Antineoplastics

Wednesday, March 02, 2011
11:28 AM

Adverse reactions:
- Most serious is the hematologic system—general bone marrow function inhibition
- Neutropenia - results in high risk of infection in patients

Cytarabine (AraC) - analog to deoxycytidine - forms dCTP, inhibits DNA synthesis

- Uses: See table
- Metabolism: Drug activation involved in pyrimidine metabolism

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Pyrimidine antagonist

- Formyl derivative of tetrahydrofolate acid
- Prodrug
- Folate antimetabolite (similar structure vs folic acid)

- Similar cytotoxic profiles in tumor cells
- Acts as a bifunctional blocking agent - both strand links

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Methotrexate (antimetabolite) (alkylating agent) (Cyclo NON-SPECIFIC, but more active in AILN phase)

- Uses: See table
- Metabolism: Drug activation involves polyglutamation

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Cisplatin (antimetabolite) (alkylating agent) (Cyclo NON-SPECIFIC, but more active in 5p phase)

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Docetaxel (anticancer agent - taxane family)

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Carmustine (alkylating agent) (Cyclo NON-SPECIFIC)

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Anticancer agent etoposide associated with acute non-lymphocytic leukemia

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Mitomycin C (antimetabolite) (alkylating agent) (Cyclo NON-SPECIFIC, but more active in 5p phase)

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5-Fluorouracil (antimetabolite) (purine nucleoside antimetabolite) (Cyclo NON-SPECIFIC, but more active in 5p phase)

- Uses: See table
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Cytarabine (AraC) (antimetabolite) (purine nucleoside antimetabolite) (Cyclo NON-SPECIFIC, but more active in 5p phase)

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Blood Page 1
Pharmacology: 
Methotrexate: cytotoxic, antimetabolite; inhibits folate reduction.

Osteosarcoma: high-risk therapy.


Myelosuppression: result of increased capillary permeability.

Estrogen: hormone (endocrine agent).

SERM (mimics estrogen): Tamoxifen (neoplastic agent).

Mix of glycoproteins: Bleomycin (antibiotic).

Antibiotics: Doxorubicin (antimitotic agent).

Paclitaxel (antimitotic agent): Vincristine.

Camptothecins: Interacting Agents.

Leucovorin: SPECIFIC; M PHASE.

Specific; M PHASE.

Metaphase: SPECIFIC; M PHASE.

Advanced breast cancer in postmenopausal patients:

Dependent on estrogen for function and proliferation.

Metastatic breast cancer have ER (+).

Testicular cancer (combination).

Lymphoma (combination).

Sarcomas.

Thyroid carcinoma.

Ovary carcinoma.

Solid tumors (combination therapy).

Leukemias (not a major use, due to increased toxicity).

Metastatic breast cancer (after failure of previous treatment).

Non-small cell lung cancer.

Advanced ovarian cancer.

Breast cancer (different target vs paclitaxel).

Liver metastasis.

Malignant (endocrine) prostate.

CARCINOGENESIS: FROM OBESITY TO CANCER.

Resistance: increased expression of P-glycoprotein.

Resistance: adenosine A2A receptor occupancy process (limiting effectiveness of drug).

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Epidermal growth factor receptor (EGFR) mAb

- Inhibits activation of the receptor tyrosine kinase

Anti-angiogenic agents

- Bind to tyrosine kinase receptors to inhibit transduction of the growth factor signaling pathways

- Reduce blood flow to tumors

- Inhibit neoangiogenesis

- Reduce overall survival in patients with EGFR expression

Humanized mAb against extracellular domain of HER2 protein

- Highly selective for proteins required for survival and proliferation of specific cancer cells

- Acts by directly inhibiting HER2

- Blocks HER2 dimerization and receptor activation

- Inhibits HER2-mediated signal transduction pathways and perturbation of cell proliferative, survival, and adhesive properties

- Inhibits HER2 tyrosine kinase activity

- Blocks tyrosine kinase activation of HER2 protein and prevents phosphorylation of downstream proteins

- Blocks HER2 neuregulin signaling

- Blocks HER2 activation of Akt

- Blocks HER2-mediated activation of RAF, MEK, and ERK

- Blocks HER2-induced activation of multiple downstream proteins

- Blocks HER2-mediated activation of multiple signal transduction pathways

- Inhibits HER2-mediated activation of Akt

- Selectively inhibits HER2 signaling in a variety of in vitro and in vivo models

- Associated with a reduced risk of disease progression

- Associated with improved overall survival

- Associated with improved disease-free survival

- Associated with improved progression-free survival

- Associated with improved overall survival

- Associated with improved progression-free survival

- Associated with improved overall survival

-Carcinoid syndrome (due to serotonin production)

- Severe hypotension

- Torsades de pointes

- Acute respiratory distress syndrome

- Cardiac arrhythmias

- Sudden death

- Malignant hyperthermia

- Acute respiratory failure

- Acute renal failure

- Acute liver failure

- Acute psychiatric disorders

- Depression

- Seizures

- Anxiety

- Mania

- Delirium

- Agitation

- hallucinations

- Visual disturbances

- Lethargy

- Nausea

- Vomiting

- Diarrhea

- Constipation

- Anorexia

- Fever

- Chills

- Rash

- Urticaria

- Angioedema

- Dizziness

- Headache

-Sedation

- Hypersensitivity reactions

- Acute respiratory distress syndrome

- Pericardial effusion

- Myocardial infarction

- Congestive heart failure

- Cardiac arrest

- Death

Rasburicase (xanthine oxidase inhibitor)

- Reduces uric acid levels

- Prevents complications from hyperuricemia

- Reduces risk of uric acid nephropathy

- Prevents uric acid crystals from forming in the kidney

- Decreases the risk of gout attacks

- Reduces the risk of renal failure

- Reduces the risk of acute kidney injury

- Reduces the risk of chronic kidney disease

- Reduces the risk of cardiovascular events

- Reduces the risk of mortality

- Reduces the risk of hospitalization for uric acid nephropathy

- Reduces the risk of acute coronary syndrome

- Reduces the risk of stroke

- Reduces the risk of myocardial infarction

- Reduces the risk of sudden cardiac death

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- Reduces the risk of hospitalization for uric acid nephropathy
Nutrition
Friday, March 04, 2011
2:57 PM

Dietary Supplement Health and Education Act (DSHEA)

Dietary supplement (definition) product (excluding tobacco) intended to supplement diet that bears or contains one or more of the following dietary ingredients: a vitamin, mineral, amino acid, herb, or other botanical - or A dietary substance for use in voluntarily increasing the total dietary intake; - or - Concentrate, metabolite, constituent, extract, or combination of any ingredient described above - or
Intended for ingestion in forms of capsules, powders, softgels, and not represented as a conventional food or as a dietary supplement - or placed under special category under general umbrella of FOODS and NOT DRUGS - or requirement for every supplement to be labeled as a dietary supplement - or requirement for ingredient labeling - include name and quantity of each dietary ingredient or total quantity of all dietary ingredients in herbal blend - labeled must: Product as dietary supplement - Herbal and botanical remedies must state part of the plant the ingredients derived from - labels must provide nutritional labeling and nutritional information must provide ingredient statements on product label

Facts that manufacturer is responsible for determining that dietary supplements that it produces and/or distributes are safe and any representations or claims made about them is substantiated by adequate evidence to show that they are not false or misleading

FDA regulations for dietary and herbal supplements
FDA does not "approve" dietary supplements for SAFETY OR before reaching the consumer
Not required to record, investigate, or forward reports of injury or illness that may be related to the use of the product - require of voluntary action on adverse event reports, product sampling, information in scientific literature, other sources for evidence of danger - essentially, FDA does not monitor or regulate thousands of individual products
Manufacturers do not need to register company nor their dietary supplement products with the FDA before producing or selling them

Supplement claims:
1. Health claims: relationship between food substance and disease or health-related condition
   1. Oversight: 2
      1) Literature review
      2) Authorization statement of a scientific body of US government or National Academy of Sciences
      3) "Certain qualified health claims" used for supplement (claim that there is more evidence for claims vs against

2. Structure/function claims: benefits to nutrient deficiency disease as long as statement also tells how widespread it is in the US; needs to tell what the nutrient or dietary ingredient is intended to do for the consumer
   Manufacturer is responsible for ensuring accuracy and truthfulness of the claims (no oversight over this by FDA) - must have disclaimer that FDA has not evaluated the claim, eg "not intended to diagnose, treat, cure, or prevent disease"
   As only a drug can make such a statement

3. Nutrient content claims: describe level of nutrient or dietary substance in product using terms like "good source," "high," or "free"
   Claim can only be made if FDA has regulation specifying criteria that food must meet in order to use claim
   Can use percentage of total daily value for claims for which there is no established daily value

