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Essentials of Pharmacology for Complementary Health Practitioners

Note: Cancer Drugs are Covered in the Adjunctive Nutritional Management of Cancer Subject on this Platform

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Why Study Pharmacology

1. Many patients/clients you see are taking medications

2. You should know the effect each drug is having on the patient's physiology before making dietary, exercise or supplementation recommendations (e.g. beta-blocker and aerobic exercise)

3. You should be on the look out for drug side effects masquerading as primary health conditions (e.g. tinnitus from aspirin, back pain from statins) that physician may have missed

4. There are 8 important drug-supplement considerations that must be factored in to the dietary, exercise and supplementation recommendations you recommend:

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The 8 Key Drug-Supplement Considerations

1. Some drugs can do things that supplements can not (e.g. muscle relaxants)

2. Some supplements can do things that drugs can not (e.g. rebuild cartilage, increase synthesis of acetylcholine in brain)

3. Some supplements work **synergistically** with a drug, reducing drug dosage where the drug is known to produce adverse side effects (e.g. acetaminophen damage to liver)

4. Some supplements can potentiate the effects of drugs producing serious side effects (e.g. bleeding disorders, serotonin syndrome etc)

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5. Some supplements reduce the efficacy of a drug by stimulating its detoxification (e.g. St John's Wort and Birth Control Pill)

6. Some supplements are contra-indicated in certain health conditions (e.g. Wilson's disease and copper)

7. Certain supplements require specific monitoring or physician approval in specific cases (e.g. organ transplants and immuno-suppressive drugs, liver or kidney disease, cancer)

8. In pregnancy and breast feeding certain supplements must be removed and replaced by others to protect the small fetal body

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Brief History Of Drugs

- Pharmaceutical Industry did not begin until 1941, when Chain and Florey (during WWII) discovered that penicillin could be taken orally to fight bacterial infections.

- In 1928 Alexander Fleming discovered that penicillin spores (from the penicllin mold) that had become air-borne from the lab below were able to prevent the growth of the staphylococcus bacteria he was studying in the lab above (an accidental innoculation).

- Until 1941, penicillin was only used to treat topical bacterial infections, until Chain and Florey discovered that it could be used internally. This was the birth of the pharmaceutical industry

- However, The use of Digitalis purpurea extract containing cardiac glycosides for the treatment of heart conditions dates back to 1785

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- In a very short period of time Pharmaceutical companies have convinced medical doctors, and most of the modern world, to ignore all previously used natural remedies and focus only on their synthetic drugs

- Prior to 1941, only natural medicines were available to treat patients.(e.g. colloidal silver to treat TB and infections)

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The Pendulum Has Swung So Far To One Side That Natural Remedies Have Been Dismissed

However, in recent years the use of, and search for, drugs and dietary supplements derived from plants have accelerated.

Pharmacologists, microbiologists, botanists, and natural-products chemists are combing the Earth for phytochemicals and leads that could be developed for treatment of various diseases.

Integrative Cancer Therapies Program taught by the American Academy For The Advancement Of Medicine empahasizes many supplements

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Impact Of Adverse Drug Effects:

- The Institute of Medicine found that as many as 98,000 hospitalized Americans die every year and 1 million more are injured as a result of preventable medical errors that cost the nation as estimated $29 billion.

- Adverse drug reactions were the **4th leading cause of death** in the United States in the year 2000 - more common than breast cancer, AIDS or traffic accidents - with costs of more than $170 billion.

- In addition to these costs, The Centers for Medicare and Medicaid stated in a recent report that the nation spent **$140.6 billion in the year 2000 on prescription drugs**.

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Cardiovascular Section

Part 1. Anti-hypertensive Drugs:

1. Diuretics
2. Beta-blockers
3. Calcium-Channel blockers
4. ACE-Inhibitors
5. ARBs
6. Renin-blockers

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Diuretic Drugs

A. **Diuretics**: elevate rate of urination and water loss

This reduces blood volume and thus reduces systolic and diastolic pressure – less total pressure in system

Several categories of diuretics:

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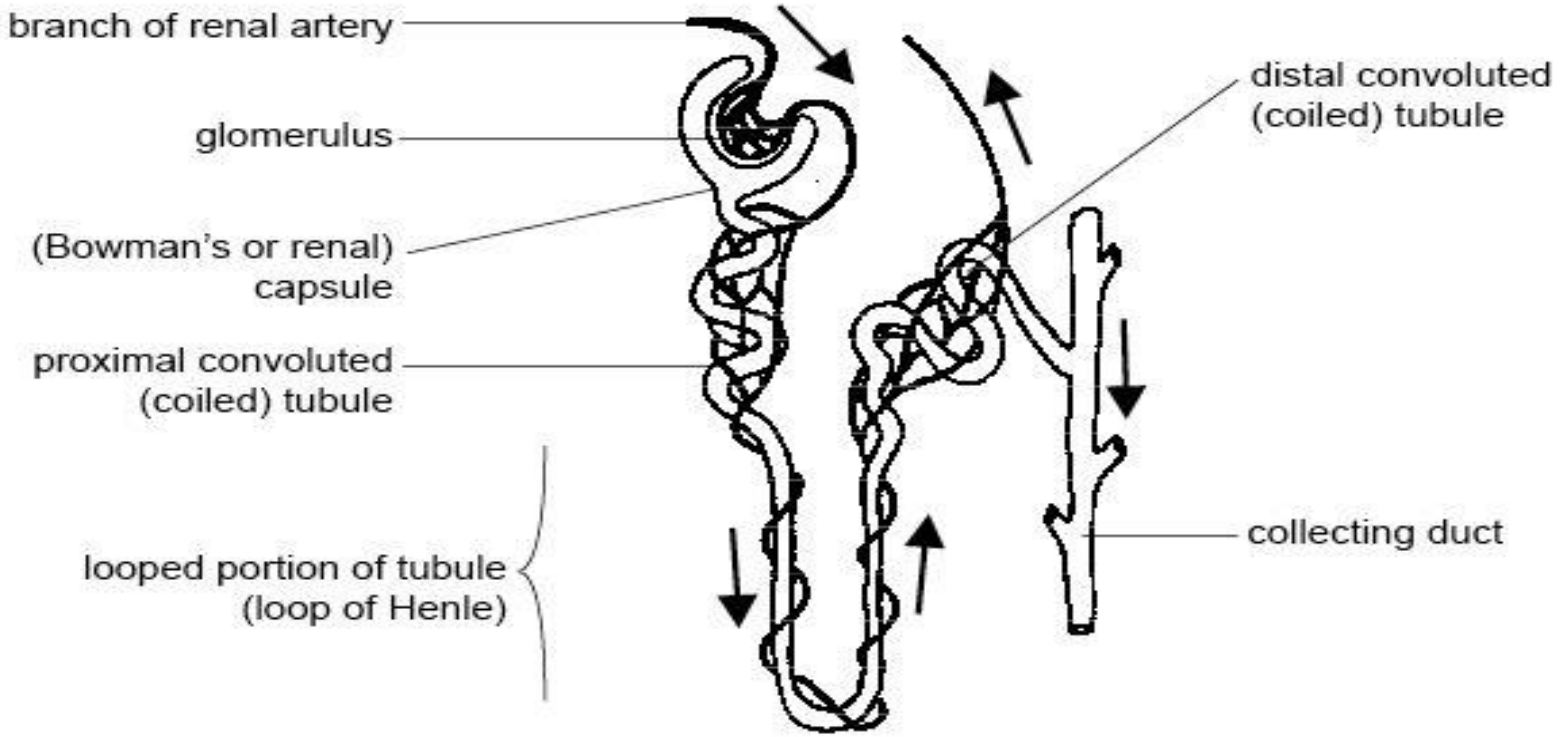
Distal Tubule Diuretics

- **Kidneys** – 21% of cardiac output filtered by kidneys
- **About 1200 ml/min** is rate of blood flow through both kidney (70 kg man)
- **99% of filtrate** reabsorbed (1% becomes urine)



