- Hypersensitivity reactions.
Ocular Adverse Reactions:
with systemic administration:
- ocular side affects usually depend upon route of administration;
  intravenous or spinal injection having the most effect.
- transient paralysis of cranial nerves VI, III, and IV resulting in
  nystagmus, diplopia and poor ocular motility
- decreased vision
- Horner's syndrome (ptosis, miosis, anhyrosis)
- color defects
with ocular administration:
- decreased vision
- paresis of extraocular muscles
- decreased intraocular pressure

Contraindications and Precautions:
- spinal and epidural anesthetics contraindicated in cases of serious CNS
  or spinal chord disease, spinal deformities, severe anemia, extreme youth or
  advanced age, high or low blood pressure
- anesthetics containing vasoconstrictors contraindicated for use in the
  extremities (fingers, nose, etc.) and in patients taking monoamine
  oxidase inhibitors or tricyclic antidepressants
- anesthetics containing vasoconstrictors should be used with caution in
  elderly patients or patients with cardiovascular disease
- amide anesthetics contraindicated in patients with hepatic dysfunction
- there is a greater chance of cross-sensitivity among agents of the same
  chemical groups: esters of PABA, esters of meta-amino benzoic acid,
  esters of benzoic acid, and the amides.

Drug Interactions:
all of the above anesthetics:
- antimyasthenics: myasthenic symptoms are worsened when
  local anesthetics are injected
- CNS depressants are made less effective
- MAO inhibitors increase hypertension with local anesthetics
- neuromuscular blocking agent's blocking affects are increased
- opioid anesthetics decrease blood pressure, heart rate and
  respiratory rate when used with local anesthetics
chloroprocaine and procaine:
- cholinesterase inhibitors have an increased risk of toxicity
- sulfonamides' antibacterial affects are increased
lidocaine:
- beta-adrenergic blocking agents and cimetidine increase
  lidocaine's toxicity
TOPICAL LOCAL ANESTHETICS

Indications for Use:
used to relieve or prevent pain, itch, reflexes or irritation of the skin and mucosa

Mechanism of Action:
most topical anesthetics act by accumulating in nerve cell membranes, causing them to expand and lose their ability to depolarize, thus blocking the transmission of impulses

<table>
<thead>
<tr>
<th>major drugs</th>
<th>things to remember</th>
</tr>
</thead>
</table>
| benoxinate  | - an ester of para-aminobenzoic acid  
|             | - combined with sodium fluorescein in the ophthalmic solution, Fluores, for use in applanation tonometry |
| benzocaine  | - for sunburn, pruritis, hemorrhoidal itching and pain, tooth and mouth sores |
| dibucaine   | - to treat painful skin and mucosal conditions such as sunburn, abrasions, and hemorrhoids |
| ethyl chloride | - refrigerant action freezes the skin to produce anesthesia  
|             | - for insect stings, burns, myofascial and visceral pain syndromes |
| lidocaine   | - an amide  
|             | - used on mucous membranes  
|             | - used before insertion of urethral catheters and before gastroscopy |
| proparacaine | - an ester of meta-amino benzoic acid  
|             | - for ophthalmic application prior to tonometry, gonioscopy, corneal suture removal, foreign body removal, cataract and glaucoma surgeries |
| tetracaine  | - an ester of meta-amino benzoic acid  
|             | - for ophthalmic application prior to tonometry, gonioscopy, corneal suture removal, foreign body removal, and other minor surgeries |

Adverse Reactions:
- the same CNS and cardiac reactions as those due to injectable local anesthetics may occur
- ethyl chloride and other refrigerants may produce frostbite
- hypersensitivity reactions involving rash, itching, hives, swelling of the mouth and throat, and breathing difficulty may occur
Ocular Adverse Reactions:
with ocular application:
- prolonged pain, redness, increased corneal permeability
- prolonged use can lead to keratitis, corneal opacities, scarring, and delayed corneal wound healing

Contraindications and Precautions:
- there is a greater chance of cross-sensitivity among agents of the same chemical groups: esters of PABA, esters of meta-amino benzoic acid, esters of benzoic acid, and the amides. For example, if a patient reports an allergy to the para-amino benzoic acid, procaine (Novacaine), then there would be less chance of an allergic reaction to proparacaine, a meta-amino benzoic acid, then to benoxinate, a para-amino benzoic acid.
- refrigerant anesthetics should not be applied to broken skin or mucus membranes
- use benzocaine with caution in children because of risk of methemoglobinemia
- use proparacaine cautiously in patients with cardiac disease or hyperthyroidism

Drug Interactions:
- cholinesterase inhibitors increase the risk of anesthetic toxicity with ester derivatives
- ester derivatives impair the the effectiveness of sulfonamides
- beta-adrenergic agents can increase risk of lidocaine toxicity
- ophthalmic application of tetracaine may interfere with antibacterial action of sulfonamides
ADENOHYPOPHYSIAL HORMONES

Δ corticotropin (ACTH) (Acthar)
Δ cosyn tropin (ACTH) (Cortrosyn)
Δ somatrem (GH) (Protropin)
arginine HCl

"Δ" indicates major drugs -- see table

Background Information:
The adenohypophysis is the anterior lobe of the pituitary gland. It secretes six major hormones: growth hormone (GH), adrenocorticotropic hormone (ACTH), thyroid simulating hormone (TSH), follicle-stimulating hormone (FSH), Lutinizing Hormone (LH), and prolactin. They regulate growth, development, and sexual characteristics by stimulating the actions of other endocrine glands.

Indications for Use:
There are both diagnostic and therapeutic uses for these hormones. Except for somatrem, they are not effective when taken orally, so they are not used for replacement therapy in deficiency states. Some adenohypophyseal hormones are used diagnostically to differentiate between primary failure (failure of the thyroid to produce its hormones) and secondary failure (failure of the target organ or gland to respond to hormones produced by the thyroid).

Mechanism of Action:
Interaction of these hormones with specific plasma membrane receptors triggers a "signal" within the cell to produce enzymatic actions which effect the metabolic rate of target organs. The "signal" is a direct change in membrane permeability or stimulation of cyclic AMP production, which transmits the hormone signal within the cell.

<table>
<thead>
<tr>
<th>major drugs</th>
<th>things to remember</th>
</tr>
</thead>
<tbody>
<tr>
<td>corticotropin</td>
<td>- diagnostic testing</td>
</tr>
<tr>
<td></td>
<td>- for adrenocortical insufficiency (Addison's disease)</td>
</tr>
<tr>
<td></td>
<td>- used like corticosteroids for many anti-inflamatory</td>
</tr>
<tr>
<td></td>
<td>and immunosuppressive purposes</td>
</tr>
<tr>
<td></td>
<td>- for acute episodes of multiple sclerosis</td>
</tr>
<tr>
<td></td>
<td>- to increase muscle strength in myasthenia gravis</td>
</tr>
<tr>
<td>cosyn tropin</td>
<td>- used diagnostically to differentiate between primary</td>
</tr>
<tr>
<td></td>
<td>(adrenal) and secondary (pituitary) adrenal</td>
</tr>
<tr>
<td></td>
<td>insufficiency</td>
</tr>
<tr>
<td>somatrem</td>
<td>- for replacement therapy in linear growth failure</td>
</tr>
<tr>
<td></td>
<td>due to hormone deficiency</td>
</tr>
<tr>
<td></td>
<td>- for replacement therapy before epiphyseal closure</td>
</tr>
<tr>
<td></td>
<td>in cases of GH deficiency</td>
</tr>
</tbody>
</table>

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Adverse Reactions:
- allergic reactions are the most frequent side effect and occur more frequently with animal preparations than with synthetic hormone drugs.
- hyperglycemia, electrolyte and mineral imbalances, sodium and water retention.
- ACTH: impaired wound healing, Cushing's disease, immunosuppression, dizziness, convulsions, euphoria.
- cosyntropin: pruritis, facial flushing.
- somatrem: pain at injection site, glucose intolerance, transient hypothyroidism.

Ocular Adverse Reactions:
- immunosuppressive effects can cause exacerbation of ocular herpes simplex and other ocular infections.
- posterior subcapsular cataracts, glaucoma, exophthalmos.

Contraindications and Precautions:
- diabetic patients may need to increase doses of insulin or oral antidiabetic agents if taking ACTH.
- ACTH is contraindicated in adrenocortical hyperfunction, primary andrenal insufficiency, patients who have had recent surgery, patients with ocular herpes simplex, congestive heart failure, scleroderma, osteoporosis, fungal infections, hypertension, or hypersensitivity to porcine proteins.
- ACTH should be used with caution in pregnant women, lactating mothers, and in children as it inhibits linear growth. Also, use cautiously in patients with latent tuberculosis, hypothyroiditis, impaired hepatic function, diabetes, abscesses, pyogenic infections, or diverticulitis.

Drug Interactions:
- ACTH decreases blood levels of aspirin.
- live vaccines are contraindicated during ACTH therapy.
- amphetamines, estrogens & lithium affect diagnostic tests of cosyntropin.
- glucocorticoids diminish growth stimulating potential of somatrem and act synergistically to increase hyperglycemic effects.
- concurrent use of thyroid hormones and androgens may precipitate epiphyseal closure, reducing the effectiveness of somatrem.
# THYROID AND ANTITHYROID DRUGS

### Thyroid Agents

- Thyroid USP
- Levothyroxine
- Liothyronine
- Liotrix
- Thyroglobulin
- Thyrotropin (thyroid stimulating hormone, TSH)
- Protirelin (thyrotropin-releasing hormone or TRH)

### Antithyroid Agents

- Methimazole
- Propylthiouracil
- Iodine
- Radioactive iodine

*"Δ" indicates a major drug -- see table
"ΔΔ" indicates a Top 200 Drug in 1991 -- note ranking after trade name

## Thyroid Agents

### Indications for Use:

- Thyroid agents act as replacement or substitute hormones when the body’s hormone level cannot meet its need, such as the case of hypothyroidism.
- To prevent goitrogenesis and hypothyroidism, thyroid agents are used in combination with antithyroid agents.
- As diagnostic agents thyroid drugs and antithyroid drugs are used to differentiate between primary hypothyroidism (thyroid gland dysfunction) and secondary hypothyroidism (pituitary dysfunction) and tertiary hypothyroidism (hypothalamic dysfunction).

### Mechanism of Action:

- The primary effect of exogenous thyroid hormones is an increased metabolic rate in body tissues.
### Major Drugs and Things to Remember

<table>
<thead>
<tr>
<th>Major Drugs</th>
<th>Things to Remember</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid USP</td>
<td>Obtained from animals</td>
</tr>
<tr>
<td></td>
<td>For thyroid hormone replacement in hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>For suppression of thyrotropin secretion in patients with goiters or chronic lymphocytic thyroiditis</td>
</tr>
<tr>
<td>Levothyroxine</td>
<td>Drug of choice for thyroid hormone replacement in hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>Drug of choice for TSH suppression therapy</td>
</tr>
<tr>
<td>Thyrotropin</td>
<td>For differential diagnosis between primary and secondary hypothyroidism</td>
</tr>
<tr>
<td>Protirelin</td>
<td>For differential diagnosis of secondary and tertiary hypothyroidism</td>
</tr>
</tbody>
</table>

### Adverse Reactions:
- GI reactions: diarrhea, cramps, weight loss, increased appetite
- Cardiovascular: palpitations, sweating, tachycardia, increased BP...
- CNS: headache, tremors, nervousness, insomnia, psychosis

### Ocular Adverse Reactions:
- Decreased vision, eye lid edema and hyperemia, photophobia, visual hallucinations, exophthalmos, and paralysis of extraocular muscles resulting in ptosis and diplopia

### Contraindications and Precautions:
- Cases of myocardial infarction, hyperthyroidism, adrenal insufficiency
- Use caution in cases of angina pectoris, hypertension, renal insufficiency, ischemia

### Drug Interactions:
- Anticoagulant's effects increased by concurrent use of thyroid agents
- Insulin and oral hypoglycemic agents have decreased effects when used with thyroid agents
- Cholestyramine binds thyroid hormones T₃ and T₄, decreasing their effects
- Phenytoin increases levels of T₄
ANTITHYROID AGENTS

Indications for Use:
- used for patients with hyperthyroidism to decrease concentrations of thyroid hormones in circulation

Mechanism of Action:
- propylthiouracil: prevents thyroid hormone synthesis by blocking the combination of iodine and tyrosine.
- iodine: inhibits thyroid hormone synthesis via the Wolff-Chaikoff effect in which above-critical concentrations of iodine deter its synthesis
- radioactive iodine: limits hormone secretion by destroying thyroid tissue

<table>
<thead>
<tr>
<th>major drugs</th>
<th>things to remember</th>
</tr>
</thead>
<tbody>
<tr>
<td>propylthiouracil</td>
<td>- for severe hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td>- drug of choice for hyperthyroidism with pregnancy</td>
</tr>
<tr>
<td>iodine</td>
<td>- for rapid treatment of hyperthyroidism</td>
</tr>
<tr>
<td></td>
<td>- used to prepare thyroid for surgery by firming the gland and reducing vascularity</td>
</tr>
<tr>
<td>radioactive iodine</td>
<td>- drug of choice for hyperthyroidism in older patients</td>
</tr>
</tbody>
</table>

Adverse Reactions:
- hypersensitivity
- potentially fatal granulocytopenia
- iodism from iodine therapy: brassy taste, burning sensation in mouth, salivation, swelling of the parotid and submaxillary glands
- radioactive iodine can give a feeling of fullness in the neck and a metallic taste and increase the risk of birth defects and leukemia

Ocular Adverse Reactions:
- keratitis and allergic reactions have been reported with these agents
- Methimazole rarely causes nystagmus and decreased lacrimation
- iodide and radioactive iodide rarely causes decreased vision, decreased accommodation, exophthalmos, and ocular irritation

Contraindications and Precautions:
- iodide and radioactive iodine: pregnant women and lactating women
- iodide: tuberculosis, hypersensitivity, hyperkalemia, laryngeal edema
- propylthiouracil contraindicated in lactating women, may be used with caution in pregnant women

Drug Interactions:
- iodide may react synergistically with lithium, causing hypothyroidism
INSULIN AND SYNTHETIC ANTIDIABETICS

insulin
\[\text{\textbullet\hspace{1em}}\text{insulin}\]

**synthetic antidiabetics** (sulfonylureas)
- \[\text{\textbullet\hspace{1em}}\text{acetohexamide (Dymelor)}\]
- \[\text{\textbullet\hspace{1em}}\text{chlorpropamide (Diabinese)}\]
- \[\text{\textbullet\hspace{1em}}\text{tolazamide (Tolinase)}\]
- \[\text{\textbullet\hspace{1em}}\text{tolbutamide (Orinase)}\]
- \[\text{\textbullet\hspace{1em}}\text{glipizide (Glucotrol #47)}\]
- \[\text{\textbullet\hspace{1em}}\text{glyburide (Micronase #28, Diabeta #46)}\]

"\text{\textbullet\hspace{1em}}" \text{indicates major drugs}

"\text{\textbullet\hspace{1em}}\text{\textbullet\hspace{1em}}" \text{indicates a Top 200 Drug in 1991 -- note ranking after trade name}

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**INSULIN**

**Indications for Use:**
- Primary use is for Type I diabetes mellitus (characterized by insufficient insulin production ability of pancreatic beta cells)
- Also used for Type II and other types of diabetes mellitus when other methods are ineffective or contraindicated
- Sometimes used for hyperkalemia because it lowers potassium levels
- Insulin is administered by injection