Requirements and marketing between supplements and drugs
Drug (definition): any article (not device) that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease

Nutrient content claims: describe level of nutrient or dietary substance in product using terms like "good source," "high," or "free"
Manufacturers do not need to register company nor their dietary supplement products with the FDA before producing or selling them

B vitamins

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| B1 (Thiamin) | Niacinamide is principle form used for supplementation
| B2 (Riboflavin) | Niacin
| B3 (Niacin) | Reduce high cholesterole levels
| B5 (Pantothenic acid) | Reduce risk of heart disease
| B6 (Pyridoxine) | Reduce risk of heart disease
| B12 (Folic acid) | Reduce risk of heart disease

Notes:
- Uses: Reduces blood vessels
- Mechanisms: Anti-inflammation effect
- Kinetics: SE
- Interactions: CI
- Notes: Liver disease

Vitamin C (ascorbic acid, Ascorbic acid, Ca ascorbate)

May prevent some cancers and cardiovascular disease
Huge doses don't seem to decrease incidence or severity of colds or influenza; pregnancy; mild to severe disease or inflammation
Antioxidant

Notes:
- Uses: Skin flushing
- Mechanisms: Skin-rich
- Kinetics: SE
- Interactions: CI
- Notes: Liver disease

Vitamin D (cholecalciferol) D3 (cholecalciferol) D2 (cholecalciferol)

Supplementation for exclusively breastfed infants - human milk may not contain enough vitamin D for infant
Osteoporosis (increase risk of hip fractures, decrease bone loss and Ca)
Possible protection vs certain cancers (colon and colorectal)

Notes:
- Uses: Reduce cholesterol levels
- Mechanisms: Anti-inflammation effect
- Kinetics: SE
- Interactions: CI
- Notes: Liver disease

Calcium: D3: fish, liver oils, milk; D2: milk, egg yolks

Notes:
- Uses: Reduce risk of heart disease levels in human LDL
- Mechanisms: Reduce fat intake
- Kinetics: SE
- Interactions: CI
- Notes: Liver disease

Niacin: D3: fish, liver oils, milk; D2: milk, egg yolks

Notes:
- Uses: Reduce risk of heart disease levels in human LDL
- Mechanisms: Reduce fat intake
- Kinetics: SE
- Interactions: CI
- Notes: Liver disease

Pyridoxine: D3: fish, liver oils, milk; D2: milk, egg yolks

Notes:
- Uses: Reduce risk of heart disease levels in human LDL
- Mechanisms: Reduce fat intake
- Kinetics: SE
- Interactions: CI
- Notes: Liver disease

Riboflavin: D3: fish, liver oils, milk; D2: milk, egg yolks

Notes:
- Uses: Reduce risk of heart disease levels in human LDL
- Mechanisms: Reduce fat intake
- Kinetics: SE
- Interactions: CI
- Notes: Liver disease

Thiamin: D3: fish, liver oils, milk; D2: milk, egg yolks

Notes:
- Uses: Reduce risk of heart disease levels in human LDL
- Mechanisms: Reduce fat intake
- Kinetics: SE
- Interactions: CI
- Notes: Liver disease
Glucosamine

- Anti-inflammatory and anti-arthritic
- Protects cartilage
- Supports joint health
- Improves mobility and function
- Reduces joint pain

Side effects:
- Stomach upset
- Gas
- Diarrhea
- Nausea

Interactions:
- Anticoagulant medications (warfarin)
- NSAIDs
- Heparin

Glucosamine is contraindicated with warfarin, NSAIDs, and heparin due to increased bleeding risk.

Omega-3 (fish oil) marine product

- Reduce risk of heart disease
- Lower triglycerides
- Lower blood pressure
- Reduce risk of stroke

Side effects:
- Heartburn
- Nausea
- Vomiting

Interaction:
- Anticoagulant medications (warfarin)

Omega-3 supplements are not recommended with anticoagulant medications due to increased bleeding risk.

Black cohosh (herbal)

- Menopausal symptoms
- Hot flashes
- Night sweats

Side effects:
- Headache
- Nausea
- Dizziness

Interaction:
- Antidepressants

Black cohosh may interact with antidepressants, so use with caution.

Echinacea (herbal)

- Anti-inflammatory
- Immune system support
- Cold and flu treatment

Side effects:
- Headache
- Nausea

Interaction:
- NSAIDs
- Excess phosphorus

Echinacea may interact with NSAIDs and impact phosphorus levels.

Ginkgo biloba (herbal)

- Improvement in memory and cognitive function
- Reduced symptoms of Alzheimer's disease
- Improved blood flow to the brain

Side effects:
- Headache
- Nausea

Interaction:
- Anticoagulant medications (warfarin)

Ginkgo biloba may interact with anticoagulant medications, so use with caution.

Antioxidant activity: nitric oxide radicals and cellular membranes, protects against peroxidation of LDL cholesterol

Most people tolerate well:
- Improved mood
- Reduced anxiety
- Decreased pain

Most people experience:
- GI upset
- Headache
- Nausea

Alpha-glucosidase inhibiting activity:
- Reduces postprandial blood glucose levels

Alpha-glucosidase inhibitors:
- Metformin
- Sulfonlureas

Antioxidant and anti-inflammatory properties:
- Reduces oxidative stress
- Protects against free radical damage

Antioxidant properties:
- Reduces damage to DNA
- Protects against cellular damage

Inflammation suppressant:
- Reduces inflammation
- Protects against tissue damage

Inflammation suppressant:
- Reduces inflammation
- Protects against tissue damage

Long term usage:
- Reduces risk of chronic disease
- Improves cardiovascular health

Long term usage may improve cardiovascular health and reduce chronic disease risk.

Caution:
- Monitor blood glucose levels
- Avoid with diabetes

Monitored for glucose levels in diabetic patients.

CAUTION: Warfarin Use

- GI upset
- Headache
- Nausea

Interaction:
- Anticoagulant medications (warfarin)

Warfarin use may interact with echinacea, so use with caution.

Blood Page 5
<table>
<thead>
<tr>
<th>Common Use</th>
<th>Side Effects</th>
<th>Possible Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valerian (herbal)</td>
<td>May cause dizziness, drowsiness, or confusion</td>
<td>May interact with CNS depression medications (such as benzodiazepines), potentially increasing sedative effects.</td>
</tr>
<tr>
<td>St. John's wort (herbal)</td>
<td>May interact with antidepressants, potentially increasing or decreasing effective doses.</td>
<td>Avoid concurrent use of high-dose St. John's wort with SSRIs, MAOIs, or tricyclic antidepressants.</td>
</tr>
<tr>
<td>Saw palmetto (herbal)</td>
<td>May interact with NSAIDs, potentially increasing the risk of bleeding.</td>
<td>May interact with warfarin, increasing the risk of bleeding.</td>
</tr>
</tbody>
</table>

---

### Beneficial Effects

- **Anxiety**
- **Mild to moderate depression**
- **Menstrual cramping**
- **Menopause**
- **Arthritis**
- **Sciatica**
- **OCD**
- **Saw palmetto** - potential to prevent and reduce the risk of prostate cancer.

### Side Effects

- **Dizziness, drowsiness, confusion**
- **GI symptoms**
- **Headache, insomnia, nausea**
- **Tender breasts**

### Interactions

- **Hepatic enzymes inhibitors** (such as certain antiretrovirals, antifungal agents, or antipsychotics) may increase the amount of valerian metabolites in the bloodstream.
- **Caffeine** may enhance the sedative effects.

### Caution

- **Avoid** during pregnancy or while breastfeeding.
- **Use with caution** in those with bleeding disorders, liver disease, or kidney disease.

---

### Notes

- **Valerian** and **St. John's wort** should be used with caution in those with certain medical conditions or taking specific medications.
- **Saw palmetto** may interact with medications that affect blood clotting or bleeding.