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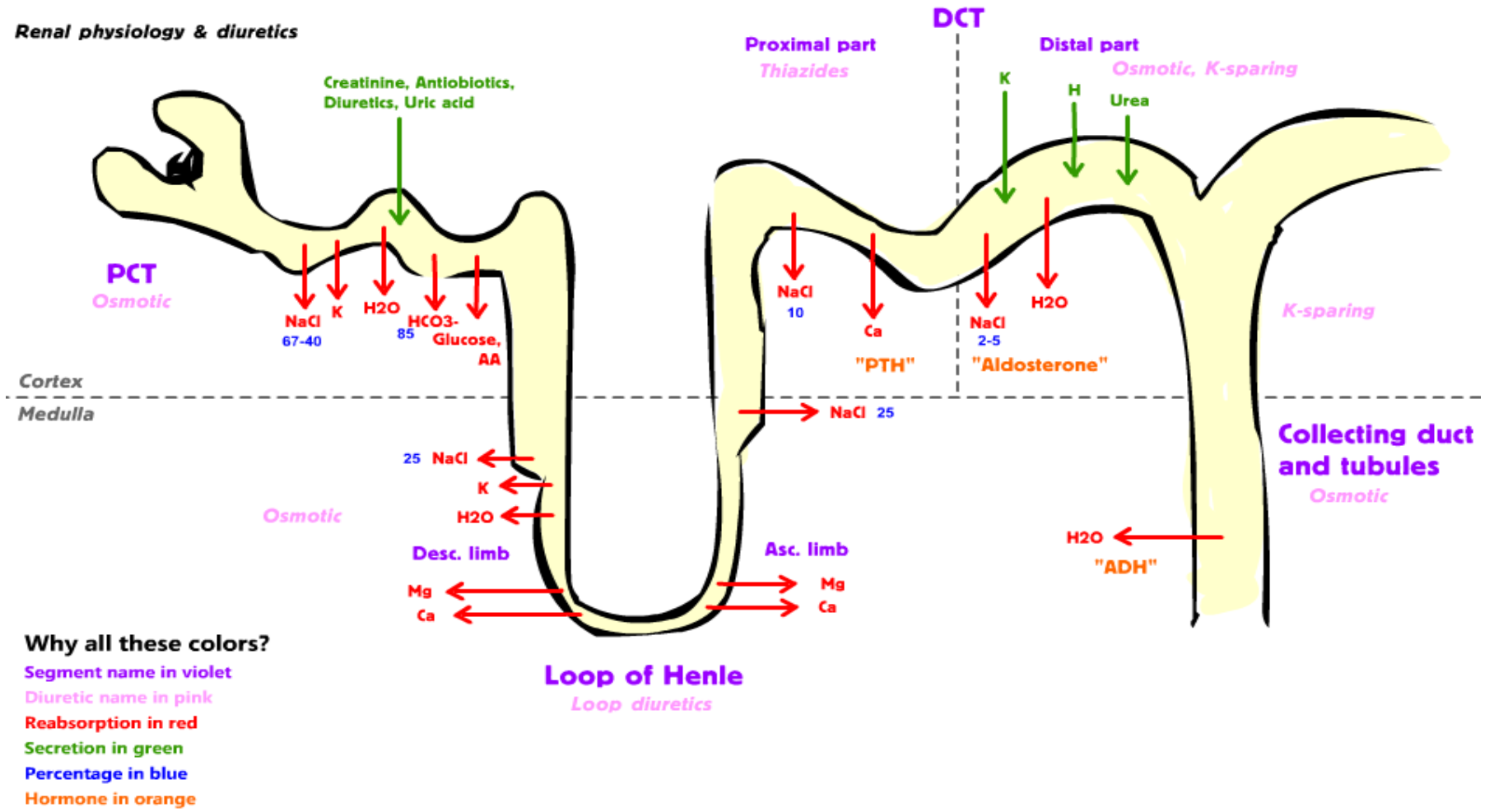
Renal Physiology and Diuretics: Note Aldosterone Effect At DCT and ADH In CD



1. **High ceiling diuretics** cause substantial diuresis - up to 25% of the filtered load of NaCl and water end up in urine.

- This is huge - normal renal sodium reabsorption leaves only ~0.4% of filtered sodium in the urine

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- **Loop diuretics** are usually “high ceiling diuretics”, which inhibit sodium resorption at the ascending loop

- **Low Ceiling Diuretic (e.g. thiazides)** - rapidly flattening dose effect curve (in contrast to "high ceiling")

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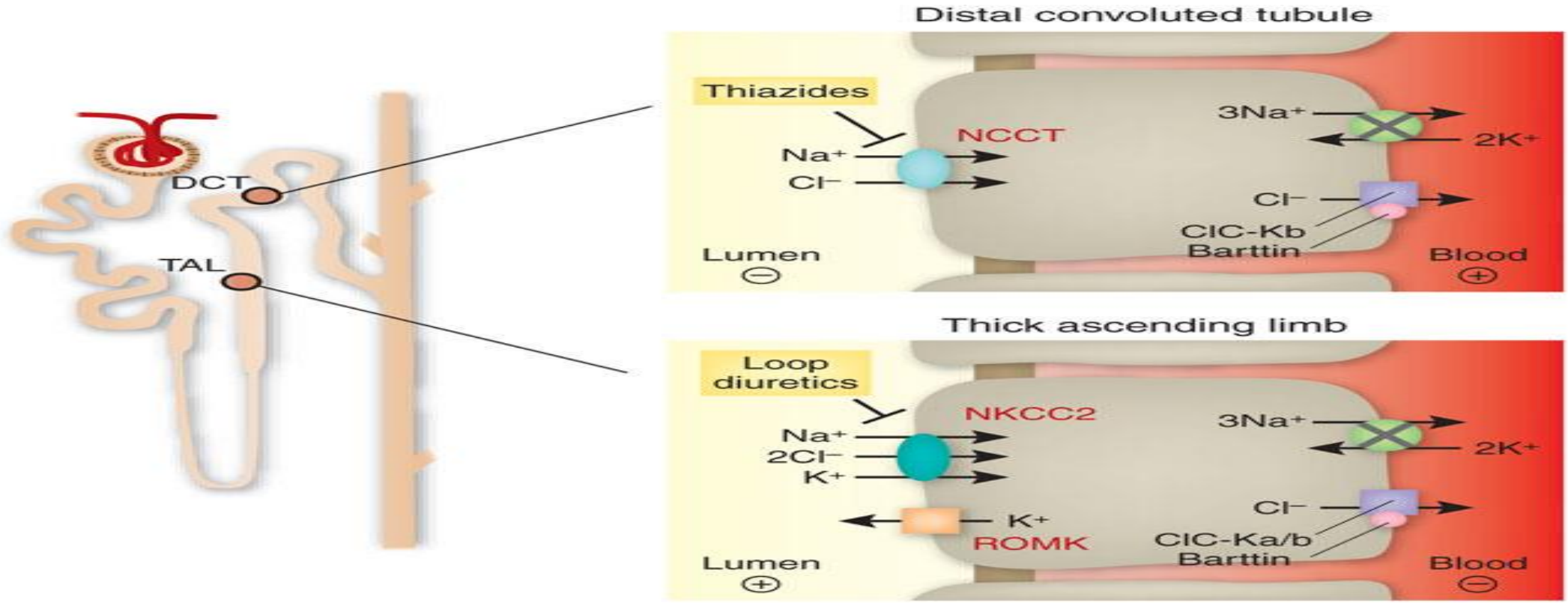
Target Sites For Diuretics

- **High Ceiling Loop diuretics** inhibit **25%** NaCl resorption in **TAL**
- The **thiazide drugs** inhibit **5–10%** of the NaCl reabsorption in **DCT**
- Excretion of NaCl drags water out of body, lowering blood volume and decreasing blood pressure



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Preventing Hypokalemia from Diuretics

- Because loop and thiazide diuretics increase sodium delivery to the distal segment of the distal tubule, this increases potassium loss (potentially causing *hypokalemia*) because the increase in distal tubular sodium concentration stimulates the aldosterone-sensitive sodium pump to increase sodium reabsorption in exchange for potassium and hydrogen ion, which are lost to the urine.

- The increased hydrogen ion loss can lead to *metabolic alkalosis*. Part of the loss of potassium and hydrogen ion by loop and thiazide diuretics results from activation of the renin-angiotensin-aldosterone system that occurs because of reduced blood volume and arterial pressure.

- Increased aldosterone stimulates sodium reabsorption and increases potassium and hydrogen ion excretion into the urine

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- **Hypokalemia** is associated with increased risk of arrhythmia in patients with cardiovascular disease, as well as increased all-**cause** mortality, cardiovascular mortality and heart failure mortality by up to 10-fold

- Derangements of potassium regulation often lead to neuromuscular, gastrointestinal and cardiac rhythm abnormalities. The normal level of plasma potassium is 3.8 – 5.1 mmol/L.

- The deviations to both extremes (hypo- and hyperkalemia) are related to the risk of cardiac arrhythmias

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Potassium-Sparing Diuretics

- A third class of diuretic are **potassium-sparing diuretics**. Unlike loop and thiazide diuretics, some of these drugs do not act directly on sodium transport.

- Some drugs in this class antagonize the actions of aldosterone (**aldosterone receptor antagonists**) at the distal segment of the distal tubule. This causes more sodium (and water) to pass into the collecting duct and be excreted in the urine.

- They are called K^+-sparing diuretics because they do not produce hypokalemia like the loop and thiazide diuretics. The reason for this is that by inhibiting aldosterone-sensitive sodium reabsorption, less potassium and hydrogen ion are exchanged for sodium by this transporter and therefore less potassium and hydrogen are lost to the urine.

- Other potassium-sparing diuretics directly inhibit sodium channels associated with the aldosterone-sensitive sodium pump, and therefore have similar effects on potassium and hydrogen ion as the aldosterone antagonists.