**Mechanism of Action:**
- Decreases blood glucose by facilitating the uptake and metabolism of glucose by insulin-dependent target cells in striated muscle and adipose tissue
- Inhibits hepatic glucose production and breakdown of glycogen, protein, and triglycerides
- Increases active transport of amino acids in muscle, thereby increasing protein synthesis
Adverse Reactions:
- Adverse reactions to insulin are usually due to drug-related hypoglycemic attacks
- hypoglycemia from too much insulin, too little food or too much exercise
- signs of hypoglycemia are nervousness, shaking, sweating, weakness, irritability, hunger, tachycardia, changes in speech, hearing or vision. If untreated, may progress to unconsciousness, convulsions, coma, death
- Somogyi phenomenon - compensatory rebound hyperglycemia may occur when a patient experiences hypoglycemia after a treatment
- allergic reactions are rare and usually due to impurities - human insulin is the least antigenic, followed by pork insulin and beef insulin
- a small inadvertant overdose of U-500 insulin (the most concentrated form) could cause death

Ocular Adverse Reactions:
- decreased vision, nystagmus, extracocular muscle paresis leading to diplopia, pupil mydriasis and reduced pupil response to light, allergic reactions of the lids, blepharitis, decreased tear lysozymes, changes in intraocular pressure

Contraindications and Precautions:
- adrenal insufficiency
- severe renal or hepatic disease
- use caution with pregnancy

Drug Interactions:
- these agents produce hypoglycemia when taken alone and if they must be used concurrently with insulin, insulin doses may need to be decreased:
  - alcohol, anabolic steroids, clofibrate, fenfluramine, guanethidine, salicylates, sulfonamides, tetracycline
- these agents produce hyperglycemia when taken alone and if they must be used concurrently with insulin, insulin doses may need to be increased:
  - corticosteroids, glucagon, isoniazid, oral contraceptives, phenothiazines, sympathomimetic agents, thiazide diuretics, thyroid hormone preparations
- beta blockers create a danger by modifying symptoms of hypoglycemia and delaying recovery from hypoglycemia
**SYNTHETIC ANTIDIABETICS**

**Indications for Use:**
- all are used for Type II diabetes mellitus if diet and exercise do not maintain near-normal blood glucose levels.
- all are administered ORALLY

**Mechanism of Action:**
- stimulate pancreatic beta cells to release insulin
- decrease liver's production of glucose
- increase number and sensitivity of cellular insulin receptors
- facilitate the completion of intracellular glucose metabolism

**Adverse Reactions:**
- hypoglycemia from too little food or too much medication
- rarely: GI reactions, skin reactions, allergic reactions
- drug failure: for unknown reasons, a patient may not respond to the drug or may respond at first, but later it loses effect.
- most hypoglycemic agents have a mild diuretic affect

**Ocular Adverse Reactions:**
- decreased vision, paresis of extraocular muscles and resultant diplopia, allergic reactions of the eyelids and conjunctiva, photosensitivity, photophobia, red-green color defects, central or cecocentral scotomas, conjunctival or retinal hemorrhages due to anemia, retrobulbar or optic neuritis

**Contraindications and Precautions:**
- pregnancy
- patients undergoing severe stress such as infection, trauma or surgery
- use with caution in cases of hepatic or renal dysfunction
Drug Interactions:
- these agents interact with insulin to produce hypoglycemia and if they must be used concurrently with insulin, insulin doses may need to be decreased:
  - allopurinol, chloramphenical, clofibrate, fenfluramine,
  - guanethidine, methyldopa, monoamine oxidase inhibitors,
  - oxyphenbutazone, phenylbutazone, probenecid, salicylates,
  - sulfonamides, tetracycline
- these agents interact with insulin to produce hyperglycemia and if they must be used concurrently with insulin, insulin doses may need to be increased:
  - beta blockers, calcium channel blockers, corticosteroids, estrogen,
  - indomethacin, isoniazid, nicotinic acid, oral contraceptives,
  - phenothiazines, phenytoin, rifampin, sympathomimetic agents,
  - thiazide diuretics, thyroid hormone preparations
- alcohol and diazoxide can produce hypoglycemia alone but sometimes interacts with sulfonylureas to cause hyperglycemia
- diazoxide may cause either hypo- or hyperglycemia
- dicumarol causes hypoglycemia and its anticoagulant effect increases
- beta blockers and clonidine create a danger by modifying symptoms of hypoglycemia
ESTROGENS, PROGESTINS & ANDROGENS

**Estrogens**
- chlorotrianisene
- dienestrol
- diethylstilbestrol
- esterified estrogens
- ΔΔ estradiol
- Δ estrogenic substances, conjugated estrone
- ΔΔ estropipate
- ethinyl estradiol
- quinestrol

**Progestins**
- hydroxyprogesterone
- ΔΔ medroxyprogesterone
- norethindrone
- progesterone

**Contraceptive agents**
- ΔΔ ethinyl estradiol / ethynodiol diacetate
- ΔΔ ethinyl estradiol / levonorgestrel
- ΔΔ ethinyl estradiol / norethindrone
- ethinyl estradiol / norgestrel
- mestranol / ethynodiol
- mestranol / norethindrone
- mestranol / norethynrel
- norethindrone
- norgestrel

**Androgens**
- danazol
- Δ fluoxymesterone
- methyltestosterone
- testosterone
- Δ testosterone cypionate
- testosterone enanthate
- testosterone propionate

"Δ" indicates major drugs -- see table
"ΔΔ" indicates a Top 200 Drug in 1991 -- note ranking after trade name

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**General Indications for Use:**
The most common uses for drugs in these classes include: replacement hormone therapy for patients with hormone deficiencies or imbalances, oral contraception, and treatment of certain cancers of the breast and prostate gland.

<table>
<thead>
<tr>
<th>major drugs</th>
<th>things to remember</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estrogens</strong></td>
<td></td>
</tr>
<tr>
<td>estrogenic substances, conjugated (Premarin)</td>
<td>- for symptoms of menopause</td>
</tr>
<tr>
<td></td>
<td>- for atrophic vaginitis, kraurosis vulvae, female hypogonadism, primary ovarian failure, postpartum breast engorgement, osteoporosis, abnormal uterine bleeding from hormonal imbalance</td>
</tr>
<tr>
<td></td>
<td>- surgical castration</td>
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<tr>
<td><strong>Progestins</strong></td>
<td></td>
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<tr>
<td>medroxyprogesterone (Provera)</td>
<td>- for amenorrhea and abnormal uterine bleeding caused by hormonal imbalance</td>
</tr>
<tr>
<td></td>
<td>- cancer treatment</td>
</tr>
<tr>
<td><strong>Androgens</strong></td>
<td></td>
</tr>
<tr>
<td>fluoxymesterone</td>
<td>- hypogonadism and impotence due to testicular deficiency</td>
</tr>
<tr>
<td></td>
<td>- breast cancer</td>
</tr>
<tr>
<td></td>
<td>- postpartum breast engorgement</td>
</tr>
<tr>
<td>testosterone cypionate</td>
<td>- male hormone deficiency and male climacteric symptoms (period of lessening sexual activity)</td>
</tr>
<tr>
<td></td>
<td>- metastatic breast cancer in women</td>
</tr>
</tbody>
</table>
Indications for Use:
- for patients with estrogen deficiency, such as postmenopausal women
- for contraception in combination with progestins
- to prevent breast engorgement for women who aren't breast feeding
- for certain cancers such as breast and prostate cancer (see antineoplastic agents)
- other specific common usages common to most estrogens are:
  - atrophic vaginitis, female hypogonadism, surgical castration,
  - ovarian failure, menopausal symptoms, osteoporosis, abnormal
  uterine bleeding caused by hormonal imbalance

Mechanism of Action:
Estrogens bind to cytoplasmic receptors in estrogen-responsive tissues
of the female breast and genitourinary tract, and the resulting estrogen­
receptor complex is transported to the nucleus to stimulate the synthesis
of specific proteins.

Adverse Reactions:
- most reactions are mild
- increased risk of endometrial cancer
- increased incidence of gall bladder disease
- thromboembolisms
- hypertension

Ocular Adverse Reactions:
- increased myopia and astigmatism (steepens cornea)
- possible contact lens intolerance
- increased risk of retinal thrombosis and optic neuritis

Contraindications:
contraindicated in these cases unless used as a therapy for advanced
inoperable cancer in men or postmenopausal women:
- pregnancy or lactating women
- cases of thromboembolic disorders
- undiagnosed abnormal genital bleeding
- estrogen dependent cancer of breast or reproductive organs
use with caution in cases of:
- asthma, hypertension, congestive heart failure, migraine
  headaches, renal or hepatic insufficiency, mental depression,
  metabolic bone disease, blood dyscrasias, gall bladder disease,
  seizure disorders, diabetes mellitus, amenorrhea, family history of
  breast or genital cancer

Drug Interactions:
- minor decrease in estrogenic activity with concurrent use of:
  rifampin, barbiturates, carbamazepine, phenytoin, primidone
- the anticoagulant effect of bishydroxycoumarin is decreased
PROGESTINS

Indications for Use:
- used in a cyclic manner with estrogens to regulate or restore the menstrual cycle and treat uterine bleeding due to hormonal imbalance and endometriosis
- to treat endometrial or renal cancer, endometriosis and premenstrual syndrome (PMS)
- for oral contraception in combination with estrogens

Mechanism of Action:
progestins have pharmacological properties similar to those of natural progesterone, which acts to prepare the endometrium for pregnancy and the breasts for lactation. As a drug, it inhibits the release of pituitary gonadotropins and may inhibit spontaneous uterine contractions.

Adverse Reactions:
- when used for several months, ovulation may not resume for several months (amenorrhea)
- changes in vaginal bleeding patterns and menstrual flow
- edema
- less common: cervical erosions, abnormal secretions, uterine fibrosis, vaginal candidiasis, weight changes, mental depression, cholastic jaundice, melasma (skin discoloration)
- CNS reactions sometimes occur: migranes, dizziness, nervousness, insomnia, fatigue

Ocular Adverse Reactions:
rare except when used in higher concentrations as in oral contraceptives (see oral contraceptives)

Contraindications and Precautions:
- use during pregnancy can result in congenital fetal defects
- contraindicated in cases of thrombophlebitis, thromboembolism, pregnancy, lactating women, cancer of breasts or female reproductive organs (unless selected for palliative therapy), hepatic disease
- use cautiously in patients with asthma, cardiac or renal insufficiency, seizure disorders, migraine headaches, mental depression, diabetes mellitus (may need to adjust dosage)

Drug Interactions:
- none reported
ORAL CONTRACEPTIVES

Background Information:
most oral contraceptives are combinations of estrogens and progestins, but a few contain only progestin

Indications for Use:
for prevention of pregnancy

Mechanism of Action:
all inhibit the release of FSH and LH from the pituitary via negative feedback, thus preventing ovarian follicular development and ovulation.

Adverse Reactions:
- most are related to dose and estrogen content
- GI reactions: nausea is #1 reaction, vomiting, abdominal cramping, diarrhea, constipation
- facial hyperpigmentation, acne may improve or worsen
- hypertension and increased risk of myocardial infarction (MI)
- increased risk of thromboembolism
- cholesterol levels may go up or down depending on relative levels of estrogen and progestin
- can effect levels of several serum proteins produced by the liver
- increased risk of liver tumors and gall bladder disease
- hypersensitivity reactions

Ocular Adverse Reactions:
- increased myopia and astigmatism (steepens the cornea)
- possible contact lens intolerance

Contraindications and Precautions:
- contraindicated in lactating women, cases of thrombophlebitis, thromboembolic disorders, cerebrovascular or coronary artery disease, MI, cancer of the breast, reproductive organs or liver, abnormal vaginal bleeding
- also contraindicated in children, women over age 35 who smoke more than 15 cigarettes per day, and all women over age 40

Drug Interactions:
- antibacterials, barbiturates, carbamazepine, phenylbutazone, phenytoin, primidone, rifampin all decrease contraceptive efficacy and lead to breakthrough bleeding.
- oral contraceptives decrease oxidative metabolism of some benzo- diazepines and increase the glucuronide conjugation of others.
- decreases the metabolism of beta-adrenergic blocking agents
- enhances anti-inflammatory action of corticosteroids
ANDROGENS

Background Information:
The androgenic steroids stimulate the growth of male accessory sex organs and produce masculinizing effects, such as facial hair growth and voice deepening. The anabolic steroids promote a positive nitrogen balance in the body, which stimulates tissue building and reverses depletion. These are the "body building" drugs athletes take to increase muscle mass and shorten recovery time between workouts. In reality, all androgenic agents have some anabolic effects and all anabolic agents have some andronergic effects.

Indications for Use:
- for androgen replacement in castrated and hypogonadal males
- to prevent postpartum breast engorgement in non-breast feeding mothers
- to treat certain types of breast cancer

Mechanism of Action:
- bind to androgen receptors in target organs (skeletal muscle, prostate gland, bone marrow), stimulating development of these organs and increasing protein synthesis.
- anabolic effects occur by blocking cortisol uptake in muscles, thus reducing muscle breakdown and thereby increasing muscle mass; also by blocking cortisol uptake in the liver, it maximizes its effect on body stress (exercise) reactions.

Adverse Reactions:
- in women, a masculinizing reaction with long-term or high dose use
- in men, conversion steroids to female sex hormone metabolites in the body cause testicular atrophy, decreased levels of pituitary reproductive hormones, prostatic hypertrophy.
- in children, premature epiphyseal closure resulting in retarded growth
- premature development of secondary sex characteristics in boys
- toxicity to liver: jaundice, peliosis hepatitis, liver cancer
- increased serum cholesterol and decreased high-density lipoproteins predisposes patient to atherosclerotic heart disease
- increases serum calcium and causes sodium and water retention

Ocular Adverse Reactions:
- decreased vision, hypersensitivity reactions of the lids, diplopia, papilledema secondary to pseudotumor cerebri, and visual field defects have occurred with the use of these drugs
Contraindications and Precautions:
- contraindicated in pregnant women and children
- contraindicated in men with prostate cancer
- use with caution in cases of cardiac, renal or hepatic disorders

Drug Interactions:
- may increase effects of oral anticoagulants, insulin, and hypoglycemic agents
**Antihypertensives:**

**Sympatholytics**
- Central acting sympathetic nervous system inhibitors
  - △△ clonidine (Catapres) #152 drug in 1991
  - guanabenz
  - △△ guanfacine (Tenex) #144 drug in 1991
  - △ methylidopa (Aldomet)

**Ganglionic blocking agents**
- mecamylamine
- trimethaphan

**Beta-adrenergic blocking agents**
- △△ atenolol (Tenormin) #12 drug in 1991
- △△ metoprolol (Lopressor) #23 drug in 1991
- △△ nadolol (Corgard) #90 drug in 1991
- pindolol
- △△ propranolol (Inderal, propranolol) #41, #196 drugs in 1991
- △ timolol (Timoptic) #60 drug in 1991

**Alpha-adrenergic blocking agents**
- phentolamine
- △ prazosin (Minipress)
- △△ terazosin (Hytrin) #98 drug in 1991

**Mixed alpha- and beta-adrenergic blocking agents**
- △ labetolol (Normodyne)

**Noradrenergic depletors**
- guanadrel
- guanethidine
- △ reserpine (Serpasil)

**Vasodilating Agents**

**Direct vasodilators**
- △ diazoxide (Hyperstat)
- hydralazine
- △△ minoxidil (Rjogaine) #146 drug in 1991
- nitroprusside

**Calcium channel blockers**
- △△ diltiazem (Cardizem) #11 drug in 1991
- △△ nifedipine (Procardia) #9 drug in 1991
- △△ verapamil (Calan, Isoptin) #17, #106 drugs in 1991