---

**Valerian (herbal)**

- **Promote sleep** (reduce sleep time, improve sleep quality)
- **Sedative effects**
- **Reduce anxiety**

**St. John's wort (herbal)**

- **Promote sleep** (reduce sleep time, improve sleep quality)
- **Sedative effects**
- **Reduce anxiety**
- **Improve mood**

**Saw palmetto (herbal)**

- **Promote sleep** (reduce sleep time, improve sleep quality)
- **Sedative effects**
- **Reduce anxiety**
- **Improve mood**

---

*Note: This information is for educational purposes only and should not replace professional medical advice.*
<table>
<thead>
<tr>
<th>Herb</th>
<th>Popular Use</th>
<th>Active Ingredient</th>
<th>Typical Dose</th>
<th>Adverse Reactions</th>
<th>Drug Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Cohosh</td>
<td>Hot flashes from menses</td>
<td>20 mg</td>
<td>None</td>
<td>Increased risk of pregnancy or pregnancy-specific cancer</td>
<td>Hormone medications, antihypertensive drugs</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Prevention and treatment of common cold, wound healing</td>
<td>300-400 mg tid</td>
<td>Unpleasant taste of achyphylaxis if used for 3-5 wk</td>
<td>Avoid use with hepatotoxic drugs and immunosuppressants</td>
<td></td>
</tr>
<tr>
<td>Feverfew</td>
<td>Migraine prophylaxis</td>
<td>Parthenolide 25-75 mg bid or tid</td>
<td>None</td>
<td>Potential cross-reactivity with chamomile, ragweed, and yarrow allergies</td>
<td>Avoid use with platelet inhibitors and anticoagulants</td>
</tr>
<tr>
<td>Garlic</td>
<td>Lipid-lowering, antithrombotic, anti-inflammatory, anti-inflammatory</td>
<td>Allicin 300 mg bid or tid</td>
<td>None</td>
<td>May potentiate hypoglycemic and antithrombotic therapy, lowers plasma level of</td>
<td>Avoid use with platelet inhibitors and anticoagulants</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Diminishes pimples</td>
<td>Flavonoids 40-80 mg/tid</td>
<td>Rarely, nonspecific GI complaints, headache, insomnia, allergic reaction, anxiety,</td>
<td>Avoid use with antibiotics, platelet inhibitors, and anticoagulants</td>
<td></td>
</tr>
<tr>
<td>Ginseng</td>
<td>Astringent, anti-inflammatory, anti-inflammatory</td>
<td>Triterpenoids 40-80 mg/tid</td>
<td>Rarely, nonspecific GI complaints, headache, insulin, allergic reaction, anxiety,</td>
<td>Avoid use with antibiotics, platelet inhibitors, and anticoagulants</td>
<td></td>
</tr>
<tr>
<td>Ginseng</td>
<td>Astringent, anti-inflammatory, anti-inflammatory</td>
<td>Organic acids 40-80 mg/tid</td>
<td>Rarely, nonspecific GI complaints, headache, insomnia, allergic reaction, anxiety,</td>
<td>Avoid use with antibiotics, platelet inhibitors, and anticoagulants</td>
<td></td>
</tr>
<tr>
<td>Saw palmetto</td>
<td>Benign prostatic hyperplasia</td>
<td>Sesels 160 mg bid</td>
<td>None</td>
<td>May reduce the absorption of thyroid medication or nutrients: zinc, iron, and calcium</td>
<td></td>
</tr>
<tr>
<td>Soy</td>
<td>Cholesterol levels</td>
<td>Isoflavones 6.25 g per serving</td>
<td>None</td>
<td>Contraindicated with pregnancy, breast feeding, or estrogen-sensitive cancer</td>
<td></td>
</tr>
<tr>
<td>St John's wort</td>
<td>Anxiety, depression, insomnia</td>
<td>Hypericin 300 mg tid</td>
<td>Rarely, hypnotic, anxiolytic, dry mouth, dreaminess, constipation, and other F1 symptoms, decrease sexual function in 2% of patients</td>
<td>Lowers plasma levels of cyclosporine (Neoral, Sandimmune), warfarin sodium (Coumadin), protease inhibitors metabolized by CYP450 and especially induced by sulfite (Crisvel), nonsteroidal anti-inflammatory agents, digoxin (Digit, Lantanne, Lanoxicaps, Lanoxin), oral contraceptive, theophylline, amphotericin B (EOl)</td>
<td>Contraindicated use of SSRIs can cause serotonin syndrome</td>
</tr>
<tr>
<td>Valerian</td>
<td>Sedative, hypnotic, anxiolytic</td>
<td>Valeric acid 400 mg/kg</td>
<td>Rarely, headache, excitement, cardiac disturbances</td>
<td>May potentiate the effectiveness of other sedatives and hypnotics</td>
<td></td>
</tr>
</tbody>
</table>
Corticosteroids

Tuesday, March 08, 2011
4:24 AM

Corticosteroids (NICE/NET): Glucocorticoids
- Treatment of adrenal, pituitary, hypothalamic deficiency
- Pharmacologic to suppress inflammation, immune responses, and edema

Mineralocorticoids
- Treatment of adrenal deficiency
- Pharmacologic for low blood pressure
- Aldosterone produced in zona glomerulosa (adrenal cortex)
- Regulated by renin-angiotensin system
- Regulated by plasma potassium concentrations

Androgens: dehydroepiandrosterone (DHEA) and androstenedone (weak androgens), testosterone - 19 carbon steroids
- Aldosterone produced in zona glomerulosa (adrenal cortex)
- Regulated by renin-angiotensin system
- Regulated by plasma potassium concentrations

Glucocorticoids (cortisol) and androgens produced in zona fasciculate (middle/inner zones)

Regulated by ACTH

- Not influenced by angiotensin II receptors

HPA axis:
- Hypothalamus: Releases corticotrophin-releasing hormone (CRH)
- Transported to pituitary by hypothalamic-pituitary system
- CRH induces release of corticotrophin

Pituitary:
- Cosyntropin/ACTH released in response to CRH
- Release triggered by CRH

ACTH reflects the diurnal/daily cycle and physiological stress state of individual

Glucocorticoids usually not curative - only treat clinical symptoms

**Corticosteroids Have Dose-Dependent Effects**
- Selective antitumor, antinflammatory actions due to effects on vascular and extracellular matrix muscle

**Main Function of Corticosteroids**
- Homeostasis and coping with stress
- Protect body from stressors of mild and stressful environmental changes

Glucocorticoids have some mineralocorticoid activity and vice versa

**Corticotropin-Stimulation Test for Adrenal Insufficiency**
- Act as a stress test to evaluate adrenal function

**Corticotropin-Stimulation Test for Adrenal Insufficiency**

<table>
<thead>
<tr>
<th>Name</th>
<th>Uses</th>
<th>Mechanism</th>
<th>Kinetics</th>
<th>SE</th>
<th>Interactions</th>
<th>CI</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>(aka corticotropin)</td>
<td>Stimulates hormone production and release in zona fasciculata and zona reticularis (glucocorticoids and androgens)</td>
<td>Consists of 19 peptides (first 20 are required for function)</td>
<td>Derived from pro-opiomelanocortin (POMC)</td>
<td>Released by pituitary</td>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; &lt; 15 min (plasma)</td>
<td>Excess ACTH: Addison’s disease - Increased pigmentation due to high MSH levels</td>
</tr>
</tbody>
</table>

**Glucocorticoids**

**Stimulating Test for Adrenal Insufficiency**

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone OR dexamethasone</td>
<td>For adrenal insufficiency</td>
<td>Stimulation test for adrenal insufficiency</td>
<td>Consists of 24 peptides of ACTH (when first 20 peptides are required for function)</td>
<td>ACTH</td>
<td>ACTH increases glucocorticoid production</td>
<td>Excess ACTH: Addison’s disease - Increased pigmentation due to high MSH levels</td>
<td>Diagnostics test for adrenal insufficiency</td>
</tr>
</tbody>
</table>

**Cortisol**

**Glucocorticoids**

- Glucocorticoids: Cortisol, aldosterone, dehydroepiandrosterone (DHEA)
- Produced in zona fasciculata and zona reticularis (glucocorticoids/cortisol)
- Stimulates hormone production and release in zona fasciculata and zona reticularis (glucocorticoids/cortisol)

**Corticotropin-Stimulation Test for Adrenal Insufficiency**

- Act as a stress test to evaluate adrenal function
null
required for activity
- OH group at C(11) NOT REQUIRED for mineralocorticoid activity

Mechanism of action:
- Bind to intracellular nuclear hormone receptors (mineralocorticoid receptors) to promote responsive genes
- Receptor distribution:
  -- Kidney: distal cortical tubules and cortical collecting ducts of kidney
  -- Colon: water and electrolyte regulation
  -- Salivary and sweat glands: water and electrolyte regulation
  -- Hippocampus: osmoregulatory homeostasis???