- Because this class of diuretic has relatively **weak effects on overall sodium balance**, they are often used in conjunction with thiazide or loop diuretics to help prevent hypokalemia

Reference: http://www.cvpharmacology.com/diuretic/diuretics

3. Potassium-Sparing Diuretics – Inhibit secretion of potassium into urine, by inhibiting aldosterone, or by blocking sodium channels.

Aldosterone Effects:

- Promotes resorption of sodium into bloodstream to increase blood pressure with **secretion of potassium into the urine**.

- Potassium-sparing diuretics counter these effects, often used with other diuretic drugs that otherwise tend to promote excess potassium loss in urine

(hypokalemia – muscle weakness and/or paralysis, atrial fibrillation etc)

Diuretic Drugs – prevent sodium resorption, but increase potassium loss in urine – hence risk of hypokalemia

Potassium-Sparing Drugs – decrease amount of potassium secreted into kidney tubule, to prevent excess loss of potassium that otherwise occurs with diuretics

e.g. Spironolactone is a Potassium-sparing diuretic that is an aldosterone antagonist

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Clinical Applications For Diuretics:

1. * Hypertension
2. *Heart failure – flush out water & reduce strain on heart
3. Liver cirrhosis
4. Certain kidney diseases

Adverse Side Effects Of Diurtetics:

1. *Lassitude, Fatigue - Hypovolemia
2. * Muscle Cramps – sodium/potassium imbalance
3. * Gout - Hyperuricemia (sodium lost in urine at expense of uric acid)
4. * Hypercholesterolemia – mild effect on cholesterol raising
5. *Arrhythmia – Hypokalemia – leading to sudden death
6. Metabolic alkalosis – from excess loss of Na and K

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Some Common Diuretic Drugs:

- Furosemide, (Lasix)
- Thiazides
- Indapamide, (Lozal)
- Mannitol, (Osmitrol)
- Chlorthalidone (Hygroton, Thalidone)

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B. Beta-Blockers

Mechanism of Action: block action of catecholamines (e.g. epinephrine and norepinephrine), on β-adrenergic receptors

Three Most Common Beta-Adrenergic Receptors (1,2,3):

- **β1**-Adrenergic receptors located mainly **heart & kidney.**
- **β2**-Adrenergic receptors located mainly in **lungs**, gastrointestinal tract, liver, uterus, **vascular smooth muscle**, and skeletal muscle.
- **β3**-receptors are located in **fat cells**.

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Effects Of Beta-Adrenergic Stimulation

Beta-1 Stimulation

Heart:

1. Positive chronotropic (increasing heart rate)
2. Inotropic (increase the strength of contraction)
3. Increases cardiac conduction velocity and automaticity.

Kidney: Renin release (increasing blood pressure via renin-aldosterone-angiotensin II system)

Beta-2 Stimulation:

1. Smooth muscle relaxation (more blood flow to muscles but vasoconstriction of many central and visceral blood vessels, raising blood pressure).
2. Tremor in skeletal muscle
3. Glycogenolysis – can increase blood sugar if sustained

Beta-3 Stimulation: induces lipolysis from fat cells (may increase triglycerides)

"Cardio-Selective beta-blockers target the beta-1 receptor, but selectivity is lost at higher doses"

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Clinical Applications of Beta-Blocker Drugs:

1. **Angina** – from negative chronotropic & inotropic effects, decreasing cardiac workload and oxygen demand.

2. **Arrhythmia** – sympathetic nervous system blockade results in:

- depression of SA node function
- AV node conduction
- prolonged atrial refractory periods

3. **Hypertension** - Blockade of the sympathetic nervous system on heart & **renin** release, leads to **reduced aldosterone** via the renin-angiotensin-aldosterone system, decreasing BP. Also, dilate central and visceral blood vessels, decreasing diastolic pressure

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Other Considerations:

1. Beta blockers can impair the relaxation of bronchial muscle - **should be avoided by asthmatics.**

2. Topically - Used to **treat glaucoma -** decrease intraocular pressure by lowering aqueous humor secretion. But diffuses into blood stream and has wide spread effects

3. Since they lower heart rate and reduce tremor, beta blockers have been used by some **Olympic marksmen** to enhance performance (beta blockers are banned by the IOC)

4. **Aerobic Training Zone –** adjust down by 10%

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Adverse Side Effects Of Beta-Blockers:

- * Cold extremities and Exacerbation of Raynaud's syndrome
- * Bradycardia – must adjust aerobic training zone down by 10%
- * Hypotension and orthostatic hypotension
- * Fatigue and Dizziness
- * Insomnia and nightmares
- * Clinical depression
- * Sexual dysfunction, Erectile dysfunction – can’t dilate blood vessels

- Nausea
- Diarrhea
- Bronchospasm
- Dyspnea
- Heart failure, heart block
- Abnormal vision
- Decreased concentration
- Hallucinations

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- * **2007 Study**: **diuretics & beta-blockers** used for hypertension **increase risk of Diabetes** while ACE inhibitors and ARB's decreased risk

- Clinical guidelines in Great Britain, but not United States, call for avoiding diuretics and beta-blockers as first-line treatment of hypertension due to the risk of diabetes – via hyperglycemic effect (*Mayor S 2006).*

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Common Beta-Blockers Drugs (common suffix – olol):

1. Sectral (acebutolol) – cardio-selective
2. Lopressor (metoprolol) – cardio-selective
3. Inderal (propranolol) – non cardio- selective

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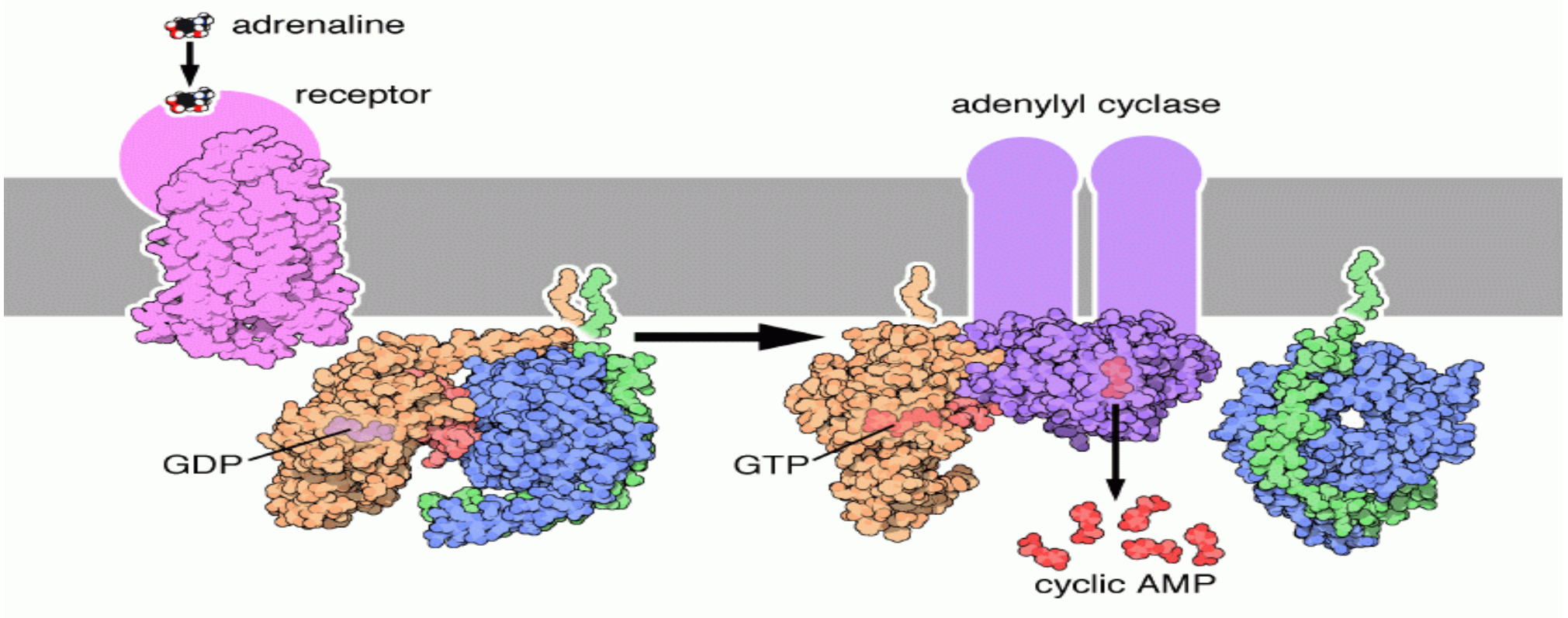
Epinephrine binds Beta-adrenergic receptor, that associates with an G protein. The G protein associates with adenylate cyclase that converts ATP to cAMP. Then cAMP initiates a chain of chemical

reactions to ultimately signal a cellular response.