**Angiotensin Antagonist Agents**
- △△ captopril (Capoten) #16 drug in 1991
- △△ enalapril (Vasotec) #10 drug in 1991
- △△ lisinopril (Zestil, Prinivil) #52, #66 drugs in 1991

" △△ " indicates a top 200 drug in 1991 -- note ranking after trade name
" △ " indicates major drugs -- see table
Indications for Use:
- antihypertensive agents treat hypertension by reducing blood pressure
- sympatholytics -- used to lower the blood pressure of patients with mild-
to-severe essential hypertension
- vasodilating agents -- used as adjuncts in the treatment of moderate to
severe hypertension, but seldom used as primary agents
- angiotensin antagonist agents -- recommended to treat hypertension in
  patients who fail to respond or have adverse reactions to other
  antihypertensives

<table>
<thead>
<tr>
<th>Major Drugs</th>
<th>Things to Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>clonidine (Catapres) #152</td>
<td>- central-acting nervous system inhibitor</td>
</tr>
<tr>
<td>drug in 1991</td>
<td>- used to treat mild to moderate hypertension</td>
</tr>
<tr>
<td></td>
<td>- used in combination with diuretic</td>
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<tr>
<td>methyldopa (Aldomet)</td>
<td>- central-acting nervous system inhibitor</td>
</tr>
<tr>
<td></td>
<td>- used orally for mild to moderate hypertension</td>
</tr>
<tr>
<td></td>
<td>- administered IV to treat hypertensive crisis</td>
</tr>
<tr>
<td></td>
<td>- adverse reactions -- sedation, bradycardia, nausea</td>
</tr>
<tr>
<td></td>
<td>- ocular adverse reactions -- conjunctivitis</td>
</tr>
<tr>
<td>metoprolol (Lopressor)</td>
<td>- beta-adrenergic blocking agent</td>
</tr>
<tr>
<td></td>
<td>- used alone or with other hypertensive drug</td>
</tr>
<tr>
<td></td>
<td>- used for hypertension, myocardial infarction,</td>
</tr>
<tr>
<td></td>
<td>angina pectoris</td>
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<tr>
<td>propranolol (Inderal,</td>
<td>- beta-adrenergic blocking agent</td>
</tr>
<tr>
<td>propranolol) #41 &amp; #196</td>
<td>- used to treat mild to moderate hypertension</td>
</tr>
<tr>
<td>drugs in 1991</td>
<td>- used orally alone or with other hypertensive</td>
</tr>
<tr>
<td></td>
<td>agents to reduce their adverse reactions</td>
</tr>
<tr>
<td>prazosin (Minipress)</td>
<td>- alpha-adrenergic blocking agent</td>
</tr>
<tr>
<td></td>
<td>- most effective in reduced doses with a thiazide</td>
</tr>
<tr>
<td></td>
<td>diuretic or a beta-adrenergic blocking agent</td>
</tr>
<tr>
<td>labetalol (Normodyne)</td>
<td>- mixed alpha- and beta-adrenergic blocking agent</td>
</tr>
<tr>
<td></td>
<td>- orally used to treat mild to severe hypertension</td>
</tr>
<tr>
<td></td>
<td>- usually well tolerated</td>
</tr>
<tr>
<td></td>
<td>- used IV to treat hypertensive crisis</td>
</tr>
<tr>
<td>diazoxide (Hyperstat)</td>
<td>- vasodilating agent, direct vasodilator</td>
</tr>
<tr>
<td></td>
<td>- used IV to treat hypertensive crisis</td>
</tr>
<tr>
<td></td>
<td>- can also be used to treat malignant hypertension</td>
</tr>
<tr>
<td>nifedipine (Procardia) #9</td>
<td>- vasodilating agent, calcium channel blocker</td>
</tr>
<tr>
<td>drug in 1991</td>
<td>- given orally to treat hypertension</td>
</tr>
<tr>
<td>captopril (Capoten) #16</td>
<td>- angiotensin antagonist agent</td>
</tr>
<tr>
<td>drug in 1991</td>
<td>- used to treat hypertension accompanied by high to</td>
</tr>
<tr>
<td></td>
<td>normal renin levels</td>
</tr>
<tr>
<td></td>
<td>- used to treat hypertension accompanied by low</td>
</tr>
<tr>
<td></td>
<td>renin levels but requires adjunctive thiazide</td>
</tr>
<tr>
<td></td>
<td>diuretics</td>
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</tbody>
</table>
SYMPATHOLYTIC AGENTS

Mechanism of Action:
- all act to inhibit or block stimulation of the sympathetic nervous system to produce decreased blood pressure from peripheral vasodilation or decreased cardiac output

Classified by site or mechanism of action
- central-acting sympathetic nervous system inhibitors
  - act in the CNS to reduce sympathetic activity and thereby decrease arteriolar vasoconstriction
- ganglionic blocking agents
  - interfere with transmission of sympathetic and parasympathetic nerve impulses through the ganglia
  - produce vasodilation to decrease the blood pressure
- beta-adrenergic blocking agents
  - compete with epinephrine for beta-receptor sites
  - antagonize the effect of epinephrine and blocks sympathetic stimulation, resulting in decreased cardiac output
- alpha-adrenergic blocking agents
  - act on sympathetic nervous system alpha receptors
  - prevent norepinephrine and epinephrine from occupying and activating the receptors
  - blocked sympathetic stimulation allows vasodilation to occur
- mixed alpha- and beta-adrenergic blocking agents
  - non-selectively block beta-adrenergic receptors
  - selectively block alpha₁ receptors
- norepinephrine depleters
  - interfere with synthesis, storage, and release of norepinephrine from nerve terminals
  - interference leads to loss of peripheral sympathetic tone, decreased peripheral resistance and reduced blood pressure

Adverse Reactions:
- central-acting and ganglionic blocking agents --
  - CNS effects -- sedation, drowsiness, depression
  - forgetfulness, vivid dreams, inability to concentrate
  - edema, vertigo, paresthesias, dry mouth, nasal congestion
  - may decrease libido and result in impotence
  - ocular adverse reaction to methyldopa -- conjunctivitis
Adverse Reactions (continued)

- beta-adrenergic blocking agents --
  - CNS effects -- sedation, drowsiness, depression
  - cardiovascular -- bradycardia, hypotension, congestive heart failure, asthma
  - nausea, vomiting diarrhea, nightmares, depression, insomnia, hallucinations
  - dry eyes, paresthesias, sore throat, breathing difficulty

- alpha-adrenergic blocking agents--
  - prazosin -- orthostatic hypotension, first-dose syncope
  - phentolamine -- anginal attacks from rebound tachycardia; hypotension, dizziness, weakness, flushing, palpitations, diarrhea, nausea, vomiting, nasal congestion

- mixed alpha- and beta-adrenergic blocking agents --
  - labetalol --
    - resembles those of the beta-adrenergic blocking agents
    - other reactions include scalp tingling, alopecia, orthostatic hypotension, eye irritation, myalgia, rash

- norepinephrine depletors --
  - produce a wide range of adverse reactions
  - reserpine --
    - drowsiness, sleep alterations, weight gain, nasal congestion, abdominal cramps, diarrhea
    - nightmares, depression, bronchoconstriction

Ocular Adverse Reactions:
- central -acting sympathetic nervous system inhibitors
  - decreased vision, decreased intraocular pressure, urticaria of eyelids or conjunctiva
  - with clonidine -- visual hallucinations, decreased lacrimation
  - with methyldopa -- allergic reactions and hyperemia of eyelids or conjunctiva, subconjunctival or retinal hemorrhages secondary to drug-induced anemia, paralysis of extraocular muscles

- ganglionic blocking agents
  - decreased vision, mydriasis may precipitate narrow-angle glaucoma, paralysis of accommodation, conjunctival edema, decreased intraocular pressure
Sympatholytic Agents (Ocular Adverse Reactions (continued))

- beta-adrenergic blocking agents
  - with atenolol, metoprolol, nadolol, pindolol (systemic use) -- decreased vision, visual hallucinations, decreased intraocular pressure, hyperemia and erythema of eyelids or conjunctiva
  - with propranolol (systemic use) -- diplopia, decreased vision, allergic reactions and erythema of eyelids or conjunctiva, decreased intraocular pressure, visual hallucinations, decreased lacrimation
  - with timolol (systemic use) -- decreased vision, allergic reactions and erythema of eyelids or conjunctiva, decreased intraocular pressure, visual hallucinations, decreased lacrimation

- alpha-adrenergic blocking agents (systemic use)
  - decreased vision, scleritis, erythema and edema of eyelids or conjunctiva, conjunctivitis, visual hallucinations

- mixed alpha- and beta-adrenergic blocking agents
  - labetalol -- decreased vision, visual hallucinations, decreased intraocular pressure, hyperemia and erythema of eyelids or conjunctiva, photophobia, ptosis, decreased lacrimation

- noripinephrine depletors
  - conjunctival hyperemia, Horner's syndrome, lacrimation, oculogyric crises, decreased vision, retinal hemorrhages, decreased intraocular pressure

Contraindications:

- check cardiac function when using antihypertensive agents in a patient with angina or coronary insufficiency due to adverse reaction risks
- central-acting nervous system inhibitors -- use cautiously in patient with coronary insufficiency, recent MI, cerebrovascular disease, or severe hepatic or renal impairment due to risks of adverse effects
- beta-adrenergic blocking agents are contraindicated for patients with asthma or emphysema and used with extreme caution in patients with heart failure or hepatic or renal impairment
- before initiating norepinephrine-depletor therapy, note patient's history of mental, cardiovascular, cerebral, renal, and GI diseases

Drug Interactions:
- sympatholytic agents can interact with many drugs to produce blood pressure changes as well as other severe reaction
VASODILATING AGENTS

Mechanism of Action:
- direct vasodilators and calcium channel blockers both decrease systolic and diastolic blood pressure by relaxing arteriolar smooth muscle, leading to arteriolar dilation and decreasing peripheral resistance
  - direct vasodilators --
    - relax peripheral vascular smooth muscles
    - lower blood pressure by increasing blood vessel caliber and reducing total peripheral resistance
  - calcium channel blockers
    - prevent calcium transport across cell membrane
    - reduces activity of vascular smooth muscle, thus producing vasodilation and lowering the blood pressure

Adverse Reactions:
- direct vasodilators --
  - palpitations, angina, tachycardia, increased myocardial work load, EKG changes, edema, fatigue, headache, rash
- calcium channel blockers --
  - hypotension, bradycardia, flushing, palpitations, tremors, insomnia, headache

Ocular Adverse Reactions:
- direct vasodilators --
  - diazoxide -- lacrimation, allergic reactions of eyelids or conjunctiva, decreased vision, oculogyric crises, cataracts, ring scotomas, diplopia
  - minoxidil -- hyperemia or erythema of eyelids or conjunctiva, conjunctivitis (nonspecific), hyperpigmentation, decreased vision
- calcium channel blockers --
  - decreased vision, erythema of eyelids or conjunctiva, photosensitivity, visual hallucinations, lacrimation, rotary nystagmus

Contraindications:
- direct vasodilators are contraindicated in patients with congestive heart failure, myocardial infarction, or pheochromocytoma
  - diazoxide --
    - use cautiously in cases of impaired ventricular function, congestive heart failure, conduction abnormalities, or impaired renal or hepatic function

Drug Interactions:
- hydralazine and minoxidil produce additive effects when given with other antihypertensive drugs
- nifedipine may promote digitalis toxicity when given with digitalis
- few other drug interactions occur with the vasodilating agents
ANGIOTENSIN ANTAGONIST AGENTS

Mechanism of Action:
- interfere with the renin-angiotensin-aldosterone system by inhibiting the enzyme that converts angiotensin I to angiotensin II
- inhibition of the enzyme decreases aldosterone release by the adrenal cortex to prevent sodium and water retention
- the inhibition also reduces peripheral arterial resistance without affecting the heart rate and CO
- the result of the inhibition is a reduced blood pressure

Adverse Reactions:
- angiotensin antagonists can produce a wide range of mild to severe adverse reactions
- captopril --
  - proteinuria, neutropenia, agranulocytosis, rash, pruritus, fever
  - orthostatic hypotension, chest pain

Ocular Adverse Reactions:
- (with systemic use) -- decreased vision, decreased intraocular pressure, angioneurotic edema of eyelids or conjunctiva, nonspecific ocular burning irritation, visual hallucinations, decreased lacrimation

Contraindications:
- use cautiously in a patient with a history of impaired renal function, autoimmune disease, or exposure to a drug that affects the white blood cell count or the immune system

Drug Interactions:
- captopril enhances hypotensive effects of diuretics and other antihypertensives
- lisinopril --
  - significant hypotension occurs when added to diuretic therapy
Agents used to treat congestive heart failure

**Cardiac Glycosides**
- ΔΔ digoxin (Lanoxin) #4 drug in 1991
- Δ digitoxin (Crystodigin)

**Bipyridines**
- Δ amrinone (Inocor)

**Vasodilating Agents**
- direct vasodilators
  - diazoxide
  - Δ hydralazine (Apresoline)
- ΔΔ minoxidil (Rogaine) #146 drug in 1991
- Δ nitroprusside (Nipride)

**Calcium channel blockers**
- ΔΔ diltiazem (Cardizem) #11 drug in 1991
- ΔΔ nifedipine (Procardia) #9 drug in 1991
- ΔΔ verapamil (Calar, Isoptin) #17, #106 drugs in 1991

"ΔΔ" indicates a top 200 drug in 1991 -- note ranking after trade name
"Δ" indicates major drugs -- see table

**Indications for Use:**
- cardiac glycosides --
  - provide primary benefit to patients with failing hearts by increasing contractility which directly increases cardiac output
  - used primarily to treat congestive heart failure and atrial dysrhythmias
  - useful in treating CHF associated with low cardiac output caused by ischemic, hypertensive, rheumatic, or congenital heart disease
  - beneficial in atrial tachycardia and fibrillation since they increase the refractoriness of the AV node, thereby slowing the ventricular response rate

- bipyridines -- positive inotropic agents for the short-term management of CHF in patients who have not responded adequately to treatment with digitalis, diuretics, and vasodilators

- vasodilating agents -- used as adjuncts in the treatment of moderate to severe hypertension, but seldom used as primary agents
**Mechanism of Action:**
- In patients with edema resulting from CHF, cardiac glycosides increase myocardial contractility and cardiac output, slowing heart rate and causing diuresis.
- Increased myocardial contractility with reduced ventricular end-diastolic pressure cause a decrease or no change in myocardial oxygen consumption — coronary blood flow remains unaffected.

**Adverse Reactions:**
- Digitalis toxicity occurs in 8% to 35% of hospitalized patients and in 18% of those on therapy in extended-care facilities.
- GI reactions — anorexia, nausea, vomiting, diarrhea, abdominal pain.
- Neurologic reactions — headache, restlessness, irritability, depression, confusion.
- Cardiac reactions — onset of bradycardia, onset of tachycardia, onset of regularity, onset of irregularity.

**Ocular Adverse Reactions:**
- Blurred or yellow vision.
- Flickering lights.
- White borders on dark objects.
- Colored dots.