Fludrocortisone
(synthetic mineralocorticoid agonist)
Mineralocorticoid actions >> anti-inflammatory actions
Fluorination at C(9) increases biological activity
Lack of -OH or -CH3 at C(16) preserves mineralocorticoid activity vs glucocorticoid (anti-inflammatory) activity

Spironolactone
(adrenocortical antagonist, mineralocorticoid antagonist)
Potassium-sparing diuretic
Hyperaldosteronism (to minimize K+ loss)
Potassium-sparing diuretic
- Na+ and H2O lost when administered
REQUIRES PRESENCE OF ALDOSTERONE

<table>
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<tr>
<th>Name</th>
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<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole</td>
<td>Anti-fungal agent</td>
<td>Inhibit steroid synthesis</td>
<td>17α-21α-monooxygenase inhibitor (higher doses): cholesterol monooxygenase</td>
<td></td>
<td></td>
<td></td>
<td>OFF LABEL USE</td>
</tr>
<tr>
<td>Mitotane</td>
<td>Adrenal carcinoma (variable efficacy)</td>
<td>Atrophy and necrosis of normal and malignant adrenal cortical cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mifepristone</td>
<td>Pituitary and adrenal tumors leading to hypercortisol</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
### NSAIDS

- **Name**: Uses, Mechanism, Kinetics, SE, Interactions, CI, Notes

<table>
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<tbody>
<tr>
<td>Acetaminophen</td>
<td>Analgesic, antipyretic, antipyretic action</td>
<td>interferes with prostaglandin synthesis</td>
<td>dosage dependent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Analgesic, anti-inflammatory, anti-inflammatory</td>
<td>prevents prostaglandin synthesis</td>
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<td>Ibuprofen</td>
<td>Analgesic, anti-inflammatory, anti-inflammatory</td>
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<td>Ketoprofen</td>
<td>Analgesic, anti-inflammatory, anti-inflammatory</td>
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<td>Naproxen</td>
<td>Analgesic, anti-inflammatory, anti-inflammatory</td>
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<td></td>
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</table>

### Interaction with GI Side Effects

- **Name**: Mechanism, Kinetics, SE, Interactions, CI, Notes

<table>
<thead>
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<tbody>
<tr>
<td>Acetaminophen</td>
<td>(reversible)</td>
<td>dose dependent</td>
<td>analgesic, antipyretic</td>
<td>increased bleeding risk</td>
<td></td>
<td></td>
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<td>Diclofenac</td>
<td>(reversible)</td>
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### NSAID PRODRUG

- **Name**: USES, MECHANISM, KINETICS, CI, NOTES

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</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Analgesic, anti-inflammatory, anti-inflammatory</td>
<td>prevents prostaglandin synthesis</td>
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### NSAID PRODRUG

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</tr>
</tbody>
</table>

---

**NSAIDs have analgesic (relief of mild to moderate pain), but effects vary.**

**Inhibition of PROSTAGLANDIN COX-1 and COX-2: Inhibition of prostaglandin synthesis**

**COX-1 = GASTRIC ULCERS**

**COX-2 = ANKHOS**

**MECHANISM**

**GI side effects:** GASTRIC ULCERS

**Notes:**

- **Antiangiogenic:** NSAIDs have antiangiogenic effects.
- **GI side effects:** NSAIDs can cause gastrointestinal side effects.
- **Renal side effects:** NSAIDs can cause renal side effects.
- **Precautions:** NSAIDs should be used with caution in patients with renal impairment or liver disease.

---

**NSAID PRODRUG:**

- **USES:**
  - Analgesic, anti-inflammatory
  - Antipyretic

- **MECHANISM:**
  - Prevents prostaglandin synthesis

- **KINETICS:**
  - Dosage dependent

- **CI:**
  - Additive with other NSAIDs

---

**NSAID INHIBITORS:**

- **USES:**
  - Analgesic, anti-inflammatory
  - Antipyretic

- **MECHANISM:**
  - Prevents prostaglandin synthesis

- **KINETICS:**
  - Dosage dependent

- **CI:**
  - Additive with other NSAIDs
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<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (paracetamol)</td>
<td>ANALGESIA (=/ - codeine ANTIPYRESIS LITTLE TO NO ANTI-INFLAMMATORY ACTION, though promoted for arthritis (and has no therapeutic effect) PREFERRED ANALGESIC IN PREGNANCY, LABOR May decrease psychological impact of pain Other formulations: +codeine: -- +3 (+30mg) -- #4 (+60mg) +oxycodone +hydrocodone +caffeine and butalbital</td>
<td>Inhibition of prostaglandin synthesis (COX-3) in brain; NO PERIPHERAL COX EFFECT</td>
<td>No platelet effects. Little protein binding Metabolism in liver; microsomal enzymes induced Minor metabolic pathway: one microsomal oxidation pathway produces electrophilic intermediate (NAPQI) that reacts with glutathione that is excreted. If glutathione is depleted, a reactive intermediate will kill hepatocytes and lead to liver failure</td>
<td>Peak concentration: 30-60min; t1/2 = 2-3 hrs.</td>
<td>Antagonist interactions; though 5HT3 antagonist interactions, though (antagonizes and is antagonized by 5HT3 drugs)</td>
<td>NO GI BLEEDING (much less ulcerogenic vs aspirin)</td>
<td>LEVER TOXICITY (greater vs aspirin) OVERDOSE: HEPATOCYTE DEATH, LIVER FAILURE, DEATH (when glutathione is depleted at very high drug doses -- refer to Kinetics) DOES NOT CAUSE METHEMOGLOBINEMIA OR ANEMIA IN HUMANS (affects dogs and cats, though)</td>
</tr>
</tbody>
</table>

Blood Page 12
**Opioid Analgesics**

**Thursday, March 10, 2011**

1:49 AM

- **Efficacy**
  - Codeine < meperidine = hydrocodone & methadone < morphine (barely), but it’s the best analgesic
  - Buprenorphine
  - Heroin depends on metabolism to morphine

- **Potency**
  - Meperidine
  - Morphine
  - Hydrocodeine

- **Mechanism**
  - Oral
  - Facilitates heat loss via SE

- **Possible Breakthrough Pain**
  - Before next dose, despite proper dosing

- **Interactions**
  - Methadone
  - Atropine
  - Diarrhea
  - 1st pass effect also occurs
  - Urine

- **Kinetics**
  - > morphine (contributes to slow elimination)

- **Notes**
  - Head injury must be able to assess mental status
  - OD treatment: naloxone

### Table: Opioid Analgesics

<table>
<thead>
<tr>
<th>Name</th>
<th>Uses</th>
<th>Mechanism</th>
<th>Kinetics</th>
<th>SE</th>
<th>Interactions</th>
<th>O</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (opioid agonist)</td>
<td>Most types of severe pain; but not alliperine (e.g., enanthate)</td>
<td>CNS effects: (1) suppression of medial thalamus, medullary raphe, midbrain/MEP, &amp; frontal cortex arrest; (2) dorsal horn of spinal cord involving substantia gelatinosa by hyperalgesia (ability to produce reflex pain and muscle spasticity); (3) changes in pain threshold and affective responses to pain in general</td>
<td>CNS:</td>
<td>CNS depression (additive effect)</td>
<td>Head injury must be able to assess mental status</td>
<td>OD: treatment: naloxone</td>
<td>Notes: opium poppy</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Analgesic; less potent than morphine, methadone, and meperidine</td>
<td>CNS effects: (1) suppression of pain in the thalamus, raphe nuclei, and the frontal cortex</td>
<td>CNS:</td>
<td>CNS depression (additive effect)</td>
<td>Head injury must be able to assess mental status</td>
<td>OD: treatment: naloxone</td>
<td>Notes: opium poppy</td>
</tr>
<tr>
<td>Methadone</td>
<td>Antitussive (relatively safe as an OTC)</td>
<td>CNS effects: (1) suppression of pain in the thalamus, raphe nuclei, and the frontal cortex</td>
<td>CNS:</td>
<td>CNS depression (additive effect)</td>
<td>Head injury must be able to assess mental status</td>
<td>OD: treatment: naloxone</td>
<td>Notes: opium poppy</td>
</tr>
<tr>
<td>Codeine (3-methylmorphine)</td>
<td>Antitussive</td>
<td>CNS effects: (1) suppression of pain in the thalamus, raphe nuclei, and the frontal cortex</td>
<td>CNS:</td>
<td>CNS depression (additive effect)</td>
<td>Head injury must be able to assess mental status</td>
<td>OD: treatment: naloxone</td>
<td>Notes: opium poppy</td>
</tr>
<tr>
<td>Heroin (3,4-dimethoxyphenylmorphine)</td>
<td>Antitussive</td>
<td>CNS effects: (1) suppression of pain in the thalamus, raphe nuclei, and the frontal cortex</td>
<td>CNS:</td>
<td>CNS depression (additive effect)</td>
<td>Head injury must be able to assess mental status</td>
<td>OD: treatment: naloxone</td>
<td>Notes: opium poppy</td>
</tr>
<tr>
<td>Morphine (opioid agonist)</td>
<td>Antitussive</td>
<td>CNS effects: (1) suppression of pain in the thalamus, raphe nuclei, and the frontal cortex</td>
<td>CNS:</td>
<td>CNS depression (additive effect)</td>
<td>Head injury must be able to assess mental status</td>
<td>OD: treatment: naloxone</td>
<td>Notes: opium poppy</td>
</tr>
<tr>
<td>Loperamid (phenylpiperidine agonist)</td>
<td>Anti-diarrheal</td>
<td>CNS effects: (1) suppression of pain in the thalamus, raphe nuclei, and the frontal cortex</td>
<td>CNS:</td>
<td>CNS depression (additive effect)</td>
<td>Head injury must be able to assess mental status</td>
<td>OD: treatment: naloxone</td>
<td>Notes: opium poppy</td>
</tr>
<tr>
<td>Diclofenac (phenylpiperidine agonist)</td>
<td>Anti-inflammatory</td>
<td>CNS effects: (1) suppression of pain in the thalamus, raphe nuclei, and the frontal cortex</td>
<td>CNS:</td>
<td>CNS depression (additive effect)</td>
<td>Head injury must be able to assess mental status</td>
<td>OD: treatment: naloxone</td>
<td>Notes: opium poppy</td>
</tr>
<tr>
<td>Naloxone (phenylpiperidine agonist)</td>
<td>Antitussive</td>
<td>CNS effects: (1) suppression of pain in the thalamus, raphe nuclei, and the frontal cortex</td>
<td>CNS:</td>
<td>CNS depression (additive effect)</td>
<td>Head injury must be able to assess mental status</td>
<td>OD: treatment: naloxone</td>
<td>Notes: opium poppy</td>
</tr>
<tr>
<td>Sufentanil (phenylpiperidine agonist)</td>
<td>Anti-diarrheal</td>
<td>CNS effects: (1) suppression of pain in the thalamus, raphe nuclei, and the frontal cortex</td>
<td>CNS:</td>
<td>CNS depression (additive effect)</td>
<td>Head injury must be able to assess mental status</td>
<td>OD: treatment: naloxone</td>
<td>Notes: opium poppy</td>
</tr>
<tr>
<td>Methadone</td>
<td>Antitussive</td>
<td>CNS effects: (1) suppression of pain in the thalamus, raphe nuclei, and the frontal cortex</td>
<td>CNS:</td>
<td>CNS depression (additive effect)</td>
<td>Head injury must be able to assess mental status</td>
<td>OD: treatment: naloxone</td>
<td>Notes: opium poppy</td>
</tr>
</tbody>
</table>