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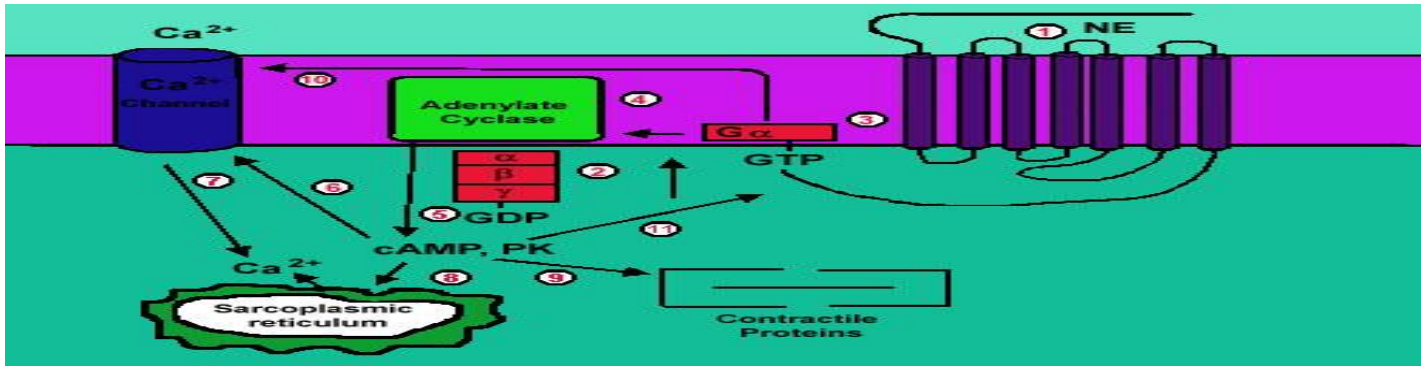

Mechanism of Beta Receptor Activation in Cardiac Muscle Goodman and Gilman's *Pharmacologic Basis of Therapeutics,* Chpt.Ten, 10th Edition.

1. Agonist binds to the myocardial beta1-adrenergic receptor. This receptor is a typical G-protein coupled receptor.
2. In the unstimulated state the G-protein is complexed with GDP
3. The receptor promotes exchange of GTP for GDP and release of G"/GTP.
4. The G"/GTP complex activates adenylate cyclase.
5. Intracellular cAMP increases and activates cAMP dependent protein kinase (PKA).
6. PKA phosphorylates the Ca2+ channel promoting Ca2+ influx.
7. Intracellular Ca2+ increases activating the contractile proteins.
8. PKA phosphorylates the sarcoplasmic reticulum leading to an increase in Ca2+ uptake and release.
9. PKA phosphorylates troponin changing its calcium binding kinetics
10. G" directly activates the Ca2+ channel.
11. Prolonged stimulation can lead to receptor down regulation via PKA and other protein kinases which phosphorylate the receptor.

- **Voltage-dependent calcium channels** (VDCC) are found in excitable cells (*e.g.*, muscle, glial cells, neurons, etc.) with permeability to the ion Ca2+.

- At physiologic or resting membrane potential, VDCCs are normally closed. They are activated (*i.e.*, opened) with depolarization of membrane (from nerve stimulation)

- Activation of VDCCs allows Ca2+ entry into the cell, which depending on the cell type, **results in muscular contraction**, excitation of neurons, up-regulation of gene expression, or release of hormones or neurotransmitters.

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Calcium and Muscle Contraction

- Calcium binds to the troponin C present on the actin-containing thin filaments of the myofibrils.
- Troponin then modulates the tropomyosin. Normally the tropomyosin obstructs binding sites for myosin on the thin filament.
- Once calcium binds to the troponin C and causes a change in the troponin protein, troponin T allows tropomyosin to move, unblocking the binding sites on mysoin
- Myosin now binds to actin in the strong binding state. This will pull the Z-bands towards each other, thus shortening the sarcomere and the I-band, resulting in muscle contraction – using ATP energy to power the reaction
- Thus, blocking calcium channels lowers blood pressure

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C. Calcium Channel Blockers

Mechanism of Action: Prevent calcium ions, needed for muscle contraction, from entering smooth and cardiac muscle cells.

This action lowers systolic and diastolic pressure and helps to reduce **angina**

- Some calcium-channel blockers, such as Procardia (nifedipine), also **slow the electrical impulses** that run through heart muscle, thus regulating **arrhythmias.**

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CCBs Applications

1. **Hypertension** - CCBs block voltage-gated calcium channels (VGCCs) in muscle cells of the heart and blood vessels.

- This prevents calcium levels from increasing as much in the cells when stimulated, leading to less muscle contraction – **decreased cardiac contractility.**

- In blood vessels, a decrease in calcium results in **less contraction of the vascular smooth muscle** and therefore an **increase vasodilation**.

- Vasodilation decreases total peripheral resistance (lowers diastolic pressure) and decrease cardiac contractility (lowers systolic pressure)

2. Angina – Vasodilation effect lowers afterload on the heart (peripheral resistance) this decreases the amount of oxygen required by the heart.

- Because calcium channel blockers result in decreased blood pressure, the **baroreceptor reflex** often initiates a reflexive increase in sympathetic activity leading to increased heart rate and contractility.

- A βeta-blocker may be combined with a calcium channel blocker to minimize these effects.

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Other Considerations:

1. **CCB's Not Used In Cardiomyopathies** – because they decrease force of contraction of myocardium CCBs are avoided (or used with caution) in cardiomyopathy.

2. Some CCBs slow conduction of electrical activity within heart resulting in a negative chronotropic effect with **risk of heart block**.

3. **Atrial Fibrillation** - The negative chronotropic effects of CCBs make them **ideal agents** for **atrial fibrillation or flutter**

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Clinical Applications Of CCBs:

1. Hypertension – main reason for use
2. Angina
3. Arrhythmias

Common side effects:

- **Fatigue ***
- Flushing
- **Swelling of the abdomen, ankles, or feet.***
- Heartburn.

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Less common side effects:

- Very fast or very slow heartbeat.
- Wheezing, coughing, or shortness of breath.
- Trouble swallowing.
- Dizziness.
- **Numbness or tingling in the hands or feet.** *
- Upset stomach.
- Constipation (especially when taking verapamil).

Rare side effects:

- **Headache**. *
- Fainting.
- **Chest pain.** *
- Yellowing of the skin or eyes (jaundice).
- Fever.
- Rash.
- Bleeding, swollen, or tender gums.
- Vivid dreams.

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Some Common CCB's:

1. Adalat (nifedipine)
2. Apo-Diltiaz (diltiazem)
3. Apo-Nifed (nifedipine)
4. Apo-Verap (verapamil)
5. Cardene (nicardipine)
6. Cardizem (diltiazem)
7. Ketoconazole

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CCB's In Cancer Treatment

New Cancer Treatment Application - some CCB's (nifidepine, verapamil, ketoconazole) used successfully to inhibit **Multi-drug-Associated-Protein Pumps**, which cancer cells use to pump chemotherapy drugs, anionic conjugates (hydrogen ions generated from glycolytic metabolism and alkylating chemo-drug metabolites) and oxidized glutathione out of the cell **to protect themselves**.

In Molecular and Genetic Testing Of Cancer Tissues Or Circulating Tumor Cells – check for up-regulation of MDR-1 expression (if positive then CCB's are indicated)

Flavonoids Also Inhibit MDR-1 Pump: Curcumin, Genistein, Quercetin

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D. ACE-Inhibitors

(Angiotensin Converting Enzyme)

Mechanism of Action: ACE-Inhibitors inhibit enzyme converting **Angiotensin I into Angiotensin II**, which decreases blood pressure and platelet stickiness