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**CARDIAC GLYCOSIDES**

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**Major Drugs** | **Things to Know**
--- | ---
Digoxin (Lanoxin) #4 drug in 1991 | Used to treat congestive heart failure and supraventricular dysrhythmias.
Digitoxin (Crystodigin) | Used to treat congestive heart failure and supraventricular dysrhythmias.
Amrinone (Inocor) | Used for congestive heart failure not responding to digitalis preparations, diuretics, or vasodilators.
Hydralazine (Apresoline) | Direct vasodilator. An adjunct to treat malignant hypertension complicated by congestive heart failure. May be used to treat hypertensive crisis.
Nitroprusside (Nipride) | Direct vasodilator. Used in hypertensive crisis for rapid reduction of blood pressure. Preferred over diazoxide in CHF patients because it doesn’t produce water and sodium retention.
CARDIAC GLYCOSIDES (continued)

Contraindications:
- use with extreme caution in patients with hypothyroidism, renal or liver failure, hypokalemia, hypercalcemia
- during cardiac glycoside therapy, patients have a decreased threshold for ventricular dysrhythmia -- use antiarrhythmics to treat digitalis-induced ventricular dysrhythmias

Drug Interactions:
- cardiac glycosides interact with several drugs and some foods
  - may produce decreased digitalis effect, increased effect, or dysrhythmias
  - decreased dietary potassium increases the chance of digitalis toxicity

BIPYRIDINES

Mechanism of Action:
- improves cardiac output by increasing contractility and decreasing systemic vascular resistance and venous return
- probably increases intracellular cAMP levels which facilitates calcium entry
- only effect on the conduction system is to facilitate AV nodal conduction

Adverse Reactions:
- occur infrequently and only in patients receiving prolonged therapy
  - dysrhythmias, thrombocytopenia, nausea, vomiting, abdominal pain

Ocular Adverse Reactions:
- none listed

Contraindications:
- contraindicated in patients hypersensitive to amrinone or to bisulfite (a preservative used in amrinone solution)
- contraindicated in patients with severe aortic or pulmonic valvular disease

Drug Interactions:
- amrinone interacts negatively with disopyramide (Norpace)
  -- concurrent administration results in hypotension and dysrhythmias
- patients receiving cardiac glycosides can receive amrinone since the combination may increase ventricular response rates due to enhancement of AV conduction
VASODILATING AGENTS

Mechanism of Action:
- direct vasodilators and calcium channel blockers both decrease systolic and diastolic blood pressure by relaxing arteriolar smooth muscle, leading to arteriolar dilation and decreasing peripheral resistance
- direct vasodilators --
  - relax peripheral vascular smooth muscles
  - lower blood pressure by increasing blood vessel caliber and reducing total peripheral resistance
- calcium channel blockers
  - prevent calcium transport across cell membrane
  - reduces activity of vascular smooth muscle, thus producing vasodilation and lowering the blood pressure

Adverse Reactions:
- direct vasodilators --
  - palpitations, angina, tachycardia, increased myocardial work load, EKG changes, edema, fatigue, headache, rash
- calcium channel blockers --
  - hypotension, bradycardia, flushing, palpitations, tremors, insomnia, headache

Ocular Adverse Reactions:
- direct vasodilators --
  - diazoxide -- lacrimation, allergic reactions of eyelids or conjunctiva, decreased vision, oculogyric crises, cataracts, ring scotomas, diplopia
  - minoxidil -- hyperemia or erythema of eyelids or conjunctiva, conjunctivitis (nonspecific), hyperpigmentation, decreased vision
- calcium channel blockers --
  - decreased vision, erythema of eyelids or conjunctiva, photosensitivity, visual hallucinations, lacrimation, rotary nystagmus

Contraindications:
- direct vasodilators are contraindicated in patients with congestive heart failure, myocardial infarction, or pheochromocytoma
  -- however exceptions exist for the two following drugs
    - hydralazine is indicated as an adjunct in treatment of hypertension complicated by CHF
    - nitroprusside is preferred over diazoxide in patients with CHF because it doesn't produce water retention
- diazoxide --
  - use cautiously in cases of impaired ventricular function, congestive heart failure, conduction abnormalities, or impaired renal or hepatic function
VASODILATING AGENTS (continued)

Drug Interactions:
- hydralazine and minoxidil produce additive effects when given with other antihypertensive drugs
- nifedipine may promote digitalis toxicity when given with digitalis
- few other drug interactions occur with the vasodilating agents
Antiarrhythmic Agents

**Class IA Antiarrhythmics**
- △△ disopyramide (Norpace) #168 drug in 1991
- △△ procainamide (Procan) #147 drug in 1991
- △ quinidine (Quinaglute)

**Class IB Antiarrhythmics**
- △ lidocaine (Xylocaine)
- tocainide
- mexiletine

**Class IC Antiarrhythmics**
- △ flecainide (Tambocor)
- encaïnide

**Class II Antiarrhythmics**
- △△ propranolol (Inderol) #3 drug in 1991
- acebutolol
- esmolol

**Class III Antiarrhythmics**
- bretylium
- △ amiodarone (Cordarone)

**Class IV Antiarrhythmics**
- △△ verapamil (Calan) #122 drug in 1991

" △△ " indicates a top 200 drug in 1991 -- note ranking after trade name
" △ " indicates major drugs -- see table
Indications for Use:

- antiarrhythmic agents limit cardiac electrical activity to normal conduction pathways, reduce automaticity, and decrease abnormally fast heart rates

- class IA antiarrhythmics --
  - used to treat a variety of atrial and ventricular dysrhythmias

- class IB antiarrhythmics --
  - used to treat ventricular ectopic beats (electrical stimulation of cardiac contraction beginning at a point other than the sinoatrial node), ventricular tachycardia, and ventricular fibrillation
  - drugs of choice in acute care setting since they produce fewer serious adverse reactions

- class IC antiarrhythmics --
  - used to treat ventricular dysrhythmias

- class II antiarrhythmics --
  - usually not the first drugs of choice to treat dysrhythmias because of the multiple effects of the drugs and possible breakthrough ectopy

- class III antiarrhythmics --
  - used to treat serious, life-threatening ventricular dysrhythmias
  - because of their adverse reactions class III drugs are not the first choices for antiarrhythmic therapy

- class IV antiarrhythmics --
  - used to treat supraventricular dysrhythmias with rapid ventricular response rates
<table>
<thead>
<tr>
<th>Major Drugs</th>
<th>Things to Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>disopyramide (Norpace)</td>
<td>- class IA antiarrhythmic</td>
</tr>
<tr>
<td>#168 drug in 1991</td>
<td>- suppresses ventricular ectopic beats and ventricular tachycardia</td>
</tr>
<tr>
<td>procainamide (Procan)</td>
<td>- class IA antiarrhythmic</td>
</tr>
<tr>
<td>#147 drug in 1991</td>
<td>- used to prevent recurrence of atrial fibrillation</td>
</tr>
<tr>
<td></td>
<td>- suppresses ventricular ectopic beats</td>
</tr>
<tr>
<td></td>
<td>- suppresses frequency and duration of atrial and ventricular tachycardia</td>
</tr>
<tr>
<td>quinidine (Quinaglute)</td>
<td>- class IA antiarrhythmic</td>
</tr>
<tr>
<td></td>
<td>- converts atrial fibrillation to normal sinus rhythm</td>
</tr>
<tr>
<td></td>
<td>- suppresses atrial and ventricular ectopic beats</td>
</tr>
<tr>
<td>lidocaine (Xylocaine)</td>
<td>- class IB antiarrhythmic</td>
</tr>
<tr>
<td></td>
<td>- used to suppress ventricular ectopic beats</td>
</tr>
<tr>
<td></td>
<td>- used for conversion and prevention of ventricular tachycardia</td>
</tr>
<tr>
<td>flecainide (Tambocor)</td>
<td>- class IC antiarrhythmic</td>
</tr>
<tr>
<td></td>
<td>- used to suppress frequent ventricular ectopy and acute self-limiting ventricular tachycardia</td>
</tr>
<tr>
<td>propranolol (Inderal)</td>
<td>- class II antiarrhythmic beta-adrenergic blocker</td>
</tr>
<tr>
<td>#3 drug in 1991</td>
<td>- effective in a variety of dysrhythmias including atrial and ventricular ectopy</td>
</tr>
<tr>
<td></td>
<td>- treatment of acute self-limiting atrial or ventricular tachycardia</td>
</tr>
<tr>
<td>amiodarone (Cordarone)</td>
<td>- class III antiarrhythmic</td>
</tr>
<tr>
<td></td>
<td>- used to prevent ventricular ectopy</td>
</tr>
<tr>
<td></td>
<td>- used to reduce ventricular tachycardia when unresponsive to other antiarrhythmic treatment</td>
</tr>
<tr>
<td>verapamil (Calan)</td>
<td>- class IV antiarrhythmic</td>
</tr>
<tr>
<td>#122 drug in 1991</td>
<td>- calcium channel blocker</td>
</tr>
<tr>
<td></td>
<td>- used to correct paroxysmal supraventricular tachycardia caused by reentry into the atria or the AV node</td>
</tr>
</tbody>
</table>
CLASS IA ANTIARRHYTHMICS

Mechanism of Action:
- exert their effects by altering the myocardial cell membrane and interfering with autonomic nervous system control of pacemaker cells
- partially block fast channel in myocardial cell membrane to reduce the influx of sodium ions
- the influx reduction alters the action potential by depressing the rate of depolarization and prolonging the plateau and repolarization
- these changes reduce the speed of conductivity and increase the effective refractory period

Adverse Reactions:
- tinnitus, headache, vertigo, fever, light-headedness
- anticholinergic effects -- dry mouth, constipation, heart failure, hypotension, chest pain, blurred vision

Ocular adverse reactions
- with disopyramide
  - blurred vision and dry eyes in up to 3-9% of patients due to anticholinergic activity
  - mydriasis with increased IOP also possible in narrow angles
- with quinidine
  - ocular effects are rare and reversible with discontinuance of drug but the list is long and many are due to anticholinergic actions
  - decreased vision, altered color vision, mydriasis, scotomas, constricted visual fields, photophobia, diplopia, night blindness, allergic reactions, of lids and conjunctiva, hemorrhaging, optic neuritis, uveitis, and myasthenic effects

Contraindications:
- contraindicated in patients with congenital prolonged Q-T interval
- use cautiously in patients with congestive heart failure, hypotension, myasthenia gravis

Drug Interactions:
- may exhibit additive or antagonistic effects with other antiarrhythmics as well as with anticholinergic and antihypertensive drugs
CLASS IB ANTIARRHYTHMICS

Mechanism of Action:
- decrease the action potential depolarization (APD) and the effective refractory period (ERP), especially of the Purkinje fibers and myocardial cells in the ventricles
- shortening the ERP eliminates unidirectional block which can otherwise act to trigger a reentry dysrhythmia
- block the slow influx of sodium during plateau (phase 2) to decrease ventricular ectopy

Adverse Reactions:
- CNS reactions -- drowsiness, confusion, light-headedness, slurred speech, tremors

Ocular Adverse Reactions:
- blurred or double vision

Contraindications:
- contraindicated in patients with 2nd or 3rd degree heart block
- lidocaine and tocainide contraindicated in patients with hypersensitivity to local anesthetics

Drug Interactions:
- may exhibit additive or antagonistic effects when administered with other antiarrhythmics
- lidocaine toxicity may result from concurrent administration of propranolol or cimetidine
CLASSIC ANTIARRHYTHMICS

Mechanism of Action:
- block influx of sodium in the cell membrane fast channel to decrease depolarization (phase 0 of the action potential)
- delays intracardial conduction in the ventricles causing conversion of unidirectional block into bidirectional block thereby interrupting reentry patterns

Adverse Reactions:
- serious reactions have been noted which may limit class IC antiarrhythmic use
- CNS effects -- dizziness, headache, blurred vision
- with flecainide --
  - produces a negative inotropic effect (negative effect on the force of muscular contractility) and may worsen congestive heart failure
  - nausea, anorexia, vomiting, dyspepsia (imperfect or painful digestion), isolated numbness

Ocular Adverse Reactions:
- blurred vision

Contraindications:
- contraindicated in patients with 2nd or 3rd degree heart block, cardiogenic shock, or hypokalemia (extreme potassium depletion in circulating blood)

Drug Interactions:
- concurrent administration of flecainide and digoxin may increase the serum digoxin level, leading to digitalis toxicity
- interactions of flecainide with alkalinizing drugs and cimetidine may produce increased adverse reactions to flecainide
CLASS II ANTIARRHYTHMICS

Mechanism of Action:
- suppress dysrhythmias by several different mechanisms of action
- block receptor sites in the conduction system of the heart slowing both SA node automaticity and conductivity of the AV node
  - the effects convert unidirectional block to bidirectional block
- exert an inotropic effect and decreases myocardial oxygen demand

Adverse Reactions:
- bradycardia, hypotension, syncope
- may exacerbate or precipitate congestive heart failure
- CNS reactions -- dizziness, confusion, fatigue, decreased libido
- transient nausea, vomiting

Ocular adverse Reactions:
- rare or transient
- may include diplopia, decreased vision, allergic reactions of conjunctiva and lids, decreased IOP, and visual hallucinations
- some evidence for a KCS-like syndrome

Contraindications:
- contraindicated in patients with asthma, sinus bradycardia, 2nd or 3rd degree heart block, diabetes mellitus
- use cautiously in patients with congestive heart failure or chronic obstructive pulmonary disease

Drug Interactions:
- interaction with phenothiazines and antihypertensive drugs may potentiate hypotension
CLASS III ANTIARRHYTHMICS

Mechanism of Action:
- prolong action potential depolarization (APD) and effective refractory period (ERP) of myocardial cells to decrease the rate of automaticity of ventricular ectopic beats

Adverse Reactions:
- many adverse reactions -- often lead to discontinuation of the drug
- cardiovascular adverse reactions --
  - bradycardia -- usually responds to dosage reduction but may require a pacemaker
  - CHF -- requires drug discontinuation
- hypotension, nausea, anorexia
- CNS reactions -- fatigue, tremors, malaise

Ocular Adverse Reactions:
- asymptomatic corneal microdeposits are present in nearly all adult patients who have been on therapy for more than 6 months
- some patients develop symptoms of halos, photophobia, and dry eyes

Contraindications:
- use amiodarone cautiously in patients with preexisting bradycardia, sinus node disease, conduction disturbances
- use bretylium cautiously in patients with digitalis-induced dysrhythmias, aortic stenosis (narrowing of the aorta), or pulmonary hypertension

Drug Interactions:
- interactions with other cardiovascular drugs produce varying effects
  - hypotension, hypoprothrombinemia (deficiency of blood clotting factor II), increased serum digoxin levels
CLASS IV ANTIARRHYTMICS

Mechanism of Action:
- blocks the influx of calcium across slow channels of myocardial electrical cells during plateau (phase 2) and depolarization (phase 4) of the action potential
- the blockade increases the effective refractory period (ERP) of the AV node and slows the conduction rate between the atria and the ventricles

Adverse Reactions:
- causes serious alterations in the cardiovascular system
  - orthostatic hypotension, bradycardia, sinus block, AV block
  - depresses myocardial contraction force which may precipitate or exacerbate congestive heart failure
- dizziness, headache, flushing, weakness, persistent peripheral edema

Ocular Adverse Reactions:
- few reported with this class of agents and most have been transient and of little significance
- blurred vision has been reported in less than 0.5% of patients

Contraindications:
- use cautiously in patients with hypotension, congestive heart failure, sick sinus syndrome (see below), AV conduction disturbances, hepatic impairment
  - sick sinus syndrome --
    - several electrocardiographic abnormalities due to malfunction of the sinoatrial node of the heart
    - may include persistent sinus bradycardia that may alternate with tachyarrhythmias; sinoatrial block; and sinus arrest