**Source:** opium poppy

**Notes:**
- Treat acute OI with naloxone
- OD treatment: naloxone (especially with long-acting agents or partial agonists); watch for withdrawal
<table>
<thead>
<tr>
<th>Name</th>
<th>Uses</th>
<th>Mechanism</th>
<th>Kinetics</th>
<th>SE</th>
<th>Interactions</th>
<th>CI</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levorphanol</td>
<td>(partial agonists in δ</td>
<td>Higher potency but no more efficacious vs morphine</td>
<td>oral</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>opioid/antagonist)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Butorphanol</td>
<td>agonist/antagonist)</td>
<td>C0 antidote</td>
<td>Pharmaol profile similar to pentazocine (a weak antagonist)</td>
<td>Morphine cogenar</td>
<td></td>
<td></td>
<td>May precipitate narcotic withdrawal if given to agonist-addicted individual</td>
</tr>
<tr>
<td></td>
<td>(morphinan/</td>
<td></td>
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<tr>
<td></td>
<td>benzomorphan</td>
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<td></td>
<td>derivative)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>(agonist/antagonist)</td>
<td>Addiction treatment</td>
<td>Agons/antagonistar receptors: p, e.</td>
<td></td>
<td></td>
<td></td>
<td>May precipitate narcotic withdrawal if given to agonist-addicted individual</td>
</tr>
<tr>
<td></td>
<td>(morphinan/</td>
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<td></td>
<td>derivative)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pentazocine</td>
<td>(weak antagonist)</td>
<td>Constipation</td>
<td>Agons (agonist) receptors: μ, e.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(weak agonist)</td>
<td></td>
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<tr>
<td></td>
<td>(morphinan/</td>
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<td></td>
<td>derivative)</td>
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<td></td>
</tr>
<tr>
<td>Naloxone</td>
<td>(antagonist)</td>
<td>constipation</td>
<td>N</td>
<td>Duration: up to 12hrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naltrexone</td>
<td>(antagonist)</td>
<td>Oral OD treatment</td>
<td>N</td>
<td>Duration: 30min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylnaltrexone</td>
<td>(antagonist)</td>
<td>Oral dependence</td>
<td>p-o</td>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nalmefene</td>
<td>(antagonist)</td>
<td>Chronic constipation</td>
<td>N</td>
<td>Duration: up to 12hrs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nalbufaxone</td>
<td>(antagonist)</td>
<td>Acute constipation</td>
<td>N</td>
<td>Duration: up to 12hrs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Name**

<table>
<thead>
<tr>
<th>Tramadol (other)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tapentadol (other)</td>
</tr>
</tbody>
</table>

**Rankings:**

efficacy
codine < meperidine (high doses) & methadone < morphine (barely?), but it's the best analgesic
Buprenorphine
heroin depends on metabolism to morphine

**Potency (least to greatest):**

deripnone & meperidine & hydrocodone & methadone & codeine & buprenorphine & levorphanol

**Duration (least to greatest):**

deripnone & meperidine & hydrocodone & methadone & codeine & tramadol & tapentadol & buprenorphine & naltrexone

**ANALGESIC EFFICACY**

--- MOST EFFECTIVE

--- MORPHINE, MEPERIDINE, FENTANYL, SUFENTANYL, DELAUDID

--- FENTANYL, HYDROCODONE, TRAMADOL, BUPRENORPHINE, NALBUPHINE, BUTORPHANOL, TRAMADOL, NALOXONE, APAP

--- ASPIRIN, NSAIDS, APAP

--- LEAST EFFECTIVE

**Patient factors to consider**

Origin of pain
Duration of pain
Pathophysiology of the pain
Nature of the pain
Adjuvant therapies (physical therapy)

Post-surgical pain and respiratory: Treat thoracic pain so patient can ventilate, too much can be fatal

Can an NSAID be used? 1 Inhibition of platelet aggregation, ulcers

Can APAP be used? 3

Opioids - Caution respiratory depression can be fatal, ESPECIALLY IN SHORT-TERM PATIENTS.

Use adequate doses

Monitor use for abuse and addiction
Hemostasis; Erythropoiesis

Thursday, March 10, 2011
1:50 AM

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**Mechanism of action:**

- Low-molecular-weight heparin (LMWH) interacts primarily in neutrophils with release of heparin released on binding to attach to other antiplatelet molecules.

- Antithrombin acts like a suicide substrate and is used as an agonist.

- Natural heparin primarily in neutrophils.

- Interactions with antithrombin III.

- Venous or arterial thrombosis.

- Inhibition of activity of activated thrombin (F Iia), FIXa, and FXII.

- Factors released on binding to other antiplatelet molecules.

- Reduced risk of thrombocytopenia vs UFH.

- Increased risk with patients with increased risk.

- Use with caution.

---

**Name**

<table>
<thead>
<tr>
<th>Name</th>
<th>Uses</th>
<th>Mechanism</th>
<th>Effects</th>
<th>SI</th>
<th>Interactions</th>
<th>CI</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractioned heparin (intravenous)</td>
<td>Treatment-resistant thrombosis, venous or arterial thrombosis, and DVT.</td>
<td>Inhibits Factor IXa and thrombin at a 2:1 ratio.</td>
<td>Inhibits Factor IXa and thrombin at a 2:1 ratio.</td>
<td>aPTT times may not always correlate with thrombotic risk.</td>
<td></td>
<td></td>
<td>Administered subcutaneously, due to inconsistent batch manufacturing</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>Lower interpatient variability in response to treatment.</td>
<td>Inhibits Factor IXa and thrombin at a 1:1 ratio.</td>
<td>Inhibits Factor IXa and thrombin at a 1:1 ratio.</td>
<td>aPTT times may not always correlate with thrombotic risk.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Venous or arterial thrombosis.</td>
<td>Inhibits Factor IXa and thrombin at a 1:1 ratio.</td>
<td>Inhibits Factor IXa and thrombin at a 1:1 ratio.</td>
<td>aPTT times may not always correlate with thrombotic risk.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Enoxaparin**

- **Name:** Unfractioned heparin
- **Uses:** Treatment-resistant thrombosis, venous or arterial thrombosis, and DVT.
- **Mechanism:** Inhibits Factor IXa and thrombin at a 2:1 ratio.
- **Effects:** Inhibits Factor IXa and thrombin at a 2:1 ratio.
- **SI:** aPTT times may not always correlate with thrombotic risk.
- **Interactions:** None.
- **CI:** None.
- **Notes:** Administered subcutaneously, due to inconsistent batch manufacturing.

---

**Notes**

- *Heparin*:
  - **Name:** Unfractioned heparin
  - **Uses:** Treatment-resistant thrombosis, venous or arterial thrombosis, and DVT.
  - **Mechanism:** Inhibits Factor IXa and thrombin at a 2:1 ratio.
  - **Effects:** Inhibits Factor IXa and thrombin at a 2:1 ratio.
  - **SI:** aPTT times may not always correlate with thrombotic risk.
  - **Interactions:** None.
  - **CI:** None.
  - **Notes:** Administered subcutaneously, due to inconsistent batch manufacturing.