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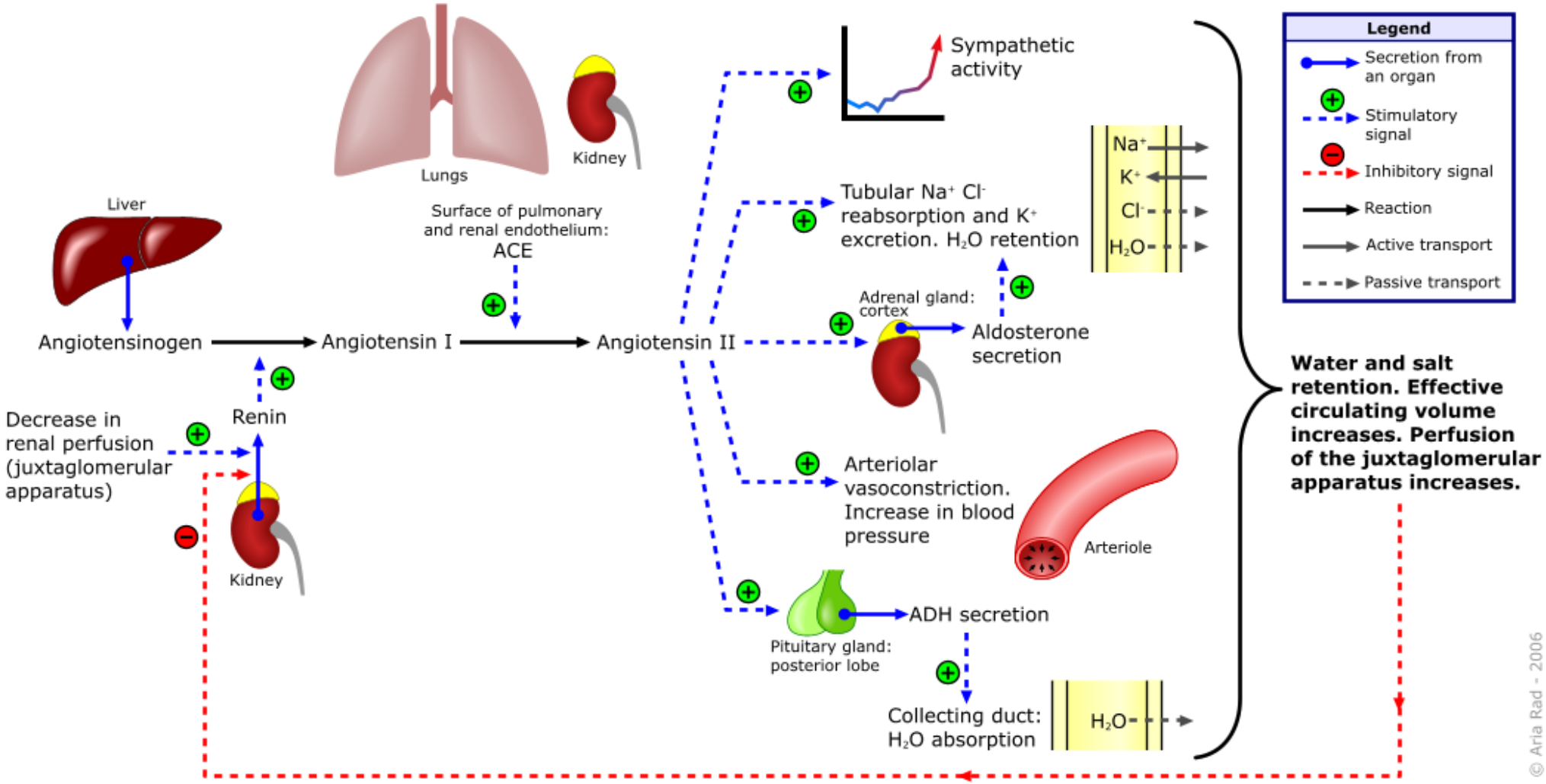
Renin-angiotensin-aldosterone system



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Angiotensin System - activated in response to:

1. Hypotension
2. Decreased sodium concentration in the distal tubule
3. Decreased blood volume
4. Renal sympathetic nerve stimulation (this could be psychological effect from stress or anxiety)

- In response, kidneys release renin which cleaves the liver-derived angiotensinogen into angiotensin I.

- Angiotensin I is then converted to angiotensin II via ACE in pulmonary circulation as well as in the endothelium of blood vessels.

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Effects of Angiotensin II

1. Vasoconstrict arteries & veins, increasing BP

2. Releases Aldosterone from adrenals, which increases re-absorption of salt and water leading to raised blood volume and raised blood pressure

3. **Increases adhesion and aggregation of platelets with production of PAI-1 and PAI-2 (plasminogen activator inhibitor**) – which decreases fibrinolysis.

   - Normally Plasminogen activator secreted by endothelial cells converts plasminogen to plasmin, which dissolves blood clots. This process is inhibited by Angiotensin II.

4. Increases release of norepinephrine - increasing heart contractility and systolic pressure

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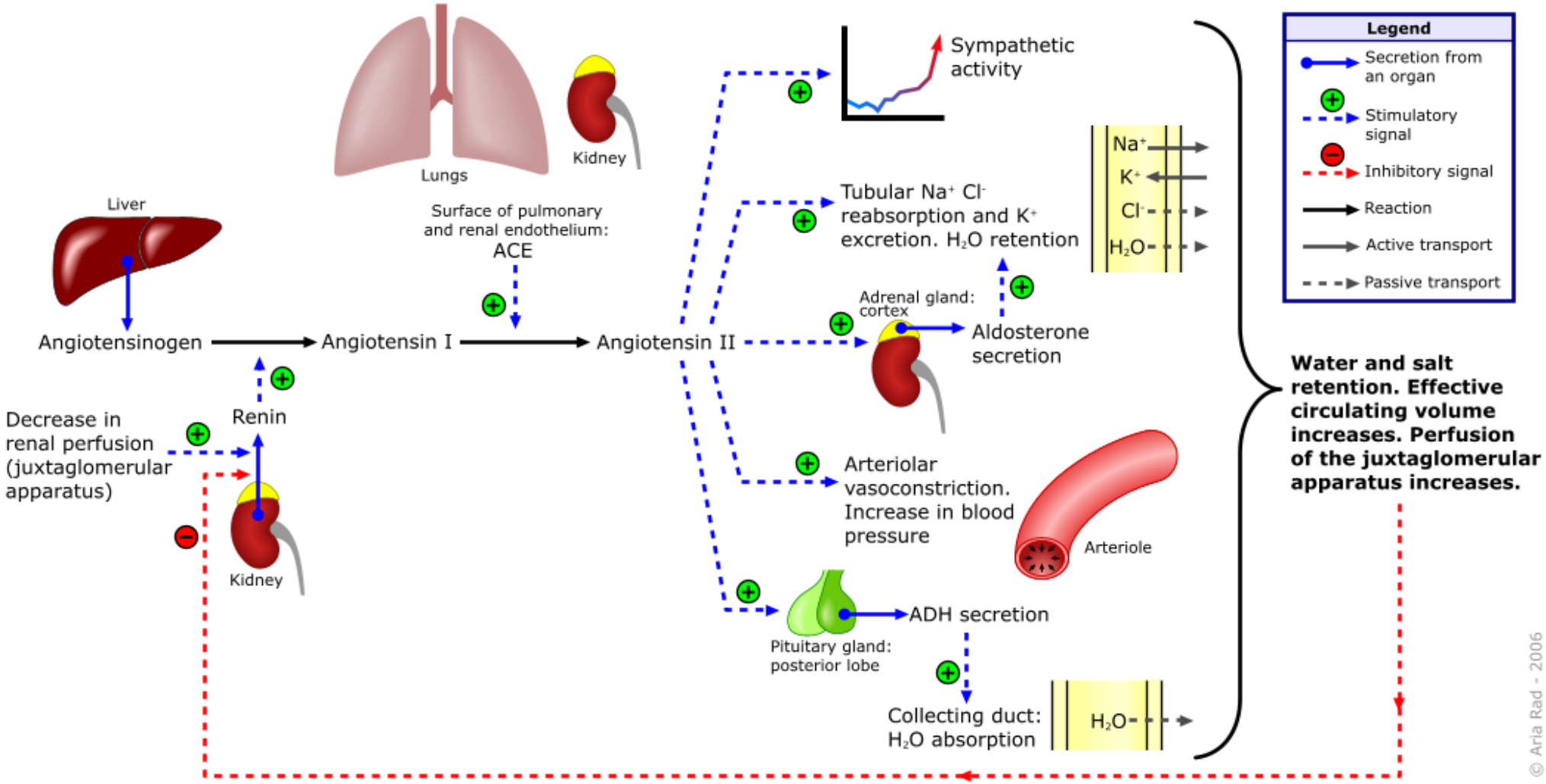
Renin-angiotensin-aldosterone system



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Thus ACE-inhibitors decrease:

1. Blood pressure

2. Platelet aggregation

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Clinical Applications Of ACE Inhibitors:

1. **High Blood Pressure,** especially in diabetes - ACE inhibitors slow progression of diabetic nephropathy, independent of blood pressure-lowering effect.

2. **Non Hypertensive Conditions:** ACE inhibitors shown to be effective for indications other than hypertension:

- Prevention of diabetic nephropathy (diabetics with normal blood pressure may take an ACE-inhibitor)
- Congestive heart failure
- Prophylaxis of cardiovascular events in high risk patients

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Adverse Side Effects Of ACE-Inhibitors

* **Cough** - 20% or more of patients develop dry cough, sometimes severe enough to require discontinuation of the drug (due to build up of bradykinins normally metabolized by ACE)

Other Adverse Side Effects (less than 1% of patients – excellent safety profile):

- Hypotension
- Hyperkalemia
- Headache
- Dizziness
- Fatigue
- Nausea
- Renal impairment

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Some Common ACE-Inhibitor Drug:
(suffix = Pril)

1. Captopril (trade name Capoten), the first ACE inhibitor
2. Zofenopril
3. Enalapril (**Vasotec**/Renitec)
4. **Ramipril** (**Altace**/Tritace/Ramace/Ramiwin)
5. Quinapril (Accupril)
6. Perindopril (Coversyl/Aceon)
7. Lisinopril (Lisodur/Lopril/Novatec/Prinivil/Zestril)
8. Benazepril (Lotensin)

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Natural ACE-Inhibitor - Hawthorn

- **Hawthorn is a natural calcium channel blocker and an ACE inhibitor** – as such hawthorn supplementation (150-300 mg per day) has been shown to lower blood pressure.