Drug Interactions:
- interactions with antihypertensives may potentiate hypotension and heart failure
- interactions with digoxin may produce an increased serum digoxin level resulting in digitalis toxicity (nausea and vomiting, irregular pulse, diarrhea, yellow vision, and frequently a distressing headache)
- interactions with other highly protein-bound drugs can cause adverse reactions associated with either verapamil or the other interacting drugs
ANTIARRHYTHMICS: GLOSSARY

aortic stenosis — narrowing of the aorta

bidirectional block —

congestive heart failure — condition of weakness, breathlessness, abdominal discomfort, edema in lower portions of body resulting from venous stasis and reduced outflow of blood from the left side of the heart

digitalis toxicity — symptoms include nausea and vomiting, irregular pulse, diarrhea, yellow vision, and frequently a distressing headache

ectopic beats — electrical stimulation of cardiac contraction beginning at a point other than the sinoatrial node

fibrillation — (atrial) extremely rapid, incomplete contractions of the atria resulting in fine, rapid, irregular, and uncoordinated movements (ventricular) condition similar to atrial fibrillation, resulting in rapid, tremulous, and ineffectual contractions of the ventricles

heart block — Condition in which the conductile tissue of the heart, the sinoatrial (S-A) and atrioventricular (A-V) nodes, bundle of His, Purkinje fibers, fails to conduct impulses normally from the atrium to the ventricles. This causes altered rhythm of the heartbeat (known as arrhythmia).

hypoprothrombinemia — deficiency of blood clotting factor II

negative inotropic effect — negative effect on the force of muscular contractility

paroxysmal supraventricular tachycardia — condition in which the heart rate suddenly increases to 100 to 200 beats/min and 1:1 A-V conduction is maintained

Q - T interval — portion of cardiac complex on the ECG that extends from the beginning of the Q wave and ends with the end of the T wave

reentry dysrhythmia — Diversion of a repolarization wave going in one direction where it is blocked to another direction where it is not blocked. The wave then goes back up the pathway that was blocked but is no longer blocked to produce a contraction. This leads to a continuing series of premature beats.

refractory period — Brief period of relaxation of a muscle during which excitability is depressed. If stimulated, it will respond, but a stronger stimulus is required and response is less.

sick sinus syndrome — several electrocardiographic abnormalities due to malfunction of the sinoatrial node of the heart — may include persistent sinus bradycardia that may alternate with tachyarrhythmias; sinoatrial block; and sinus arrest (symptoms include lightheadedness, dizziness, and syncope)

sinus block — Heart block in which there is interference in the passage of impulses from the sinoatrial node. (See "heart block" above)

sinus node disease — See "sick sinus syndrome" above

unidirectional block —
ANTIANGINAL AGENTS

Antianginal Agents

Nitrates

erthyrryl

\( \Delta \Delta \) isosorbide (Isordil) #147 drug in 1991

\( \Delta \Delta \) nitroglycerin (Nitrostat, Transderm-Nitro, Nitro-Dur II)

#61, #111, #126 drugs in 1991

pentaerythritol

Beta-adrenergic Blockers

\( \Delta \Delta \) propranolol (Inderal, Propranolol) #41, #196 drugs in 1991

\( \Delta \Delta \) metoprolol (Lopressor) #23 drug in 1991

\( \Delta \Delta \) nadolol (Corgard) #90 drug in 1991

\( \Delta \Delta \) atenolol (Tenormin) #12 drug in 1991

Calcium Channel Blockers

\( \Delta \Delta \) diltiazem (Cardizem) #11 drug in 1991

\( \Delta \Delta \) nifedipine (Procardia) #9 drug in 1991

\( \Delta \Delta \) verapamil (Calan, Isoptin) #17, #106i drug in 1991

" \( \Delta \Delta \) " indicates a top 200 drug in 1991 -- note ranking after trade name

" \( \Delta \) " indicates major drugs -- see table

Indications for Use:

- angina occurs when the myocardial oxygen demand exceeds the myocardial oxygen supply
- the antianginal agents treat angina by reducing myocardial oxygen demand, by increasing myocardial oxygen supply, or by both mechanisms

- nitrates --
  - for immediate relief of angina, prevention of angina when an attack can be expected, and long-term prevention of chronic angina

- beta-adrenergic blockers --
  - indicated for long-term prevention of angina, but not for immediate relief of an angina attack or prevention of an imminent one

- calcium channel blockers --
  - indicated only for the long-term relief of angina
  - drug of choice for Prinzmetal's angina
NITRATES

Mechanism of Action:
- act primarily as vasodilators directly on vascular smooth muscle to reduce the degree of vasoconstriction
- act primarily on venous but also somewhat on arterial smooth muscle
- because the veins dilate, less blood is returned to the heart and the volume of blood in the ventricles at the end of diastole is decreased
- by decreasing preload, nitrates reduce the myocardial demand for oxygen needed to pump blood out of the ventricles

Adverse Reactions:
- headache caused by blood vessel dilation in the meningeal layers between the brain and the skull
- hypotension due to the decreased afterload produced by arteriolar dilation
- symptoms of hypotension --
  - syncope, dizziness, weakness, clammy skin, clammy skin, nausea, vomiting
- tachycardia, up to 150 or more beats per minute, may occur to compensate for the hypotension but the shortened diastolic time that results does not allow for adequate filling of the ventricles so cardiac output is further reduced

Ocular Adverse Reactions:
- isosorbide -- with systemic administration
  - decreased intraocular pressure, decreased vision, subconjunctival or retinal hemorrhages, visual hallucinations, edema and urticaria of eyelids or conjunctiva
- nitroglycerin -- with systemic administration
  - decreased vision, decreased intraocular pressure, retinal vasodilatation, colored (yellow or blue) haloes around lights, exfoliative dermatitis of eyelids, subconjunctival or retinal hemorrhages secondary to drug-induced anemia
NITRATES (continued)

Contraindications:
- contraindicated for patients with angina from hypertrophic cardiomyopathy -- the drugs may actually aggravate this type of angina
- contraindicated for patients with head trauma or increased intracranial pressure

Drug Interactions:
- hypotension results when nitrates interact with other antianginal and antihypertensive drugs
- delayed absorption across the oral membrane may occur when the patient's mouth is dry from using a drug with anticholinergic effects, such as an antimuscarinic, a tricyclic antidepressant, a phenothiazine, or an antiparkinsonian drug

BETA-ADRENERGIC BLOCKERS

Mechanism of Action:
- compete with epinephrine for beta-receptor sites and block sympathetic stimulation, resulting in decreased cardiac output and decreased blood pressure reducing the heart's oxygen requirements

Adverse Reactions:
- can cause bradycardia and hypotension with peripheral vascular insufficiency due to inhibition of sinus node stimulation
- congestive heart failure may be exacerbated or precipitated due to decreased force of myocardial contractility
- CNS reactions -- dizziness, fatigue, lethargy, decreased libido
- GI reactions -- nausea, vomiting, diarrhea are usually transient

Ocular Adverse Reactions:
- with atenolol, metoprolol, nadolol (systemic use) -- decreased vision, visual hallucinations, decreased intraocular pressure, hyperemia and erythema of eyelids or conjunctiva
- with propranolol (systemic use) -- diplopia, decreased vision, allergic reactions and erythema of eyelids or conjunctiva, decreased intraocular pressure, visual hallucinations, decreased lacrimation

Contraindications:
- usually contraindicated for patients with asthma, sinus bradycardia, 2nd or 3rd degree heart block, cardiogenic shock, peripheral vascular disease
- never discontinue abruptly
- use cautiously in patients with diabetes mellitus, congestive heart failure, or chronic obstructive pulmonary disease
BETA-ADRENERGIC BLOCKERS (continued)

Drug Interactions:
- alter insulin and oral hypoglycimic agent requirements
- effect of slowing the heart is additive when administered concurrently with digoxin
- increased hypotension may result when administered concurrently with antiarrhythmics, antihypertensives, or phenothiazines
- aminophylline antagonizes beta-adrenergic blockers

CALCIUM CHANNEL BLOCKERS

Mechanism of Action:
- block the flow of calcium ions into myocardial and vascular smooth muscle cells to inhibit the intracellular release of additional stores of calcium ions
- decreases force of myocardial contractility, thereby decreasing oxygen demand
- prevent entry of calcium ions into arteriolar smooth muscle cells to decrease arteriolar constriction and systemic vascular resistance
- this decreasing systemic vascular resistance also decreases myocardia oxygen demand
- increase oxygen supply to the myocardium by dilating the coronary arteries

Adverse Reactions:
- hypotension, including orthostatic hypotension
- bradycardia, sinus block, AV block result from inhibition of the sinus and AV nodes
- dizziness, headache, flushing, weakness can all be produced due to the vasodilation
- GI disturbances -- nausea, vomiting, diarrhea, cramps

Ocular Adverse Reactions:
- decreased vision, erythema of eyelids or conjunctiva, photosensitivity, visual hallucinations, lacrimation, rotary nystagmus

Contraindications:
- use cautiously in patients with hypotension, congestive heart failure, sick sinus syndrome, or AV conduction disturbances

Drug Interactions:
- may interact with beta-adrenergic blockers, causing heart block or even congestive heart failure
- may displace protein-bound digoxin resulting in digoxin toxicity
**ANTICOAGULANTS AND THROMBOLYTICS**

**Anticoagulant Agents**

**Parenteral Anticoagulant**
- heparin

**Oral Anticoagulants**
- warfarin (Coumadin) #43 drug in 1991
- dicumarol (Dicumarol Pulvules)
- phenprocoumon
- anisindione

**Antiplatelet Drugs**
- aspirin (Bayer)
- dipyridamole Persantine, Dipyridamole) #140, #153 drugs in 1991
- sulfinpyrazone

**Thrombolytic Agents**
- streptokinase (Kabikinase)
- urokinase (Abbokinase)
- alteplase

"\(\Delta\)\(\Delta\)" indicates a top 200 drug in 1991 -- note ranking after trade name
"\(\Delta\)" indicates major drugs -- see table

**Indications for Use:**
- anticoagulant drugs are used to reduce clotting and prevent further coagulation in high-risk patients
  - parenteral anticoagulants (heparin) --
    - used to prevent clot formation and treat thromboembolism
    - also used whenever the patient’s blood must circulate outside the body through a machine, such as in open-heart surgery
    - heparin cannot dissolve clots, an action performed by the body’s own fibrinolytic system or hastened by thrombolytic agents
  - oral anticoagulants --
    - used to treat thromboembolism after initial treatment with heparin
    - drugs of choice for the prophylactic therapy of deep vein thrombosis and for patients with prosthetic heart valves or diseased mitral valve
  - antiplatelet drugs --
    - currently under investigation because evidence exists that platelet aggregation significantly promotes atherosclerotic plaque development
    - at injured endothelial sites, platelet aggregation and subsequent fibrin formation can create arterial clots
    - the patient’s bleeding time and platelet aggregation studies can measure the effectiveness of the antiplatelet ability of these agents
**Indications for Use:** (continued)

- thrombolytic agents --
  - drugs of choice to break down newly formed thrombi
  - have been used to dissolve thrombi in arteriovenous cannulas to reestablish blood flow

<table>
<thead>
<tr>
<th>Major Drugs</th>
<th>Things to Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>heparin</td>
<td>- parenteral anticoagulant</td>
</tr>
<tr>
<td></td>
<td>- drug of choice to treat thromboembolism and prevent clot formation in the venous system</td>
</tr>
<tr>
<td></td>
<td>- also used to treat arterial clotting and atrial fibrillation with embolization</td>
</tr>
<tr>
<td>warfarin (Coumadin) #43 drug in 1991</td>
<td>- oral anticoagulant</td>
</tr>
<tr>
<td></td>
<td>- used to treat thromboembolism after initial treatment with heparin</td>
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<tr>
<td></td>
<td>- drug of choice to prevent deep vein thrombosis in patients with prosthetic heart valves or diseased mitral valves</td>
</tr>
<tr>
<td>dicumarol (Dicumarol Pulvules)</td>
<td>- oral anticoagulant</td>
</tr>
<tr>
<td></td>
<td>- used for same clinical indications as warfarin</td>
</tr>
<tr>
<td>aspirin (Bayer Aspirin)</td>
<td>- antiplatelet drug</td>
</tr>
<tr>
<td></td>
<td>- some effectiveness in preventing aortocoronary bypass shunt thrombosis</td>
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<tr>
<td></td>
<td>- some effectiveness in reducing clot formation in patients on hemodialysis and in patients with unstable angina</td>
</tr>
<tr>
<td></td>
<td>- effective in reducing the risk of recurring transient ischemic attacks</td>
</tr>
<tr>
<td>streptokinase (Kabikinase)</td>
<td>- thrombolytic agent</td>
</tr>
<tr>
<td></td>
<td>- produces a systemic thrombolytic state in which fibrin is loosened or dissolved</td>
</tr>
<tr>
<td></td>
<td>- used to treat deep vein thrombosis, pulmonary embolism, arterial thrombosis and embolism, and coronary thrombosis and to dissolve thrombi in arteriovenous cannulas</td>
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<tr>
<td>urokinase (Abbokinase)</td>
<td>- thrombolytic agent</td>
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<tr>
<td></td>
<td>- produces a systemic thrombolytic state in which fibrin is loosened or dissolved</td>
</tr>
<tr>
<td></td>
<td>- used for dissolving acute pulmonary emboli and coronary thromboses and for clearing clotted arteriovenous catheters</td>
</tr>
<tr>
<td></td>
<td>- indicated for patients who cannot tolerate streptokinase</td>
</tr>
</tbody>
</table>
PARENTERAL ANTICOAGULANTS

Mechanism of Action:
- heparin indirectly inactivates thrombin by accelerating the interaction between thrombin and antithrombin III, a thrombin-inactivating glycoprotein found in the blood
- heparin's effect on triglycerides and platelets may impede development of atherosclerotic plaques in blood vessels
  - heparin has been shown to reduce triglyceride levels by releasing lipid-hydrolyzing enzymes from tissues into blood
  - by maintaining the electronegativity of the blood vessel surface, heparin also decreases platelet adhesiveness and release of platelet-derived growth factor

Adverse Reactions:
- potential for bleeding exists in all patients receiving high doses of heparin to treat thromboembolism
- heparin may depress the platelet count resulting in thrombocytopenia

Ocular Adverse Reactions:
- heparin (with systemic administration) -- subconjunctival or retinal hemorrhages secondary to drug-induced anticoagulation and drug-induced anemia, allergic reactions of eyelids or conjunctiva, decreased vision, lacrimation, hyphema

Contraindications:
- heparin is contraindicated in patients who are bleeding actively or who have bleeding disorders, such as hemophilia
- contraindicated in patients with severe hypertension, alcoholism, or history of GI ulcers
- contraindicated in patients undergoing brain, spinal cord, or eye surgery
- use cautiously in patients with hepatic or renal disease, because the liver and kidneys are involved in the metabolism and excretion of the drug
- use heparin cautiously in pregnant patients

Drug Interactions:
- heparin acts synergistically with all the oral anticoagulants, so the risk of bleeding increases when both types of drugs are administered
- risk of bleeding increases when the patient takes an antiplatelet drug, such as aspirin or dipyridamole, while receiving heparin
- oral contraceptives may decrease antithrombin III, increasing the potential for clot formation
- many other drugs antagonize or inactivate heparin including antihistamines, digitalis, nicotine, phenothiazine, tetracycline, quinidine, quinine, neomycin, and IV penicillin
ORAL ANTICOAGULANTS

Mechanism of Action:
- alter the synthesis of vitamin K-dependent clotting factors, including prothrombin, Factor VII, Factor IX, and Factor X
- the alteration doesn't impede the synthesis of the factors but makes them dysfunctional
- the anticoagulant effect doesn't occur until the already-circulating clotting factors are depleted which takes from several hours for Factor VII to 3 days for prothrombin