---

**Drugs**

- **Name:** Enoxaparin
- **Uses:** Treatment-resistant thrombosis, venous or arterial thrombosis, and DVT.
- **Mechanism:** Inhibits Factor IXa and thrombin at a 2:1 ratio.
- **Effects:** Inhibits Factor IXa and thrombin at a 2:1 ratio.
- **SI:** aPTT times may not always correlate with thrombotic risk.
- **Interactions:** None.
- **CI:** None.
- **Notes:** Use with caution with patients with increased risk.
Uses increased hemorrhagic events CI SE LWMH disrupts interaction of the protein to lye occlusive, pathogenic thrombi Mechanism 48 hours of Vitamin K (TXA3.0 is a general target Mechanism Warfarin Notes

Name Antiplatelet therapy [tPA] activator Streptokinase Thrombolytic drugs: Barbiturates Cholestyramine (Drug Name= DRUGS T HAT Levothyroxine (Hyperthyroidism) Acetaminophen Aspirin Antifungals of the "azole" class Amiodarone (Cordarone) Trimethoprim/Sulfamethoxazole (Bactrim) Other interactions

Antiplatelet therapy

aspirin Resistance

Drugs that impair direct thrombin inhibition

Other strategies

---

Thrombotic sugar

Anticoagulant effect of warfarin

Drugs and Risk of HEMORRHAGING

Drug Mechanism

Tissue plasminogen activator (tPA activator) Decreased surface clearance through inhibition of hepatic carboxylating enzymes Activating Anticoagulant effect of warfarin

Mechanism

Thrombotic therapy

Thrombotic therapy

Mechanism

Thrombotic therapy

Mechanism

Thrombotic therapy

Mechanism

DRUGS THAT IMPAIR DIRECT THROMBIN INHIBITION

Mechanism Direct block of activity:

Name Bolus IV continuous

Notes

Pregnancy

Notes

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Notes
Eicosanoids (prostaglandins)

- Most are small, linear molecules
- Produced by cyclooxygenase (COX) enzymes
- Some are stable, while others are metabolized to active metabolites
- COX-2 inhibition may reduce inflammation and pain
- COX-1 inhibition may reduce gastric irritation

**Mechanism**

- Inhibits the activity of thromboxane A2 (TXA2), a pro-aggregatory mediator
- Prevents the production of TXA2, reducing platelet aggregation
- Reduces prostacyclin (PGI2) production, which is a vasodilator and platelet inhibitor

**Uses**

- Treatment of pain and inflammation
- Prevention of platelet aggregation in patients with coronary artery disease
- Reduction of thrombotic events

**Interactions**

- May increase bleeding risk in patients receiving anticoagulants or antiplatelet agents
- May interact with other drugs that affect blood pressure

**Notes**

- COX-2 inhibitors are often preferred in patients with coronary artery disease
- COX-1 inhibitors are often used for pain and inflammation

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Antihypertensives

- Used to treat high blood pressure
- Lower blood pressure and reduce the risk of cardiovascular events
- Can improve patient survival and quality of life

** Mechansim**

- Reduce blood pressure by decreasing the amount of blood flowing through the body
- Lower the workload of the heart
- Can reduce the risk of heart attack, stroke, and other complications

**Uses**

- Treatment of hypertension
- Prevention of cardiovascular events in high-risk patients
- Management of hypertension in patients with diabetes

**Interactions**

- May interact with other medications that affect blood pressure
- May increase the risk of side effects

**Notes**

- Regular monitoring of blood pressure and blood tests is recommended
- Patients should report any side effects to their healthcare provider
Thyroid

Monday, March 14, 2011
12:11 PM

**NIS** – Sodium-iodide symporter. The protein that carries out uptake of I\(^{-}\) along with Na\(^{+}\).

**TRABs** – TSH Receptor antibodies that influence iodine uptake into thyroid follicular cells. TRABs could have stimulatory (also known as TSI [Thyroid-Stimulating Immunoglobulin]) or inhibitory effects.

**TSH** – TSH Releasing Hormone or thyrotropin, secreted from the hypothalamus.

**TSH** – Thyroid Stimulating Hormone; secreted from the pituitary

**Wolff-Chaikoff Effect** – acute inhibition of the synthesis of iodotyrosine and isodityrosine by iodide in the process of thyroid hormone synthesis. Excessive increase in intracellular iodide in the thyroid gland

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<table>
<thead>
<tr>
<th>Uses</th>
<th>Mechanism</th>
<th>Kinetics</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thyroid</strong></td>
<td>T3 binding to DNA-bound protein (thyroid hormone receptor) in nucleus (activates) → homodimer or heterodimer with retinoid X receptor → Acetylation of the hormone results in an open chromatin structure regulate metabolism of carbohydrates, lipids, proteins, vitamins, etc. maintain basal metabolic rate</td>
<td>T3 &gt; T4 in action by 10x (T_4 \to T_3) (conversion) Thyroid hormone carried by thyroxine-binding globulin Only free TH (not protein-bound) is active (T_4) is converted intracellularly to (T_3) for binding</td>
<td>Metabolism; (T_3) and (T_4) in the plasma are inactivated; thyroid is deaminated, deiodinated, or excreted unchanged in the feces</td>
</tr>
<tr>
<td><strong>HYPOTHYROIDISM</strong></td>
<td>primary (thyroid failure) Elevated TSH → Hashimoto’s thyroiditis antibodies present against peroxidase and thyroglobulin → goiter possible secondary (pituitary deficiency (TSH)) → tumor → postpartum infarctions (Sheehan’s syndrome) tertiary (hypothalamic deficiency (TRH)) → mass or inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HYPERTHYROIDISM</strong></td>
<td>Causes: Graves’ disease Toxic adenoma Toxic multinodular goiter Less common: Subacute thyroiditis Drugs Thyroid-hormone producing tumors ovarian stroma metastatic thyroid carcinoma (follicular or papillary) hydatidiform mole</td>
<td>Symptoms: (generally nonspecific)</td>
<td></td>
</tr>
<tr>
<td><strong>Whole Body</strong></td>
<td>Moderate weight gain</td>
<td>Weight loss</td>
<td></td>
</tr>
<tr>
<td><strong>Temperature Regulation</strong></td>
<td>Cold intolerance, cold feeling</td>
<td>Heat intolerance, warmed feeling, excessive sweating</td>
<td></td>
</tr>
<tr>
<td><strong>GI</strong></td>
<td>Constipation</td>
<td>Increased food and water intake, diarrhea, loose bowel, frequent defecation</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td>Low pulse rate, poor heart sound, dyspnea, enlargement of the heart</td>
<td>Palpitation, atrial fibrillation, increased systolic pressure, wide pulse pressure, systolic murmurs, angina</td>
<td></td>
</tr>
<tr>
<td><strong>Neuromuscular</strong></td>
<td>Muscle pain and weakness, paresthesia, delayed deep tendon reflexes</td>
<td>Fatigue, weakness, tremor, rapid deep tendon reflexes</td>
<td></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>Cold, dry and yellowish; dry, brittle, and sparse hair.</td>
<td>Warm, soft, flushed and moist; thinning but fine textured hair</td>
<td></td>
</tr>
<tr>
<td><strong>Neck</strong></td>
<td>Often thyroid enlargement (primary hyperthyroidism)</td>
<td>Often thyroid enlargement (primary hyperthyroidism)</td>
<td></td>
</tr>
<tr>
<td><strong>Fees</strong></td>
<td>Edematous eyelids</td>
<td>Prominence of the eyes (only in Grave’s disease), lid lag, retracted lid (in thyrotoxicosis in general)</td>
<td></td>
</tr>
<tr>
<td><strong>Emotional</strong></td>
<td>Depression, lethargy, increased sleepiness</td>
<td>Nervousness, irritability, insomnia</td>
<td></td>
</tr>
<tr>
<td><strong>Genitourinary</strong></td>
<td>Menorrhagia, dysmenorrhea</td>
<td>Amenorrhea or decreased menstrual flow</td>
<td></td>
</tr>
<tr>
<td><strong>THYROID TESTING:</strong></td>
<td>Decreased T4 Decreased T3 increased serum TSH level</td>
<td>Supranormal T4 Supranormal T3 Suppressed TSH &lt;0.01 (primary); stimulated (secondary)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>antibodies against TRAB, thyroglobulin, thyroid hormone in serum essentially confirms immune-mediated hyperthyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extreme levels of circulating thyroid hormone (in susceptible)</td>
<td><strong>THYROID STORM</strong> -- fever, nausea, vomiting, diarrhea, agitation, restlessness, delirium, tachycardia, atrial fibrillation MEDICAL EMERGENCY</td>
<td></td>
</tr>
<tr>
<td>THYROID TESTING: TSH, T4, and T3 Levels</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>----------------------------------------</td>
<td></td>
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</table>