- It also has inotropic effects on the heart muscle and dilates coronary blood vessels (via nitric oxide release)

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E. ARB's - Angiotensin II Antagonists or Angiotensin Receptor Blockers

Mechanism Of Action: blocks binding of angiotensin II to its receptor on target tissues.

In turn, this lowers blood pressure in a similar fashion as ACE-inhibitor drugs

Clinical Applications:

1. **Hypertension,** especially in diabetics – delay diabetic nephropathy in diabetics with hypertension

2. **Congestive Heart Failure**, in patients unresponsive to ACE-inhibitors

Adverse Side Effects – similar to ACE-inhibitors, but lower incidence of dry cough compared to ACE-inhibitors

Other – Some ARB's shown to decrease risk of Alzheimer's disease in older person with hypertension.

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Some Common ARB's (often end with suffix "sartin"):

- Losartin
- Eprosartin
- Candesartin
- Valsartin

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Renin Inhibitors - A new class of drugs that inhibit action of renin on angiotensinogen, preventing conversion to angiotensin I. Examples Include:

1. Aliskiren
2. Remikiren

Side Effects

- **Angioedema** – rapid swelling of dermis and subcutaneous tissue
- **Hyperkalemia** (particularly when used with ACE inhibitors in diabetic patients – can lead to arrhythmias
- Hypotension (particularly in volume-depleted patients)
- Diarrhea and other GI symptoms
- Rash
- Elevated uric acid and gout
- Kidney stones.

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Natural Management Of Hypertension

1. Weight Loss – 10-15 lbs can reduce pressure in 2/3 of overweight hypertensive pts (decreased insulin and sodium resorption)
2. Reduce alcohol intake (systolic pressure)
3. Sodium Restriction
4. Calcium/Magnesium supplementation (1-1.5 gms/0.6-1 gm respectively)
5. Omega-3 fats (1-2gms per day)

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6. CoQ10 and Hawthorn – 4-6 capsules Cardio Essentials:

   CoQ10 – 120 – 180 mg per day

   Hawthorn – 150 – 225 mg per day

7. Garlic supplementation - 4,000 mcg allicin content (1/2-1 clove) – screen for prothrombin and ulcers – Kyolic is better choice (no GI bleeds and reduces plaque calcification, may reverse plaque and increased NO release) – but risk of bleeding is still present

8. Aerobic Exercise – decreased basal adrenaline levels (decreasing systolic pressure and arteriole resistance)

9. Autogenic training (biofeedback, meditation etc)

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Complementary Considerations:

1. 75% of Hypertensive cases are mild to moderate, which can be managed via lifestyle and natural interventions (WHO)

2. The use of diet, exercise and supplementation can lower the patient's requirement or dosage of medication, reducing potential side effects

3. To prevent diabetic nephropathy, keeping the LDL-C below 1.8 mmol/L via diet, exercise, supplementation is as critical as blood pressure regulation and use of ACE-inhibitors

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B. **Cholesterol and Lipid Lowering Drugs:**

- Statins
- Bile Acid Sequestrants
- Fibric Acid Derivatives
- High Dose Niacin

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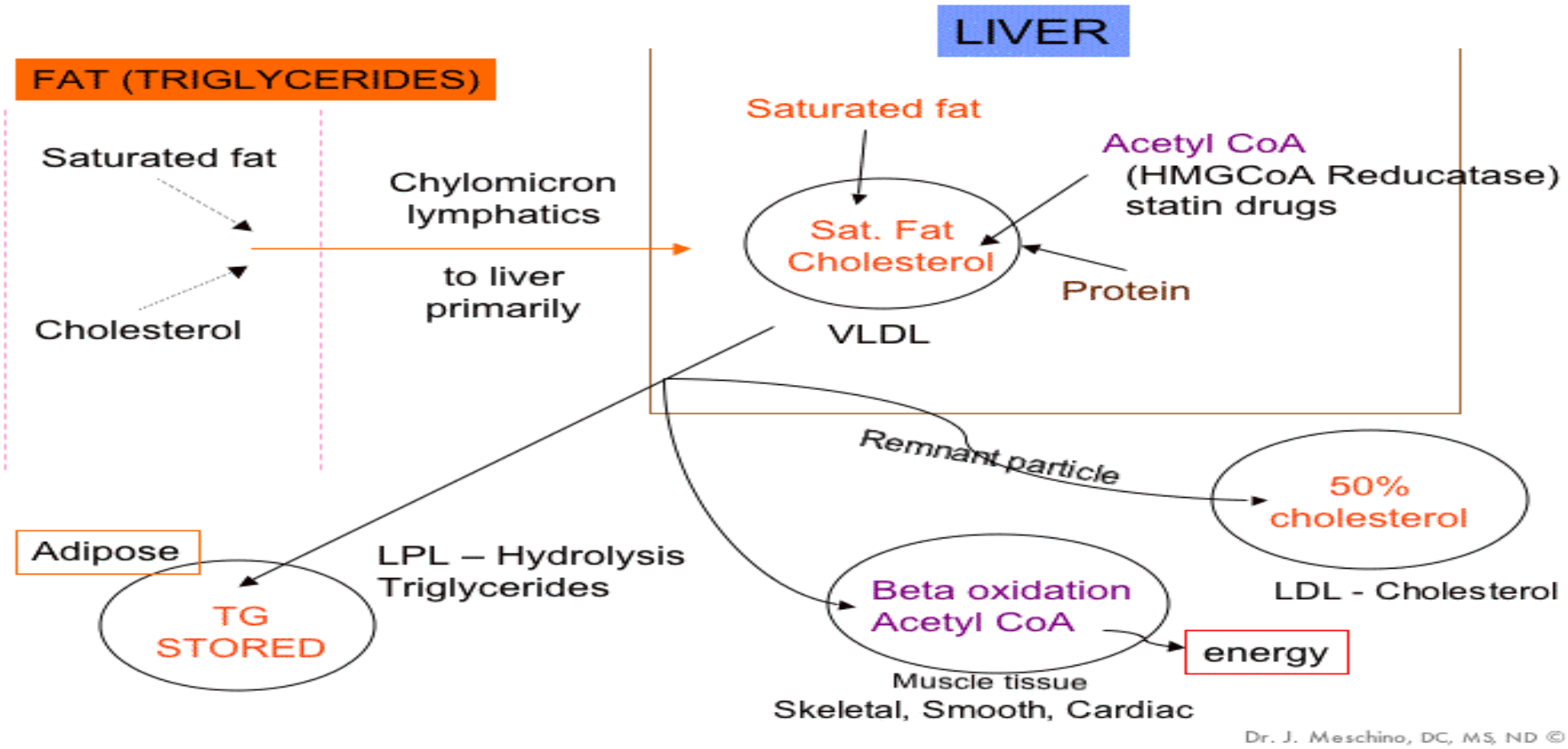
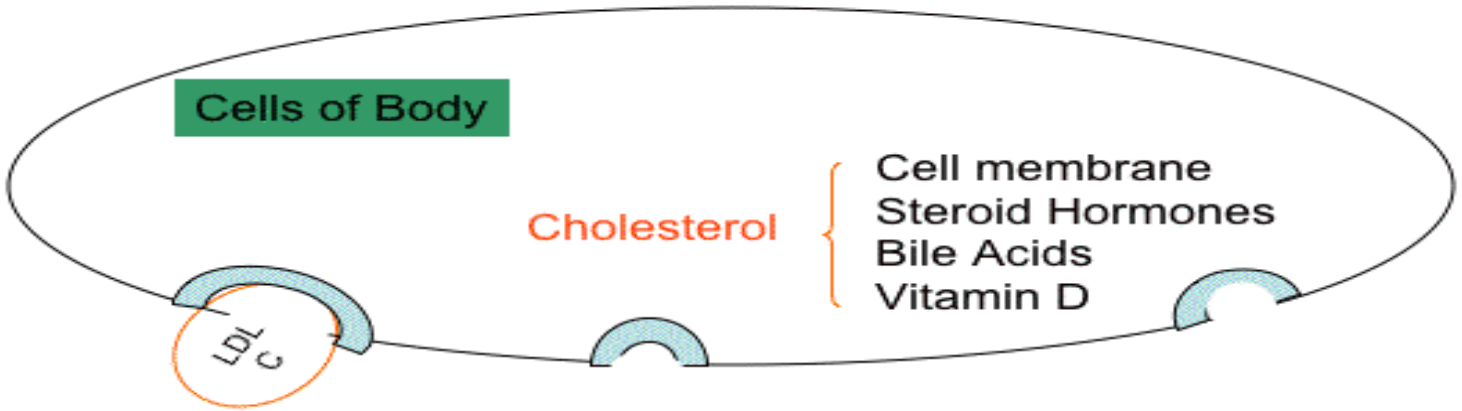
How To Lower Cholesterol Naturally





Too much
LDL
atherosclerosis
LDL – C uptake by macrophages form Foam Cells

HDL - C
Made in Liver (thin, aerobic, female estrogen)

HDL -C → Vacuums up cholesterol and transports it to liver

High TC: HDL Ratio Increases Risk of Vascular Disease

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1. Statin Drugs:

Action: Inhibit HMG CoA Reductase enzyme, thereby slowing cholesterol synthesis

Also inhibit CoQ10 synthesis – increasing risk of congestive heart failure -100-200 mg CoQ10 recommended as concurrent treatment

Side Effects:

Liver Damage - (requires liver function tests).