Adverse Reactions:
- may produce bleeding complications from inadequate monitoring of prothrombin time (PT) and from drug interactions that increase the anticoagulant effect of the drugs
- severe bleeding may occur in the GI or urinary tract, or in the uterus

Ocular Adverse Reactions:
- subconjunctival or retinal hemorrhages secondary to drug-induced anticoagulation or drug-induced anemia, allergic reactions and urticaria of eyelids or conjunctiva, hyphema, color vision defect (acenocoumarol), lacrimation, decreased vision

Contraindications:
- contraindicated in patients with active or past intestinal bleeding, thrombocytopenia, malignant hypertension, recent neurologic or eye surgery, bacterial endocarditis, chronic alcoholism, or hepatic or renal disease
- contraindicated in pregnant or lactating women
- contraindicated in patients with conditions requiring intensive salicylate therapy, such as arthritis

Drug Interactions:
- many clinical significant interactions with other drugs occur
- the most frequently prescribed drugs that interact with the oral anticoagulants include barbiturates, salicylates, and phenylbutazone
- many foods also interact with the oral anticoagulants
  - however, only a diet containing high amounts of vitamin K is likely to cause problems
ANTIPLATELET DRUGS

Mechanism of Action:
- interfere with platelet activity in different drug- and dose-related ways
- aspirin -- in larger doses irreversibly inhibits platelet aggregation through acetylation of platelet cyclo-oxygenase to prevent synthesis of thromboxane A_2, which is a potent vasoconstrictor and inducer of platelet aggregation and platelet release reaction
- dipyridamole -- mechanism has not been fully elucidated
  - may relate to 1) inhibition of RBC uptake of adenosine
  2) inhibition of phosphodiesterase leading to increased cAMP within platelets 3) inhibition of thromboxane A_2 formation which is a potent stimulator of platelet activation

Adverse Reactions:
- GI tract signs and symptoms are the most common adverse reactions associated with the aspirin dosage used to prevent arterial clotting
  - stomach pain, heartburn, nausea, constipation, hematemesis, melena, slight gastric blood loss
- repeated large dosages of aspirin may cause salicylism
  - dizziness, tinnitus, difficulty hearing, nausea, vomiting, diarrhea, mental confusion, lethargy
- dipyridamole -- usually well tolerated but adverse reactions may include headache, dizziness, nausea, flushing, syncope, mild GI distress

Ocular Adverse Reactions:
- ocular effects minimal
- systemic effects of dizziness and headache may be presented to you

Contraindications:
- contraindicated in patients with aspirin hypersensitivity
- use with extreme caution in patients taking heparin or oral anticoagulants because of the increased risk of bleeding

Drug Interactions:
- risk of bleeding increases in patients receiving both heparin and large doses of aspirin
- dipyridamole used with aspirin or with warfarin produces an additive effect which has been used to prevent thromboembolic disorders in patients with aortocoronary bypass grafts or prosthetic heart valves
- sulfinpyrazone administered concurrently with many other drugs can cause some serious adverse reactions
THROMBOLYTIC AGENTS

Mechanism of Action:
- streptokinase --
  - indirectly activates plasminogen by forming an activator complex
  that later converts residual plasminogen into the proteolytic
  enzyme plasmin
  - the circulating activator diffuses into the thrombus to activate
    adsorbed preplasmin II which hydrolyzes fibrin leading to
    endogenous lysis
  - plasmin generated in the circulation binds to antiplasmin and is
    released at the thrombus site resulting in the external lysis of
    the clot
- urokinase --
  - an active protease, urokinase directly converts plasminogen to
    plasmin within and on the surface of thrombi and emboli
  - the plasmin breaks down fibrin, fibrinogen, and other
    procoagulant plasma proteins
  - also produces an anticoagulant effect by dissolving fibrinogen and
    increasing the level of fibrin degradation products
- alteplase --
  - causes local fibrinolysis where it converts plasminogen to plasmin

Adverse Reactions:
- major reactions associated with the thrombolytic agents are bleeding
  and allergic responses
- bleeding can occur at a sutured wound or any puncture site since
  streptokinase and urokinase dissolve fibrin deposits in all areas and
  not just at the coronary or pulmonary arterial thrombus site
- allergic reactions to streptokinase are common because most patients
  possess circulating streptococcal antibodies
  - symptoms include urticaria, itching, flushing, nausea, headache,
    musculoskeletal pain
- alteplase may cause fever, hypotension, dysrhythmias, bleeding,
  nausea, and vomiting

Ocular Adverse Reactions:
- urokinase (with local ophthalmic use or exposure)
  - hypopyon
  - uveitis
  - intraocular pressure is increased or decreased
  - abnormal ERG
  - corneal edema
Contraindications:
- contraindicated in patients who:
  - have had a prior allergic response to streptokinase
  - have active bleeding lesions
  - have had a cerebrovascular accident, transient ischemic attack, or neoplasm with the last 2 months
  - have had recent cardiopulmonary resuscitation
  - have bleeding disorders such as hemophilia
  - have had recent GI bleeding
  - have severe uncontrolled hypertension

Drug Interactions:
- interact with heparin, the oral anticoagulants, and the antiplatelet drugs to increase the patient’s risk of bleeding
- aminocaproic acid (Amicar) inhibits streptokinase and can be used to reverse its fibrinolytic effects
ANTIHYPERLIPIDEMIC AGENTS

Antihyperlipidemic Agents

Bile-Sequestering Agents
△△ cholestyramine (Questran) #191 drug in 1991
colestipol

Fibric Acid Derivatives
△ clofibrate (Atromid-S)
△△ gemfibrozil (Lopid) #42 drug in 1991

Cholesterol Synthesis Inhibitors
probucol
△△ lovastatin (Mevacor) #22 drug in 1991

Other Antihyperlipidemic Agents
△ niacin (Nicotinic Acid)

"△△" indicates a top 200 drug in 1991 -- note ranking after trade name
"△" indicates major drugs -- see table

Indications for Use:
- Antilipemic agents are used to lower abnormally high blood levels of lipids

- Bile-Sequestering Agents --
  - drugs of choice for treating elevated serum cholesterol (familial hypercholesterolemia) in patients not responding to dietary management

- Fibric Acid Derivatives --
  - primarily used to reduce triglyceride levels
  - especially very-low-density triglycerides
  - secondarily used to reduce blood cholesterol levels
  - used in patients with elevated serum cholesterol when niacin does not produce an adequate response

- Cholesterol Synthesis Inhibitors --
  - used to treat various types of hyperlipoproteinemia

- Niacin --
  - used to treat certain kinds of hyperlipoproteinemia
  - one of the first-line drugs used to treat elevated serum cholesterol
**BILE-SEQUESTERING AGENTS**

**Mechanism of Action:**
- lower blood levels of low-density lipoproteins (LDLs)
- form insoluble complexes with bile acids in the GI tract to lower the gallbladder’s bile acid levels
  - this triggers the liver to synthesize more bile acids from their precursor, cholesterol
  - cholesterol leaving the bloodstream to replace the lost bile acids lowers blood cholesterol levels

**Adverse Reactions:**
- severe reactions can result from long-term use
- GI reactions -- abdominal pain, distention, flatulence, belching, nausea, vomiting, diarrhea
  - headache, dizziness, anorexia, weakness, fatigue

**Ocular Adverse Reactions:**
- no reported ocular adverse reactions

**Contraindications:**
- note prothrombin times for a patient also receiving a coumarin anticoagulant
- note any signs of vitamin A and D deficiencies, such as night blindness and rickets, in patients on long-term therapy

**Drug Interactions:**
- bind with acidic drugs in the GI tract, decreasing their absorption and effectiveness
- may reduce absorption of lipid-soluble vitamins, such as vitamins A, D, E, and K

<table>
<thead>
<tr>
<th>Major Drugs</th>
<th>Things to Know</th>
</tr>
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<tbody>
<tr>
<td>cholestyramine (Questran)</td>
<td>- used to treat hypercholesterolemia when dietary changes fail to produce the desired response</td>
</tr>
<tr>
<td>clofibrate (Atraomid-S)</td>
<td>- primarily used to treat hyperlipoproteinemia (mixed hyperlipidemia, and mixed hypertriglyceridemia)</td>
</tr>
<tr>
<td>lovastatin (Mevacor)</td>
<td>- may become the drug of choice for treating all types of hypercholesterolemia</td>
</tr>
<tr>
<td>niacin (Nicotinic Acid)</td>
<td>- one of the first-line drugs used to treat elevated serum cholesterol</td>
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</table>
FIBRIC ACID DERIVATIVES

Mechanism of Action:
- exact mechanism of action has not yet been established
- the drugs may reduce cholesterol formation early in the biosynthetic process, mobilize cholesterol from the tissues, increase sterol excretion, decrease lipoprotein synthesis and secretion, and decrease triglyceride synthesis

Adverse Reactions:
- GI reactions -- abdominal pain, distension, flatulence, nausea, vomiting
- clofibrate --
  - increases incidence of calculi in the gallbladder and the need for excision of the gallbladder
  - associated with malignant liver tumors in humans
  - pancreatitis, cardiac dysrhythmias, thromboembolic events, angina

Ocular Adverse Reactions:
- gemfibrozil -- only ocular adverse reaction reported is blurred vision

Contraindications:
- note any patient history of ulcers, diabetes, jaundice, gallstones, or liver disease
- note any dysrhythmias, or if the patient has a history of CAD or angina

Drug Interactions:
- can displace anticoagulants in the plasma to increase anticoagulant effect
- displace sulfonylurea from serum albumin sites and increase insulin secretion to increase the hypoglycemic effect
- oral contraceptives and rifampin both antagonize clofibrate action and result in blood lipid levels remaining high
CHOLESTEROL SYNTHESIS INHIBITORS

Mechanism of Action:
- exact mechanism of action is not well understood
- drugs lower lipid levels by interfering with cholesterol synthesis
  - probucol --
    - may inhibit cholesterol transport form the intestine, inhibiting cholesterol synthesis and increasing the secretion of cholesterol and bile acid
    - reduces blood cholesterol levels and lowers LDL and HDL cholesterol levels
  - lovastatin --
    - may inhibit the enzyme (HMG CoA reductase) that catalyzes the conversion of cholesterol's precursors
    - may also stimulate LDL receptors in the liver to reduce hepatocytic cholesterol synthesis
    - the result is lowered LDL levels and increased HDL levels

Adverse Reactions:
- probucol --
  - has affected cardiac nerve conduction in animals
  - has also prolonged the Q-T interval of the cardiac cycle
  - GI effects -- abdominal pain, flatulence, distention, flatulence, nausea, vomiting, diarrhea
  - women should avoid becoming pregnant for at least 6 months after treatment ends
- lovastatin --
  - transient GI effects
  - has caused elevations in liver function

Ocular Adverse Reactions:
- lovastatin may be associated with cataract formation

Contraindications:
- female patients should avoid becoming pregnant for at least 6 months after probucol therapy is discontinued
- avoid combining probucol therapy with clofibrate therapy
- note EKG and blood cholesterol levels in patients receiving probucol
- monitor liver functions every 4 to 6 weeks

Drug Interactions:
- tend not to interact with other drugs
- probucol can produce additive effects when given with clofibrate
  - interaction markedly reduces HDL levels
OTHER ANTIHYPERLIPIDEMIC AGENTS

Mechanism of Action:
- niacin --
  - theorized to inhibit the release of free fatty acids from lipid tissues

Adverse Reactions:
- niacin --
  - produces skin flushing which disappear in 2 to 6 weeks
  - GI effects -- abdominal pain, jaundice, activation of peptic ulcer, nausea, vomiting, diarrhea
  - abnormal liver function test results, abnormal prothrombin times, hypoalbuminemia, hyperglycemia, hyperuricemia

Ocular Adverse Reactions:
- niacin --
  - toxic amblyopia
  - cystoid macular edema
  - decreased vision
  - proptosis

Contraindications:
- niacin --
  - contraindicated in patients with arterial hemorrhage, severe hypotension, liver disease, active peptic ulcer disease

Drug Interactions:
- niacin may interact with adrenergic-blocking agents to provide an additive vasodilating effect and may produce postural hypotension
- probenecid's and sulfinpyrazone's uricosuric effect may be inhibited by niacin
**Thiazide and Thiazide-like Diuretics**
- bendroflumethiazide
- benzthiazide (Aquapres)
- chlorothiazide
- cyclothiazide
- hydrochlorothiazide (Hydrochlorothiazide) #132, #197 in 1991
- hydroflumethiazide
- indapamide (Lozol) #80 drug in 1991
- methyclothiazide
- polythiazide
- trichlormethiazide
- chlorthalidone (Hygroton)
- metolazone (Zaraxolyn)
- quinethazone

**Loop Diuretics**
- bumetanide (Bumex) #130 drug in 1991
- ethacrynate sodium
- ethacrynic acid (Edecrin)
- furosemide (Lasix) #32 drug in 1991 (Furosemide) #113, #120, #129, #194 drugs in 1991

**Potassium-sparing Diuretics**
- amiloride (Midamor)
- spironolactone (Aldactone)
- triamterene and hydrochlorothiazide (Diazide, Maxzide) #14 & #51 drugs in 1991

**Carbonic Anhydrase Inhibitors**
- acetazolamide (Diamox)
- dichlorphenamide (Daranide)
- ethoxzolamide
- methazolamide

**Osmotic Diuretics**
- mannitol (Osmitrol)
- urea

**Diuretic Drug Combinations**
- Hydrochlorothiazide and Triamterene (Dyazide, Maxzide)
  see under triamterene in table

"ΔΔ" indicates a top 200 drug in 1991 -- note ranking after trade name
"Δ" indicates major drugs -- see table
Indications for Use:
- diuretics are used clinically to increase urine volume and the net excretion of solutes and water
  - these agents act at different sites within the nephrons (structural and functional units of the kidney) to produce diuresis

- thiazide and thiazide-like diuretics --
  - primarily used to treat hypertension and edema from mild or moderate CHF
  - also used to prevent the development and recurrence of calcium nephrolithiasis (presence of calcium in the kidney) in hypercalciuric (excessive calcium in the urine) and normal calciuric patients

- loop diuretics --
  - primarily used to treat edema associated with congestive heart failure, hepatic or renal disease, or nephrotic syndrome
  - also used to treat mild hypertension in patients with renal impairment in whom thiazides may be ineffective

- potassium-sparing diuretics --
  - often used with other diuretics to potentiate their action or to counteract their potassium-wasting effects
  - used primarily to treat edema and diuretic-induced hypokalemia (extreme potassium depletion in circulating blood) in patients with CHF, cirrhosis, nephrotic syndrome, or hypertension

- carbonic anhydrase inhibitors --
  - primarily used to decrease the formation of aqueous humor by the ciliary body and control the excessive intraocular pressure associated with glaucoma
  - also used to treat edema related to cardiac disorders, periodic paralysis, and acute altitude sickness