**Type of Hyperthyroidism** | **Cause** | **Mechanism** | **Effects** |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves’ Disease</td>
<td>Autoimmune production of antibody to TSH receptor in thyroid follicular cells</td>
<td>TSH receptor antibody (stimulatory TRAb) that binds to TSH receptor and stimulates thyroid hormone production. TRAB production has been suggested to be due to a defect in suppressor T lymphocytes in certain individuals.</td>
<td>Hyperplasia of the entire thyroid gland, diffuse goiter, and increased secretion of T₄ and T₃.</td>
</tr>
<tr>
<td>Toxic multinodular goiter or Toxic adenoma</td>
<td>Increased number of thyroid follicular cells that produce thyroid hormones</td>
<td></td>
<td>Increased mass of thyroid gland, irregular goiter, increased synthesis and secretion of T₁ and T₂.</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>Increased thyroid hormone synthesis and secretion</td>
<td>Increased iodine supply e.g., amiodarone</td>
<td>Normal thyroid gland, increased T₁ and T₂ synthesis and secretion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypothyroidism</th>
<th>Uses</th>
<th>Mechanism</th>
<th>Kinetics</th>
<th>SE</th>
<th>Interactions</th>
<th>CI</th>
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</tr>
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<tbody>
<tr>
<td>Liothyronine Sodium</td>
<td>NOT for maintenance therapy</td>
<td>Oral, fast onset</td>
<td>Thyrotoxicosis (high T₃ toxicity) - palpitation, tachycardia, weight loss, tremor, headache, insomnia, heat intolerance.</td>
<td>3</td>
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**Preparation** | Content | Advantages/Disadvantages | Outcome |
<table>
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<tr>
<td>Liothyroxine Sodium</td>
<td>Pure synthetic T₄</td>
<td>Long half-life (~7 days), inexpensive, slow onset of action, drug interactions uncommon. About 10 days to maximum effects and about 2 weeks to wear off completely.</td>
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<td>Liothyronine Sodium</td>
<td>Pure synthetic T₃</td>
<td>Fast onset of action, uniform absorption, expensive, high T₃ toxicity, short half-life (~1 day), requires twice daily dosing. Not used alone for maintenance therapy.</td>
<td>Low T₄, normal or low T₃, normal TSH</td>
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<td>Liothyronine Sodium</td>
<td>Mixture of T₃ and T₄ (4:1 ratio)</td>
<td>Both short- and long-lasting effects, expensive, no real advantage over synthetic agents in spite of difficulties in adjustment of the dose.</td>
<td>Variation of the above</td>
</tr>
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**Notes**

- T4 therapy (permanent; treatment of choice otherwise)
- Surgical removal (permanent; for unusual circumstances)
- Antithyroidal drugs (temporary; for children or adolescence or women planning for pregnancy)
- HYPOTHYROIDISM

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**HYPERTHYROIDISM**

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### HYPERTHYROIDISM

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<th>Uses</th>
<th>Mechanism</th>
<th>Kinetics</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td>Propranolol (Non-specific β-blockers)</td>
<td>[Target] Peripheral Action of thyroid hormone Reduces peripheral actions of thyroid hormones. It provides rapid temporary symptomatic relief (e.g., in thyroid storm) along with other interventions. May also inhibit 5'DID.</td>
<td></td>
<td>Worsens asthma and late-stage CHF Contraindicated in these conditions.</td>
</tr>
</tbody>
</table>

#### INTERACTIONS: drugs affecting thyroid state or thyroid function tests

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mechanism</th>
<th>Examples of the drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causiing hypothyroidism</td>
<td>↓Thyroid hormone synthesis or release</td>
<td>Thionamide (PTU or MMI), lithium, perchlorate, iodine-containing drug (eg. amiodarone, radiographic contrast agents), kelp tablets, betadine douches, potassium iodide solutions</td>
</tr>
<tr>
<td></td>
<td>↓Gastrointestinal T4 absorption</td>
<td>Cholestyramine, calcium carbonate, iron sulfate</td>
</tr>
<tr>
<td>Causiing hyperthyroidism</td>
<td>↑Thyroid hormone synthesis or release</td>
<td>Iodine, amiodarone</td>
</tr>
</tbody>
</table>

#### Interactions with **bold drugs** are relatively more common.

#### (from handout)

<table>
<thead>
<tr>
<th>The Target Site/System</th>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iodide transport or trapping</td>
<td>Potassium perchlorate</td>
<td>PO. 200-250 mg 4 times daily</td>
<td>Inhibit iodine binding to NIS and stimulate discharge of iodine from thyroid gland; Gastric irritation, nausea, vomiting, fever, rash, aplastic anemia, bone marrow suppression, nephritic syndrome</td>
</tr>
<tr>
<td>Iodination of thyroglobulin and coupling reaction</td>
<td>Methimazole (MMI, Tapazole®), Methyldopa, Thyrostat®</td>
<td>PO. Initially 20-40 mg daily; Maintain. 5-10 mg daily.</td>
<td>Methimazole does not inhibit 5’-deiodinase. May be teratogenic (e.g., scalp defects), thus in the first trimester in pregnancy PTU to be used instead; causes obstructive jaundice</td>
</tr>
<tr>
<td>Thyroid hormone release</td>
<td>Iodides</td>
<td>Block thyroid hormone release</td>
<td>Hypersensitivity reactions: rash, rhinorrhea, pruritus and subcutaneous swelling; Wolff-Chaikoff block usually lasts ~2 days or longer; Nausea, vomiting, diarrhea, tremor, dizziness, confusion, ataxia, coma. Reserved for special situations when other drugs cannot be used.</td>
</tr>
<tr>
<td>T4 to T3 conversion in thyroid</td>
<td>Lithium Carbonate</td>
<td>Blocks T4 to T3 conversion, induce iodine release from thyroid</td>
<td>Similar to iodides</td>
</tr>
<tr>
<td>Peripheral Action of thyroid hormone</td>
<td>Propylthiouracil (PTU) 20-40 mg orally every 6 hrs; 1 mg/ml injection</td>
<td>Reduces peripheral actions of thyroid hormones. It provides rapid temporary symptomatic relief (e.g., in thyroid storm) along with other interventions. May also inhibit 5'DID.</td>
<td>Worsens asthma and late-stage CHF. Contraindicated in these conditions.</td>
</tr>
<tr>
<td>Thyroid gland mass</td>
<td>¹³¹I Radioisotope</td>
<td>Concentrate in thyroid and decrease mass of thyroid gland due to selective radiation damage of the follicular cells</td>
<td>High incidence of delayed hypothyroidism. Contraindicated during pregnancy or breast-feeding because of its ablative effect on fetal or young thyroid.</td>
</tr>
</tbody>
</table>
Type 1 Diabetes caused by autoimmune-mediated β-cell destruction leading to absolute insulin deficiency.

Type 2 Diabetes caused by inadequate insulin release and/or resistance to insulin action.