Muscle pain (up to 30% of users myalgia) –maybe prevented by CoQ10 supplementation

Impotence

Rhabdomyolysis - Fever-flu symptoms, yellowing of skin, eyes, abdominal pain, unexplained fatigue, - can be fatal (dark urine is sign along with muscle weakness, pain, fever, vomiting)

More recently- increased risk of **Diabetes** and **Memory loss**

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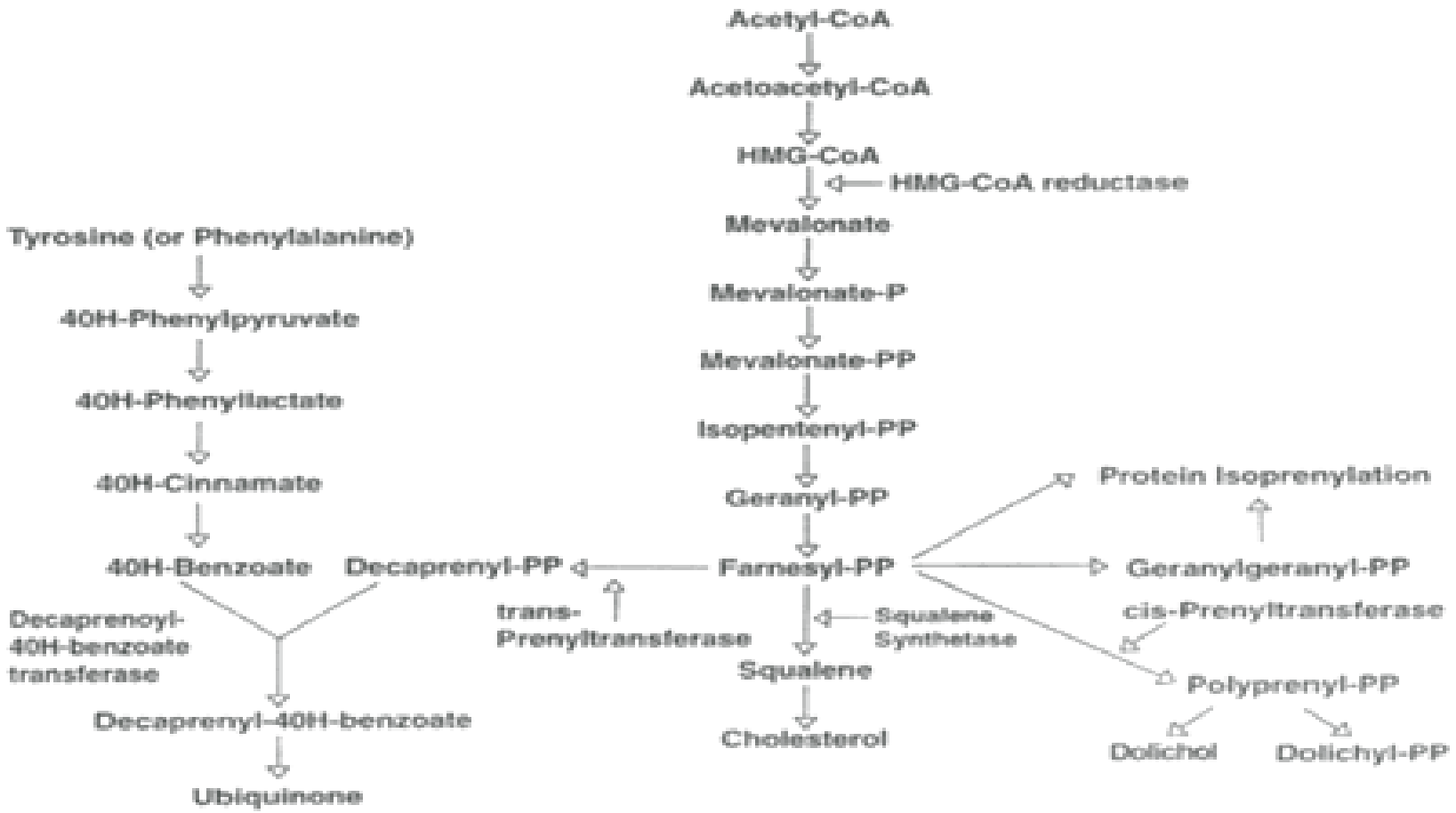
CoQ10 (Ubiquinone Synthesis) And Statin Drugs



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Statin Stats:

Statin drugs are used by more than 13 million Americans and an additional 12 million patients around the world, producing $27.8 billion in sales in 2006.

Half went to Pfizer (PFE) for its leading statin, Lipitor.

Source: Business Week, Jan 17, 2008

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Statin Drugs: Cholesterol Lowering Effects:

- TC Reduction - 22-42%
- LDL-C Reduction - 27-55%
- HDL:LDL Ratio – modest effect
- May stabilize plaque
- Shown to lower risk of heart attack by 30% over 5 years
- Most appropriate for persons who have suffered previous CVD events

Dosage – 10,20,40 up to 80 mg/daily

Health Benefit Plans – report most expensive employee drug expense for many companies

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2. Bile Acid Sequestrants

Function- act like soluble fiber dragging bile and cholesterol out of the body via the fecal route

Results in increased LDL clearance by liver to make required bile, which is then eliminated by bile acid sequestrants, which clears more LDL-C from circulation

Cholesterol Lowering Effect – 10-15% average

Dosage – usually 8 gms/d (cholestyramine)

Side effects – drag fat soluble vitamins from intestinal tract (potential def), bloating and GI discomfort.

Good Safety Profile – colon cancer?

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3. Fibric Acid Derivatives

Gemfibrozil, Fenofibrate

Clinical Applications:

1. Lower triglycerides
2. Elevate HDL
2. Promote uric acid excretion (gout application as well)

Mechanism Of Action – increase LPL activity (clears triglycerides and suppress FFA release from adipose)

May increase Apo1 (which raises HDL synthesis)

Efficacy:

- Triglyeride Reduction - 20-50%
- Cholestesterol Reduction – 20-25%
- HDL Elevation – 10-15%

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Contra-indicated in liver, gallbladder, kidney disease

Side Effects: GI, rare-rash fever, fibrillation, anemia, leukopenia, but generally well tolerated

Dosage: 300-600 mg, twice daily

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4. High Dose Niacin

Clinical Application – most effective drug to lower triglycerides and raise HDL. Also 10-15% reduction in LDL-C.

Mechanism Of Action:

- Inhibits Hormone Sensitive Lipase – blocks release of fats from adipose, which lowers VLDL synthesis
- May increase LPL activity as well
- Can raise HDL 15-35% (unknown mechanism)

Dosage- titrate up to 1,000 mg, three times daily

Contra-indications – liver, gallbladder disease, active ulcer, glucose intolerance, increased uric acid (gout)

*Requires periodic liver function tests

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Niacin: Side Effects and Precautions:

1. Liver damage is common (monitoring required)

2. Myopathy with elevated creatine kinase

3. Diabetics, who have high triglyc and low HDL, require glucose monitoring if placed on niacin therapy – fibric acid derivatives better choice in this case

4. Not appropriate for gout or ulcer patients

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Natural Management Of Hyperlipidemia:

Reviewed Cardiovascular Disease Section

- Diet
- Exercise
- Supplementation

Up to 90% of people can hit ideal cholesterol levels without use of drugs
(W. Castelli MD – Framingham Heart Study)- primary prevention

But in patients with previous heart attack or CVD events, some cases of kidney disease, statin drugs can play a key role in secondary prevention of CVD events.

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Cholesterol Targets:

- Non-High Risk CVD Person - LDL- 2.5 mmol/L (I prefer under 2.0 mmol/L)

- LDL- High Risk – 1.8 mmol/L (Candidates- more than 20%- 10yr risk in Framingham Profile, diabetes, kidney disease, previous cardiovascular event or heart procedure – bypass, angioplasty etc.)