- osmotic diuretics --
  - primarily used to reduce intracranial pressure and to prevent acute renal failure
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<td>benzthiazide (Aquapres)</td>
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<td>chlorthalidone (Hygroton)</td>
<td>used to treat edema and hypertension</td>
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<tr>
<td>hydrochlorothiazide</td>
<td>used to treat edema and hypertension</td>
</tr>
<tr>
<td>#132, #197 drugs in 1991</td>
<td></td>
</tr>
<tr>
<td>metolazone (Zaraxyly)</td>
<td>used to treat hypertension and the edema secondary to CHF, hepatic disease, or renal disease</td>
</tr>
<tr>
<td>&amp; #14 drugs in 1991</td>
<td></td>
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<tr>
<td>&amp; #51 drugs in 1991</td>
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<tr>
<td><strong>Loop Diuretics</strong></td>
<td></td>
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<tr>
<td>bumetanide (Bumex)</td>
<td>used to treat edema and hypertension</td>
</tr>
<tr>
<td>#130 drug in 1991</td>
<td>may be substituted for furosemide in patients hypersensitive to that drug</td>
</tr>
<tr>
<td>furosemide (Lasix)</td>
<td>used primarily to treat acute pulmonary edema and other forms of edema</td>
</tr>
<tr>
<td>#32 drug in 1991; generic ranked #113, #120, #129, #194 drugs in 1991</td>
<td>also used to treat hypertensive crisis, acute and chronic renal failure, hypertension, and hypercalcemia (promotes urinary calcium excretion)</td>
</tr>
<tr>
<td><strong>Potassium-sparing Diuretics</strong></td>
<td></td>
</tr>
<tr>
<td>amiloride (Midamor)</td>
<td>used to treat hypertension or edema associated with CHF</td>
</tr>
<tr>
<td>&amp; helps to restore normal serum potassium levels in patients with hypokalemia</td>
<td></td>
</tr>
<tr>
<td>spironolactone (Aldactone)</td>
<td>used to treat essential hypertension, edema, primary aldosteronism, refractory edema</td>
</tr>
<tr>
<td>may be used in combination with other drugs to potentiate their action or to decrease potassium loss</td>
<td></td>
</tr>
<tr>
<td>triamterene and hydrochlorothiazide (Dyazide, Maxzide)</td>
<td>used in combination with other diuretics to treat hypertension</td>
</tr>
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<td>also used to treat edema associated with CHF, cirrhosis, and nephrotic syndrome</td>
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<td>Carbonic Anhydrase Inhibitors</td>
<td></td>
</tr>
<tr>
<td>acetazolamide (Diamox)</td>
<td>used to treat edema and glaucoma</td>
</tr>
<tr>
<td>primarily used to treat open-angle glaucoma that is unresponsive to miotics alone</td>
<td></td>
</tr>
<tr>
<td>also used to lower IOP before eye surgery</td>
<td></td>
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<tr>
<td>Osmotic Diuretics</td>
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<tr>
<td>mannitol (Osmitrol)</td>
<td>used primarily to prevent oliguria (diminished amount of urine formation) and acute renal failure</td>
</tr>
<tr>
<td>also used to treat increased intracranial pressure, increased intraocular pressure</td>
<td></td>
</tr>
<tr>
<td>used to treat drug intoxication from secobarbital, imipramine, aspirin, or carbon tetrachloride</td>
<td></td>
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THIAZIDE AND THIAZIDE-LIKE DIURETICS

Mechanism of Action:
- interfere with the transport of sodium ions across renal tubular epithelium at the cortical-diluting, or distal, segments of the nephrons
- create some minor carbonic anhydrase inhibition to result in increased sodium, chloride, and water excretion
- may also decrease the glomular filtration rate

Adverse Reactions:
- most common include
  - blood volume depletion
  - orthostatic hypotension -- decrease of blood pressure below normal occurring upon suddenly arising from a recumbent position or changing from a standing still position
  - hypokalemia -- extreme potassium depletion in circulating blood
  - may result in drowsiness, confusion, apathy, coma, and irritability
- predictable adverse reactions also include
  - glucose intolerance
  - hypercalcemia -- excessive amount of calcium in the blood
  - symptoms may include constipation, anorexia, nausea, vomiting
  - hypophosphatemia -- decreased amounts of phosphates in circulating blood -- symptoms include anorexia, muscle weakness, and osteomalacia (softening of bones so they become flexible and brittle) with bone pain
- GI reactions -- anorexia, nausea, and pancreatitis

Ocular Adverse Reactions:
- transient blurred vision

Contraindications and Precautions:
- contraindicated in patients hypersensitive to the thiazides or the sulfonamides
- use cautiously in patients with renal disease or impaired hepatic function due to the fluid and electrolyte imbalances produced through use of the thiazide diuretics
- check patient's serum potassium levels and note signs and symptoms of hypokalemia -- drowsiness, confusion, apathy, coma, irritability
- note signs and symptoms of metabolic alkalosis (excessive alkalinity of body fluids) -- hypoventilation, dysrhythmias, irritability, tetany, belligerence, confusion
- patients receiving concurrent digitalis and thiazide therapy run an increased risk for developing digitalis toxicity from potassium depletion
Drug Interactions:
- many drugs interact with thiazide and thiazide-like diuretics to cause severe fluid and electrolyte imbalances and other potentially serious problems
- with oral hypoglycemic agent -- hyponatremia (low sodium blood levels), thiazide resistance, hyperglycemia
- with corticosteroids, amphotericin B, extended-spectrum penicillins -- may cause hypokalemia (extreme potassium depletion in circulating blood)
- with antihypertensive drugs -- may cause orthostatic hypotension
- with alcohol -- may cause orthostatic hypotension
- with digitalis -- may cause digitalis toxicity
LOOP DIURETICS

Mechanism of Action:
- most potent diuretics available; produce the greatest volume of diuresis and have a high potential for causing severe adverse reactions
- inhibit sodium and chloride reabsorption in the renal tubules by direct action on the thick ascending limb of the loop of Henle
- may also inhibit sodium, chloride, and water reabsorption in the proximal tubule while increasing the excretion of ammonium and titratable acids in the distal tubule
- increased excretion of potassium from the distal tubule may result from the accelerated exchange with sodium ions caused by the increased volume of sodium delivered to the distal tubule

Adverse Reactions:
- the most severe reactions involve frequently occurring fluid and electrolyte imbalances
- common adverse reactions include:
  - fluid volume depletion
  - orthostatic hypotension
  - hypokalemia
  - hypochloremic alkalosis -- excessive alkalinity of body fluids due to loss of chloride
  - transient deafness, abdominal discomfort or pain, diarrhea, impaired glucose tolerance, and dermititis can also occur

Ocular Adverse Reactions:
- blurred vision

Contraindications and Precautions:
- loop diuretics are contraindicated in anuric patients (patients with absence of urine formation)
- furosemide and bumetanide are contraindicated for patients hypersensitive to sulfonamides, because they may have a corresponding hypersensitivity to the loop diuretics
- check patients also receiving digitalis for toxicity which may result from the potassium-depleting effect of the loop diuretics
- check patients who are also receiving oral anticoagulant therapy for bleeding because the loop diuretics may potentiate anticoagulant effects

Drug Interactions:
- a variety of drugs -- including aminoglycosides, oral anticoagulants, and corticosteroids -- interact with the loop diuretics causing altered renal function, fluid and electrolyte imbalances, and specific enhanced drug effects
POTASSIUM-SPARING DIURETICS

Mechanism of Action:
- direct action on the distal renal tubules produces mild diuretic and antihypertensive effects that increase the urinary excretion of sodium, chloride, and calcium ions and reduce the excretion of potassium and hydrogen ions
- the effects of the potassium-sparing diuretics lead to increased serum potassium levels and urine pH

Adverse Reactions:
- hyperkalemia (excessive potassium in the blood) is the major risk, especially if given with a potassium supplement or a high-potassium diet
  - signs and symptoms include confusion, hyperexcitability, muscle weakness, paresthesias (sensation of numbness, prickling, or tingling), dysrhythmias, diarrhea
- other predictable reactions include megaloblastic anemia (pernicious anemia in which large, nucleated abnormal red blood corpuscle are found in the blood), dizziness, hypotension, sore throat, dry mouth, nausea and vomiting
- use of spironolactone -- may produce headache, abdominal cramps, diarrhea
- use of amiloride -- may produce headache, nausea and vomiting, anorexia, diarrhea, muscle cramps

Contraindications and Precautions:
- contraindicated in patients with anuria or renal impairment, severe hepatic disease, or hyperkalemia
- use cautiously in patients with impaired hepatic function or diabetes mellitus as well as in pregnant or lactating women
- because of the drugs potassium-sparing effects, check for signs and symptoms of hyperkalemia: confusion, hyperexcitability, muscle weakness, paresthesias, dysrhythmias, diarrhea

Drug Interactions:
- few drug interactions are associated with the use of potassium-sparing diuretics -- those that do occur are related to the potassium-sparing effects
- with norepinephrine -- increases vasopressor effects (contraction of the muscles of capillaries and arteries)
- with potassium supplements -- may cause hyperkalemia
- spironolactone with ammonium chloride -- may cause metabolic acidosis
- spironolactone with digitalis -- decreases renal excretion
CARBONIC ANHYDRASE INHIBITORS

Mechanism of Action:
- inhibits hydrogen ion secretion by the renal tubule through inhibition of the enzyme carbonic anhydrase to cause increased excretion of sodium, potassium, bicarbonate and water, thus producing an alkaline diuresis
  - alkalinize the urine through the increased potassium and bicarbonate excretion and decreased citrate, ammonium, and chloride excretion
  - prolonged treatment with carbonic anhydrase inhibitors can lead to metabolic acidosis
  - carbonic anhydrase inhibitors also decrease intraocular pressure by decreasing the rate of formation of aqueous humor

Adverse Reactions:
- major predictable adverse reactions are fluid and electrolyte imbalances, especially potassium and bicarbonate depletion
- other reactions -- drowsiness, hyperchloremic acidosis, hemolytic anemia, paresthesias, nausea, vomiting, and anorexia

Ocular Adverse Reactions:
- transient myopia that subsides upon drug diminution or discontinuance

Contraindications and Precautions:
- contraindicated for patients with
  - narrow-angle (acute) glaucoma -- since organic closure of the angle may occur while worsening glaucoma is masked by lowered IOP
  - hypersensitivity to carbonic anhydrase inhibitors or sulfonamides
  - chronic pulmonary obstruction with inability to increase alveolar ventilation -- since acidosis may be increased
  - renal failure
  - hepatic insufficiency
  - hyponatremia (depressed sodium serum levels), hypokalemia (depressed potassium serum levels), or hyperchloremic acidosis
  - also contraindicated during pregnancy
- use cautiously in patients with:
  - diabetes because carbonic anhydrase inhibitors may increase blood glucose levels
  - history of hypercalciuria (excessive calcium in the urine) or gout
Drug Interactions:
- with amphetamines, ephedrine, flecainide, pseudoephedrine, quindine --
  - since carbonic anhydrase inhibitors alkalinize the urine, the renal
    excretion of these agents may be decreased
- with digitalis -- carbonic anhydrase inhibitors may induce hypokalemia,
  which sensitizes the patient to digitalis toxicity
- with salicylates -- combined therapy may result in severe metabolic
  acidosis, increasing potential for salicylate toxicity (eg, drowsiness,
  confusion, lethargy, hyperventilation, tinnitus, anorexia)
OSMOTIC DIURETICS

Mechanism of Action:
- act by increasing the osmolality of the plasma, glomerular filtrate, and tubular fluid by remaining in high concentrations in the renal tubules
  - this decreases the reabsorption of fluid and electrolytes, increasing the excretion of water, chloride, and sodium and slightly increasing the excretion of potassium

Adverse Reactions:
- transient expansion of plasma volume during infusion
  - results in circulatory overload and tachycardia, electrolyte imbalances, volume depletion, cellular dehydration, headache, nausea and vomiting
- use of mannitol -- may cause rebound intracranial pressure 8 to 12 hours after diuresis and aginalike chest pain
  - CNS -- headache, blurred vision, convulsions, dizziness
  - GI -- nausea, vomiting, diarrhea
  - other -- dry mouth, thirst, rhinitis, arm pain, skin necrosis

Ocular Adverse Reactions:
- blurred vision

Contraindications and Precautions:
- contraindicated in patients with diagnosed acute renal failure, cardiac dysfunction, congestive heart failure, active intracranial hemorrhage, or severe dehydration

Drug Interactions:
- no significant drug interactions occur with the use of mannitol or urea
altitude sickness — symptoms produced by decreased oxygen in the environment; headache, shortness of breath, malaise, decreased ability to concentrate, lightheadedness, fainting

anuria — absence of urine formation

calciuric — pertaining to calcium

hypercalciuric — excessive calcium in the urine

hyperchloremic acidosis — excessive acidity of body fluids in which there is an abnormally high level of chloride in the blood serum

hyperkalemia — excessive potassium in the blood

hypochloremic alkalosis — excessive alkalinity of body fluids due to loss of chloride

hypokalemia — extreme potassium depletion in circulating blood - may result in drowsiness, confusion, apathy, coma, and irritability

hyponatremia — depressed sodium serum levels

hypophosphatemia — decreased amounts of phosphates in circulating blood - symptoms include anorexia, muscle weakness, and osteomalacia (softening of bones so they become flexible and brittle) with bone pain

megaloblastic anemia — pernicious anemia in which large, nucleated abnormal red blood corpuscles are found in the blood

metabolic acidosis — excessive acidity of body fluids due to an accumulation of acids other than carbonic acid; possible causes are excessive ingestion of acids, ketosis, severe dehydration

metabolic alkalosis — excessive alkalinity of body fluids - symptoms include hypoventilation, dysrhythmias, irritability, belligerence, confusion

nephrolithiasis — presence of calculi in the kidney

nephrotic syndrome — end result of variety of diseases that damage the capillary wall of the arteries of the glomerulus - leads to loss of large amounts of protein in the urine, which results in hypoalbuminemia and edema

oliguria — diminished amount of urine formation

orthostatic hypotension — decrease of blood pressure below normal occurring upon suddenly arising from a recumbent position or changing from a standing still position

primary aldosteronism — disorder in which the blood contains abnormally high levels of aldosterone due to disorders of the adrenal gland

refractory edema — edema of the lens or cornea of the eye

salicylate toxicity — symptoms include drowsiness, confusion, lethargy, hyperventilation, tinnitus, anorexia
URICOSURIC AGENTS

\[ \Delta \text{probenecid} \] (Benemid, Sk-Probenecid)
\[ \Delta \text{sulfinpyrazone} \] (Anturane)

"\(\Delta\)" indicates major drugs -- see table

**Indications for Use:**
- for patients with chronic gouty arthritis and tophaceous gout to prevent or minimize joint changes and renal impairment
- for patients experiencing hyperuricemia secondary to thiazide and other related diuretics

**Mechanism of Action:**
These agents act by increasing the excretion of uric acid in the urine by inhibiting the active reabsorption of uric acid at the proximal convoluted tubules. This, in turn, reduces chronic joint destruction and tophi formation caused by deposition of monosodium urate crystals in the joints.