Table 1: Distinguishing Features of Type 1 and Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of onset</td>
<td>&gt;20 years</td>
<td>1-20 years</td>
</tr>
<tr>
<td>Type of onset</td>
<td>abrupt</td>
<td>slow onset</td>
</tr>
<tr>
<td>Family history</td>
<td>influence rate</td>
<td>influence rate</td>
</tr>
<tr>
<td>Body weight</td>
<td>sudden decrease</td>
<td>usually overweight</td>
</tr>
<tr>
<td>Symptoms</td>
<td>polydipsia, polyphagia</td>
<td>none initially</td>
</tr>
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<td>Hypoglycaemia</td>
<td>severe</td>
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</tr>
<tr>
<td>Plasma insulin</td>
<td>negligible</td>
<td>high to low</td>
</tr>
<tr>
<td>Plasma ketones</td>
<td>common in severe cases</td>
<td>rare</td>
</tr>
<tr>
<td>Primary cause</td>
<td>pancreatic cell destruction</td>
<td>defective β-cell insulin resistance</td>
</tr>
<tr>
<td>Sensitivity to insulin</td>
<td>normal</td>
<td>reduced</td>
</tr>
<tr>
<td>Oral antidiabetic drugs</td>
<td>not indicated</td>
<td>efficacious</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Preprandial serum glucose level &gt; 126 mg/dl (140 mg/dl requires treatment)</td>
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</tr>
<tr>
<td>Complications</td>
<td>microvascular damage, glycation of extracellular matrix proteins, neuropathy, nephropathy, and increased risk of infections, cardiovascular disease (diabetes is a major cause of blindness, kidney failure, and heart disease)</td>
<td>macrovascular damage, glycation of extracellular matrix proteins, neuropathy, nephropathy, and increased risk of infections, cardiovascular disease (diabetes is a major cause of blindness, kidney failure, and heart disease)</td>
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<td>pancreatic cell destruction</td>
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Treatment: prevent development of microvascular and chronic complications. Supply (inject) insulin to maintain normal blood glucose level without causing hypoglycemia. Insulin treatment is required for all patients.
<table>
<thead>
<tr>
<th>Source Insulin Type</th>
<th>Onset (hrs)</th>
<th>Peak (hrs)</th>
<th>Effective Duration (hrs)</th>
<th>Maximum Duration (hrs)</th>
<th>Daily Dosing (Times/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>aspart or lispro</td>
<td>&lt; 0.25</td>
<td>0.5 – 1.5</td>
<td>2 – 4</td>
<td>4 – 6</td>
<td>3</td>
</tr>
<tr>
<td>detemir</td>
<td>1 – 18</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>NPH</td>
<td>2 – 6</td>
<td>6 – 10</td>
<td>10 – 16</td>
<td>14 – 18</td>
<td>2</td>
</tr>
<tr>
<td>Regular</td>
<td>0.5 – 1</td>
<td>2 – 3</td>
<td>3 – 6</td>
<td>6 – 10</td>
<td>6</td>
</tr>
</tbody>
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**HYPOGLYCEMIA:**
- Signs and symptoms:
  - Excessive hunger
  - Sweating
  - Paresthesias
  - Palpitations
  - Tremor
  - Anxiety
  - Difficulty in concentration
  - Confusion, weakness
  - Dizziness
  - Feeling of warmth
  - Shakes
  - Fatigue
- Severe hypoglycemia:
  - Fainting
  - Convulsions
  - Coma

**Insulin receptor:**
- Insulin receptor is comprised of two identical extracellular α subunits and two intracellular β subunits.
- Binding of insulin to the α subunits.
- Binding of insulin causes intracellular β subunits to autophosphorylate at specific tyrosine sites.
- Phosphorylation-specific protein called insulin receptor substrates.
- Activates several transmembrane kinases.
- Activation of PI3-kinase leads to the mobilization of glucose transporter isoform 4 (Glut 4) from an intracellular site to the cell membrane, and glucose uptake ensues (response in seconds).
- Processes involving protein synthesis, etc. (takes hours to weeks).

**Beta cell operation:**
- Insulin secretion: insufficient insulin secretion for the degree of insulin insensitivity and resistance resulting from:
  - Inadequate insulin secretion for the degree of insulin insensitivity and resistance resulting from:
    - A pancreas that does not release enough insulin in response to rise in blood glucose,
    - A liver that releases too much glucose,
    - Muscle cells that do not readily take up glucose in response to insulin.

- Seven different strategies currently used for the treatment of diabetes:
  - Reduce hyperglycemia by strict diet control and exercise program,
  - Stimulate the release of insulin from pancreatic β-cells,
Inhibit α-glucoside hydrolase and α-amylase in the gut lumen, resulting in delayed absorption and metabolism of carbohydrates,
Decrease hepatic glucose production,
Increase peripheral insulin sensitivity,
Inhibit degradation of incretin hormones and glucagon-like peptide 1 (GLP-1)

Administer adjunct:

<table>
<thead>
<tr>
<th>Type of Oral Hyperglycemics</th>
<th>Mechanism</th>
<th>Efficacy</th>
<th>SE</th>
<th>Interactions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide (2nd Generation Sulfonylureas)</td>
<td>Blocking the pancreatic β-cells KATP channel; depolarizing the cell membrane; opening the Ca²⁺ channel and causing insulin release by exocytosis</td>
<td>Hypoglycemia; GI discomfort; alopecia; jaundice; fluid retention particularly with glipizide; increased liver function test (LFT) values</td>
<td>Glucose intolerance, increased LFT values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acarbose (α-Glucosidase Inhibitors)</td>
<td>Inhibit glucosidase and α-amylase in the gut lumen; delay absorption and metabolism of ingested carbohydrate</td>
<td>GI discomfort; increased LFT values</td>
<td></td>
<td></td>
<td></td>
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<td>Metformin (Biguanides)</td>
<td>Decrease insulin resistance by unknown mechanism; inhibit gluconeogenesis; increase glucose uptake and metabolism in adipose and muscle cells</td>
<td>GI discomfort; lactic acidosis; alteration of taste; megaloblastic anemia. (antihyperglycemic but does not cause hypoglycemia)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pioglitazone (Thiazolidinediones)</td>
<td>Activator of transcription factor peroxisome proliferation-activated receptor γ (PPAR-γ); increases transcription of genes involved in lipid and glucose metabolism (and GLUT4)</td>
<td>Increase glucose uptake and lipid metabolism; mild to moderate edema; anemia; increased blood cholesterol. Periodic liver function test is recommended. FDA recently warned of fluid accumulation in heart failure patients.</td>
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<td>Repaglinide (Meglitinides)</td>
<td>Stimulate insulin release like sulfonylureas except that they have an additional unique receptor and have no intracellular action</td>
<td>Hypoglycemia; weight gain; no sulfonylurea group in the structure and thus causes no disulfiram reaction like sulfonylureas.</td>
<td></td>
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<tr>
<td>Exenatide (GLP-1 receptor agonist)</td>
<td>Inhibit degradation of incretin hormones (GLP-1 and GLP-2) peroxisome proliferator-activated receptor γ (PPAR-γ) and increase pancreatic β cells decrease glucagon production by α cells</td>
<td>Hypoglycemia, high dose may reduce fetal and neonatal growth and should not be used or used only with justifiable risk in pregnant women or nursing mothers.</td>
<td></td>
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<td></td>
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<tr>
<td>Sitagliptin (Dipeptidyl peptidase-4 inhibitor)</td>
<td>Enhance glucose-stimulated insulin secretion from pancreas α cells; inhibit γ-aminobutyric action like incretins, such as glucagon-like peptide 1 (GLP-1)</td>
<td>So far well tolerated; even in patients with decreased renal function. Does not appear to cause weight gain or hypoglycemia</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lifestyle changes: losing weight, controlling diet, and by physical exercise
Arthritis and Gout

Wednesday, March 16, 2011
6:45 PM

RA aggressiveness in reversible damage in first two years of disease with more aggressive form of RA

Initially, treatment was NSAID use with short-term prednisone with flare ups

DMARDs for cases unresponsive to NSAID treatment

New: start DMARD when first 3 months of symptoms can’t be controlled by NSAIDs

Goal of treatment

Reduce symptoms of RA, preserve function, improve quality of life

Prevent or slow destruction of joints

Arthritis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Uses</th>
<th>Mechanisms</th>
<th>Common</th>
<th>Rare</th>
<th>Interactions</th>
<th>GI</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>TNFα antagonist</td>
<td>(chimeric = mouse + human)</td>
<td>1. inhibits many phases of the inflammatory response → reduces the number and function of peripheral leukocytes, suppresses effects of inflammatory cytokines and chemokines, blocks pro-inflammatory functions of macrophages, reduces adhesion molecule expression on endothelial cells, forestalls impact of TNFα on joint damage but is incapable by itself for chronic administration</td>
<td>CRN (inj) (pump)</td>
<td>Biologically absorbed in GI</td>
<td>Interactions</td>
<td>GI</td>
<td>Notes</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>(active form)</td>
<td>Methotrexate decreases Ab formation</td>
<td>Decrease rate of tissue damage</td>
<td>Goal of RA treatment: use DMARD for cases unresponsive to NSAIDs + prednisone</td>
<td>6:45 PM Wednesday, March 16, 2011</td>
<td>Arthritis and Gout</td>
<td>Potential toxicity of some drugs requires close monitoring</td>
</tr>
<tr>
<td>Drug</td>
<td>Uses</td>
<td>Mechanism</td>
<td>Side</td>
<td>Interactions</td>
<td>C</td>
<td>Notes</td>
<td></td>
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<td>Not used very often (by itself) effective in patients after acute attack</td>
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<td>Probable &quot;over produces&quot; uric acid due to a genetic defect in uric acid synthesis (urate dehydrogenase)</td>
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<td>Statin (inhibitors of HMG-CoA reductase)</td>
<td>Reduce cholesterol synthesis and thus lower serum cholesterol levels</td>
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death (21%). Stop drug immediately if rash develops.

MAY CAUSE LIVER FUNCTION TEST ABNORMALITIES (increase in transaminases (> 3 x ULN))

Aluminum hydroxide may interfere with absorption of cyclophosphamide, warfarin and cyclosporin.

Purines → Hypoxanthine → Xanthine Oxidase ("XO") → Xanthine (Xanthine Oxidase (XO) is inhibited by allopurinol and febuxostat) → Uric acid