**Adverse Reactions:**
- probenicid can increase the risk of an acute gouty attack (administration of colchicine during the first 3 to 6 months of therapy can prevent this)
- probenicid: headache, anorexia, nausea, vomiting, flushing, dizziness, frequent urination, sore gums, anemia.
- sulfinpyrazone: nausea, dyspnea, GI pain, blood loss, dizziness, rash, vertigo, tinnitus, edema, and more rarely anemia, leukopenia, agranulocytosis, thrombocytopenia.
* probenicid produces less severe GI and hematologic effects than sulfinpyrazone, while sulfinpyrazone produces fewer rashes and hypersensitivity reactions than probenicid

<table>
<thead>
<tr>
<th>major drugs</th>
<th>things to remember</th>
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<tbody>
<tr>
<td>probenicid</td>
<td>- for chronic gouty arthritis</td>
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<td></td>
<td>- for hyperuricemia secondary to diuretic use</td>
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<tr>
<td>sulfinpyrazone</td>
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<td></td>
<td>- for hyperuricemia secondary to diuretic therapy</td>
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</tbody>
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Contraindications and Precautions:
- both drugs contraindicated in cases of known hypersensitivity
- both drugs are contraindicated during acute gouty attacks because they only prolong inflammation
- contraindicated for hyperuricemia secondary to cancer chemotherapy because they increase the risk of developing uric acid nephropathy
- use caution in patients with history of peptic ulcers
- probenecid contraindicated in patients with blood dyscrasias or history of uric acid calculus formation

Drug Interactions:
- with aspirin: may cause prolongation of bleeding time, antagonizes action of probenicid
- penicillins, sulfonamides and cephalosporins: increase plasma concentration of antibiotics
- anticoagulants: anticoagulant activity increased by uricosurics
- thiazide diuretics: diuretic effects enhanced, may precipitate acute gouty arthritis
- oral hypoglycemic agents: uricosurics enhance hypoglycemic action
- antineoplastic drugs: increase serum urate concentrations
Vitamins

fat-soluble vitamins
- vitamin A (retinol)
- vitamin D
- vitamin E
- vitamin K

water-soluble vitamins
B-complex vitamins
- thiamine (B₁)
- riboflavin (B₂)
- nicotinic acid (B₃)
- pyridoxine (B₆)
- biotin
- choline
- inositol
- folic acid
- cyanocobalamin (B₁₂)

vitamin C (ascorbic acid)

Minerals

trace minerals
- iodine
- zinc
- manganese
- copper
- selenium
- chromium

electrolytes
- calcium
- sodium
- potassium

hematinic agents
- iron
- vitamin K
**FAT-SOLUBLE VITAMINS**

**Vitamin A**

**Dietary Sources:**
- primarily found in fish oils, liver, egg yolk, whole milk
- the precursors of vitamin A are the alpha-, beta-, and gamma-carotenes, which occur in plants

**Actions in the Body:**
- essential for normal growth, for strong bones and teeth, and for healthy skin
- a precursor, beta-carotene is an effective anti-oxidant that helps protect the body from free radical damage - often used to help slow progression of cataracts and macular degeneration
- an important component of the photopigments necessary for vision

**Indications for Use:**
used to treat acne, psoriasis, sun burn and vitamin A deficiencies

**Effects of Deficiency:**
Storage in the Kupffer's cells of the liver is sufficient to sustain the body for long periods of dietary deprivation. Deficiencies of vitamin A are usually due to failure to absorb, as seen in cystic fibrosis, bile duct obstruction, or treatment with lipid lowering drugs. Effects include:
- dry, rough skin, loss of appetite, diarrhea, lowered resistance to infection and weak bones and teeth
- Ocular effects: night blindness, xerosis (conjunctival drying), Bitot's spots (white patches on conjunctiva, corneal drying and softening, and keratomalacia (opaqueness due to drying). Collectively, these findings are known as Xerophthalmia.

**Effects of Overdose:**
Prolonged excess intake of vitamin A is known as hypervitaminosis A.
- lethargy, irritability, pain and tenderness in the bones, headache, dry itchy skin, increased intracranial pressure.
Vitamin D

**Dietary Sources:**
Vitamin D is the name given to a group of substances including cholecalciferol, which is found in animal products, particularly fish oils and whole milk. It is also produced in the skin through photo-oxidation of a derivative of cholesterol.

**Actions in the Body:**
Vitamin D regulates calcium and phosphate levels by enhancing the intestinal absorption of calcium, regulating calcium and phosphate release from bone, and modulating their excretion by the kidney.

**Indication for Use:**
Vitamin D therapy is only required in cases of malabsorption, breast-fed infants, premature infants, and patients with dietary deficiency.

**Effects of Deficiency:**
- rickets (an inadequate mineralization of bone) can occur in children due to lack of exposure to sunlight or a vitamin D deficient diet
- osteomalacia, a generalized decrease in bone density, occurs in adults

**Effects of Overdose:**
Vitamin D is excreted from the body at a slow rate, and excessive intake may result in a toxicity involving weakness, fatigue, lassitude (exhaustion), headache, gastrointestinal problems, changes in blood pressure, and deposition of calcium in soft tissue leading to heart, kidney and vessel damage.

Vitamin E

**Dietary Sources:**
Alpha-Tocopherol, or vitamin E, is found in animal and plant fats and oils

**Actions in the Body:**
acts as an antioxidant by preventing or slowing oxidation of unsaturated fatty acids in cell membranes by peroxyl free radicals

**Indication for Use:**
administered to premature infants exposed to high concentrations of oxygen to reduce the incidence and severity of retinopathy of prematurity.
WATER-SOLUBLE VITAMINS

Thiamine (B₁)

**Dietary Sources:**
meat, yeast, whole grains, nuts

**Actions in the Body:**
In the body thiamine is converted to coenzyme thiamine pyrophosphate (TPP) that is involved in the metabolism of carbohydrates and nerve, muscle and heart function.

**Indications for Use:**
Thiamine deficiencies occur in patients with alcoholism, beriberi, Wernicke's encephalopathy, peripheral neuritis, hepatic disease, GI disease, pregnancy, increased physical activity, hyperthyroidism and infection.

**Effects of Deficiency:**
Alcoholism is the most common cause of thiamine deficiency. Thiamine deficiency causes beriberi, characterized by extensive damage to the nervous and circulatory systems, muscle wasting and edema. Mild forms of deficiency can cause neuritis, sensory disturbances, hyperesthesia or anesthesia, loss of strength and even limb paralysis. Demyelination of the optic nerve and optic tract may occur. Other results of deficiency are Wernicke's encephalopathy and Korsakoff's psychosis.

**Effects of Overdose:**
Because the excess is excreted in the urine, overdose does not occur.

Riboflavin (B₂)

**Dietary Sources:**
Riboflavin is found in milk, cheese, organ meats, eggs, green leafy vegetables, whole-grain cereals and breads. It is also produced by the bacteria in the intestine.

**Actions in the Body:**
Riboflavin is used to make the coenzymes FMN and FAD which are essential for carbohydrate, protein, and fat metabolism.

**Indications for Use:**
used to treat thiamine deficiency

**Effects of Deficiency:**
The first signs of riboflavin deficiency is a sore throat and angular stomatitis, followed by glossitis, cheilosis (red, denuded lips), seborheic dermatitis of the face, dermatitis of the trunk and extremities, and later, anemia and neuropathy

Ocular effects include: corneal vascularization and photophobia, decreased acuity, dryness, burning and cataract formation.

**Effects of Overdose:**
no adverse reactions have been reported
WATER-SOLUBLE VITAMINS (Continued)

Niacin, Nicotinic Acid (B₃)

Dietary Sources:
Niacin is found in liver, meat, fish, poultry, whole grain breads and cereals, nuts and legumes. It can also be synthesized in the body from the amino acid tryptophan at a rate inadequate to maintain good health.

Actions in the Body:
Niacin is converted to the coenzymes NAD and NADP, which are involved in the metabolism of carbohydrates and fats and are important to the function of the nervous system and the maintenance of healthy skin.

Indications for Use:
Niacin is useful in the treatment of hyperlipoproteinemia.

Effects of Deficiency:
Deficiency can result in pelagra, characterized by dermatitis, diarrhea and dementia (the "three D's")

Effects of Overdose:
The side effects of doses necessary in the treatment of hyperlipoproteinemia are cutaneous flush and pruritis.

Pyridoxine (B₆)

Dietary Sources:
meat, liver, whole-grain breads, cereals, soybeans, and vegetables

Actions in the Body:
In the body, pyridoxine is converted to the coenzyme pyridoxal phosphate, involved in metabolic transformation of amino acids.

Indications for Use:
Deficiencies occur in patients with alcoholism, hepatic disorders, uremia, malabsorption syndromes. Pyridoxine is given prophylactically with Isoniazid, due to its effects on the formation of the coenzyme form of pyridoxine.

Effects of Deficiency:
The effects of deficiency involve the skin, blood, and nervous system. The signs are seborrhea-like skin lesions on the face, glossitis, stomatitis, convulsive seizures, and anemia.

Effects of Overdose:
Very large doses may result in nervous system damage.
WATER-SOLUBLE VITAMINS (Continued)

Biotin

**Dietary Sources:**
- organ meats, egg yolk, milk, fish, and nuts

**Actions in the Body:**
- Biotin plays an important role in carbohydrate and fat metabolism and is helpful in exceting the waste products of protein metabolism.

**Indications for Use:**
- used in the treatment of biotin deficiency

**Effects of Deficiency:**
- Deficiencies are rare, but can occur in individuals who consume large amounts of egg-white, which contains the biotin-binding agent, avidin. Signs include dermatitis, glossitis, hyperesthesia, muscle pain, lassitude (exhaustion), anorexia, anemia and cardiac changes.

Folic Acid

**Dietary Sources:**
- Virtually all food sources are rich in folates, especially fresh green vegetables, liver, yeast, and some fruits.

**Actions in the Body:**
- The folates are converted to a series of coenzymes which transport carbon fragments from one compound to another during amino acid metabolism and nucleic acid synthesis.

**Indications for Use:**
- used to treat folic acid deficiency

**Effects of Deficiency:**
- The most common cause is alcoholism, but may also result from diseases of the small intestine. A deficiency of folic acid leads to impaired cell division and protein synthesis. The earliest sign of deficiency is megaloblastic anemia (formation of macrocytic red blood cells).
Cyanocobalamin (B₁₂)

Dietary Sources:
Vitamin B₁₂ is found in animal products such as meat, liver and kidney.

Actions in the Body:
Vitamin B₁₂ is converted to coenzymes which interact with the coenzymes from folate in the synthesis of DNA and in the production of red blood cells. It is also important in the process of myelinization of the nerves.

Indications for Use:
It is important for people on strict vegetarian diets to take vitamin B₁₂ supplements.

Effects of Deficiency:
Deficiencies are usually due to malabsorption from the GI tract. For such patients it is necessary to inject the vitamin intravenously. Deficiencies are similar to folate deficiency and can result in anemia and demyelinization of the nerves.

Ascorbic Acid (Vitamin C)

Dietary Sources:
fresh fruits and vegetables

Actions in the Body:
The major function of vitamin C is to aid in the formation of collagen. It is also necessary for the utilization of folic acid, drug metabolism in the liver, and conversion of dopamine to the neurotransmitter, norepinephrine. It is also helpful in the intestinal absorption of iron and functions as an antioxidant.

Indications for Use:
used in the prevention and treatment of vitamin C deficiency

Effects of Deficiency:
Deficiencies can occur from poor diet, smoking, stress or prolonged use of antibiotics. The deficiency is called skurvy and involves a defect in collagen synthesis causing slow wound healing, defects in tooth formation, and capillary eruption.

Effects of Overdose:
kidney stones, loose bowels, skin rashes, and rebound skurvy can occur with megadoses of vitamin C.
Iodine

**Dietary Sources:**
- drinking water, vegetables, and table salt

**Actions in the Body:**
- Iodine is involved in the production of the hormones thyroxine and triiodothyronine that regulate metabolism.

**Effects of Deficiency:**
- Dietary deficiency of iodine results in a goiter (thyroid hyperplasia).

Zinc

**Dietary Sources:**
- Zinc is found in most foods, especially meat, liver, eggs, seafood, and whole grain products.

**Actions in the Body:**
- Zinc is involved in most of the body's metabolic pathways and is also associated with the antioxidant system.

**Effects of Deficiency:**
- A zinc deficiency can mimic a vitamin A deficiency, because zinc is required to convert retinol to retinal, and therefore less photopigment is created causing night blindness and reduced color sensitivity. Other effects of zinc deficiency are: slow growth in children, poor appetite, impaired taste acuity, skin changes and immunological abnormalities.

Manganese

**Dietary Sources:**
- whole grains, cereal products, fruits and vegetables

**Actions in the Body:**
- essential for the production of certain metaloenzymes

**Effects of Deficiency:**
- Although rare, the signs of manganese deficiency are: poor reproductive performance, growth retardation, congenital malformations of offspring, abnormal formation of bones and cartilage, impaired glucose tolerance.
Copper

Dietary Sources:
Organ meats (especially liver), seafood, nuts and seeds

Actions in the Body:
essential part of several proteins and enzymes, such as antioxidants and those responsible for the proper utilization of iron

Effects of Deficiency:
Copper deficiency is extremely rare but can occur in individuals with intestinal bypass surgery, those on parenteral nutrition, and malnourished infants.

Selenium

Dietary Sources:
seafood, kidney, liver, grains and seeds

Actions in the Body:
- essential for the antioxidant enzyme glutathione peroxidase.
- Suggested for the treatment and prevention of high blood pressure, strokes, heart attacks, cancer and arthritis.

Effects of Deficiency:
a link between Selenium deficiency and Keshan disease, a cardiomyopathy has been reported

Chromium

Dietary Sources:
yeast, liver, beef, whole grains, and vegetables

Actions in the Body:
chromium is a part of the glucose tolerance factor that acts with insulin to enhance glucose entry into cells

Effects of Deficiency:
Deficiency is fairly common due to low soil concentrations of chromium. Deficiency can result in glucose intolerance and a diabetes-like syndrome.
# ELECTROLYTES

## Calcium

**Dietary Sources:**
- dairy products are the chief source

**Actions in the Body:**
- 99% of calcium is joined with phosphate in the bones and teeth.
- 1% is essential for nerve, muscle, cardiac function, membrane integrity, blood coagulation and hormone function.

**Effects of Deficiency:**
- Calcium deficiency may result from inadequate dietary intake, inadequate intake of vitamin D, hypoparathyroidism, and renal insufficiency.
- Signs include: tetany, paresthesias, increased neuromuscular excitability, laryngospasm, muscle cramps, convulsion, lens opacities.

**Effects of Large Levels:**
- Hypercalcemia can result from excess intake of calcium, hyperparathyroidism or vitamin D excess and may result in kidney lesions, painful bone cysts and osteoporosis.

## Sodium

**Dietary Sources:**
- While most foods contain some sodium, the primary dietary intake is from the salt that is added to food.

**Actions in the Body:**
- Sodium is the primary regulator of extracellular fluid volume, osmolarity, acid-base balance, and the membrane potentials of cells. Sodium levels are maintained by the effects of the hormone aldosterone on the kidneys.

**Effects of Deficiency:**
- Dietary deficiencies do not occur with normal diets, and even heavy sweating does not normally create a need for salt supplements.

**Effects of Overconsumption:**
- Chronic overconsumption has been linked to systemic hypertension.
ELECTROLYTES (continued)

Potassium

**Dietary Sources:**
fruits, vegetables, fresh meats

**Actions in the Body:**
important in the transmission of nerve impulses, skeletal muscle contractility, and maintaining normal blood pressure.

**Effects of Deficiency:**
Potassium deficiency is rare, but can occur due to excessive potassium excretion while being treated with diuretic agents. Signs are: weakness, anorexia, nausea, listlessness, drowsiness, irrational behavior, and potentially fatal cardiac arrhythmia.

HEMANTINIC AGENTS

Iron

**Dietary Sources:**
liver, egg yolk, vegetables, legumes

**Actions in the Body:**
needed for the heme portion of hemoglobin and myoglobin and in the production of cytochromes involved in metabolism

**Effects of Deficiency:**
- Deficiency may be due to malabsorption due to low vitamin C intake, or by high intake of calcium, phosphate, phylates, bran, polyphenols and antacids. Also, blood loss from hemorrhage or menstruation may lead to iron deficiency.
- Signs are: microcytic anemia (characterized by small red blood cells and low hemoglobin concentration) and CNS transmission problems.
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