- Triglycerides should be kept below 1.5 mmol/L (132 mg/dL) and fasting glucose below 5.0 mmol (90 mg/dL) are best targets for longevity

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CVD Assessment Form

Practitioner Cardiovascular Disease Screening Form

- **Patient's Name** _____
- **Assessment Date**_____
- **Gender** ____**Age**____ **Blood Pressure: SBP**____ **DBP**____
- **Diabetes:** Yes___ No____ comment:_____
- **Smoking:** Yes____ No____
- **Total Cholesterol**_____(to convert cholesterol from mg/dl into mmol/L multiply by 0.026) – ideal is less than 3.9 mmol/L
- **LDL-Cholesterol**_____(ideal is less than 1.8 mmol/L)
- **HDL-Cholesterol**_____ (ideal is above 1.17mmol/L – Men; Females: above1.56 mmol/L)
- **TC:HDL Ratio**_____ (ideal is less than 3:1 ratio)
- **Fasting Glucose** _____ (ideal is under 90 mg/dl or 5 mmol/L – conversion factor is .055)
- **Fasting Triglycerides**_____(ideal is 132 mg/dl or 1.5mmol/L – conversion factor is 88.57)
- **C-Reactive Protein** _____ (less than 0.2 mg/dL or 2 mg/L) – conversion factor is 10
- **Fibrinogen** _____ (less than 300 mg/dL or 0.88 umol/L - conversion factor is 0.0294)

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- **Body Mass Index or BMI** (wt/ht squared) – wt is kg and ht is in metes-squared

  Multiply weight in pounds by .45 to get weight in kg

  Multiply height in inches by .025 to get height in meters (then multiply height in meters by itself to get height in meters squared)

  (BMI of 27 or higher increases risk of high BP, Diabetes, Dyslipidemia and some Cancers) BMI = _____

- **Waist Circumference** _____inches (under 36 for men and 33 for women)

- **Personal History** of Heart Disease, Stroke, Deep Vein Thrombosis, Chronic Renal Disease or any vascular problems or vascular procedures (angioplasty, by-pass surgery, coronary stent) Yes___ No___ Comment:
  _____

- **Exercise Program**
  _____
  _____

- **GFR** (eGFR < 60 mL/min is a concern) _____

- **Blood Creatinine** _____Normal is 0.6 to 1.2 mg/dl 60-110 µmol/L) in adult males and 0.5 to 1.1 mg/dl (45-90 µmol/L) in adult females

- **Albumin:Creatinine Ratio** – **24 hour urine sample evaluated** (An elevated albumin/creatinine ratio (men: > 2.0 mg/mmol, women: > 2.8 mg/mmol) is associated with an increased risk of heart disease and stroke_____

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- **Metabolic syndrome**: Metabolic syndrome includes three or more of the following criteria: Abdominal obesity (waist circumference: men > 102 cm or 40 inches; women > 88 cm or 35 inches);Triglycerides ≥ 1.7 mmol/L (; HDL (men < 1.0 mmol/L, women < 1.3 mmol/L); BP > 130/85 mm Hg; Fasting glucose 5.7-6.9 mmol/L (103 -124mg/dl) – conversion from mg'dl to mmol'L is .055. Evidence of Metabolic Syndrome? Yes_____ No_____

- 10 Year Heart Disease Risk Score (based on LDL reference form)_____% - completed in office
- 10 Year Heart Disease Risk Score (based on Total Cholesterol reference form_____% - completed in office

- Current CVD Medications (cholesterol, triglyceride, blood pressure, other):
  _____
  _____
  _____
  _____
  _____
  _____

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Coronary Disease Risk Prediction Score Sheet for Men Based on LDL Cholesterol Level

Step 1

Age	
Years	Points
30-34	-1
35-39	0
40-44	1
45-49	2
50-54	3
55-59	4
60-64	5
65-69	6
70-74	7

Step 2

LDL - Cholesterol		
(mg/dl)	(mmol/L)	Points
<100	<2.59	-3
100-129	2.60-3.36	0
130-159	3.37-4.14	0
160-189	4.16-4.91	1
>190	>4.92	2

Key	
Color	Risk
green	Very low
white	Low
yellow	Moderate
race	High
red	Very High

Step 3

HDL - Cholesterol		
(mg/dl)	(mmol/L)	Points
<35	<0.90	2
35-44	0.91-1.16	1
45-49	1.17-1.29	0
50-59	1.30-1.55	0
>60	>1.56	-1

Step 4

Blood Pressure					
Systolic (mmHg)	Diastolic (mmHg)				
	<80	80-84	85-89	90-99	>100
<120	0				
120-129		0 pts			
130-139			1		
140-159				2	
>160					3 pts

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 6

Diabetes	
	Points
No	0
Yes	2

Step 8

Smoker	
	Points
No	0
Yes	2

Risk estimates were derived from the experience of the NHLBI's Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

Step 7 (sum from steps 1-6)

Adding up the points	
Age	_____
LDL Cholesterol	_____
HDL Cholesterol	_____
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point Total	_____

Step 8 (determine CHD risk from point total)

CHD Risk	
Point Total	10 Yr CHD Risk
<-3	1%
-2	2%
-1	2%
0	3%
1	4%
2	4%
3	6%
4	7%
5	9%
6	11%
7	14%
8	18%
9	22%
10	27%
11	33%
12	40%
13	47%
>14	>56%

Step 9 (compare to man of the same age)

Comparative Risk		
Age (years)	Average 10 Yr CHD Risk	Low* 10 Yr CHD Risk
30-34	3%	2%
35-39	5%	3%
40-44	7%	4%
45-49	11%	4%
50-54	14%	8%
55-59	18%	7%
60-64	21%	9%
65-69	25%	11%
70-74	30%	14%

*Low risk was calculated for a man the same age, normal blood pressure, LDL cholesterol 100-129 mg/dL, HDL cholesterol 45 mg/dL, non-smoker, no diabetes

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Coronary Disease Risk Prediction Score Sheet for Women Based on LDL Cholesterol Level

Step 1

Age	
Years	Points
30-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	7
60-64	8
65-69	8
70-74	8

Step 2

LDL - Cholesterol		
(mg/dl)	(mmol/L)	Points
<100	<2.59	-2
100-129	2.60-3.36	0
130-159	3.37-4.14	0
160-189	4.15-4.91	2
≥190	≥4.92	2

Key	
Color	Risk
green	Very low
white	Low
yellow	Moderate
rose	High
red	Very high

Step 3

HDL - Cholesterol		
(mg/dl)	(mmol/L)	Points
<35	<0.90	5
35-44	0.91-1.16	2
45-49	1.17-1.29	1
50-59	1.30-1.55	0
≥60	≥1.56	-2

Step 4

Blood Pressure					
Systolic	Diastolic (mmHg)				
(mmHg)	<80	80-84	85-89	90-99	≥100
<120	-3 pts				
120-129		0 pts			
130-139			0 pts		
140-159				2 pts	
≥160					3 pts

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes	
	Points
No	0
Yes	4

Step 6

Smoker	
	Points
No	0
Yes	2

Risk estimates were derived from the experience of the NHLBI's Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

Step 7 (sum from steps 1-6)

Adding up the points	
Age	_____
LDL Cholesterol	_____
HDL Cholesterol	_____
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point Total	_____

Step 8 (determine CHD risk from point total)

CHD Risk	
Point Total	10 Yr CHD Risk
<-2	1%
-1	2%
0	2%
1	2%
2	3%
3	3%
4	4%
5	5%
6	6%
7	7%
8	8%
9	8%
10	11%
11	13%
12	15%
13	17%
14	20%
15	24%
16	27%
≥17	≥32%

Step 9 (compare to women of the same age)

Comparative Risk		
Age (years)	Average 10 Yr CHD Risk	Low* 10 Yr CHD Risk
30-34	<1%	<1%
35-39	1%	<1%
40-44	2%	2%
45-49	5%	3%
50-54	8%	5%
55-59	12%	7%
60-64	12%	8%
65-69	13%	8%
70-74	14%	8%

*Low risk was calculated for a woman the same age, normal blood pressure, LDL cholesterol 100-129 mg/dL, HDL cholesterol 55 mg/dL, non-smoker, no diabetes

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Coronary Disease Risk Prediction Score Sheet for Men Based on Total Cholesterol Level

Step 1

Age	
Years	Points
30-34	-1
35-39	0
40-44	1
45-49	2
50-54	3
55-59	4
60-64	5
65-69	6
70-74	7

Step 2

Total Cholesterol		
(mg/dl)	(mmol/L)	Points
<160	<4.14	-3
160-199	4.16-5.17	0
200-239	5.18-6.21	1
240-279	6.22-7.24	2
≥280	≥7.25	3

Key	
Color	Risk
green	Very low
white	Low
yellow	Moderate
rose	High
red	Very high

Step 3

HDL - Cholesterol		
(mg/dl)	(mmol/L)	Points
<35	<0.90	2
35-44	0.91-1.16	1
45-49	1.17-1.29	0
50-59	1.30-1.55	0
≥60	≥1.56	-2

Step 4

Blood Pressure					
Systolic (mmHg)	Diastolic (mmHg) <80	80-84	85-89	90-99	≥100
<120	0				
120-129	0 pts				
130-139			1		
140-159				2	
≥160					3 pts

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes	
	Points
No	0
Yes	2

Step 6

Smoker	
	Points
No	0
Yes	2

Risk estimates were derived from the experience of the NHLBI's Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

Step 7 (sum from steps 1-6)

Adding up the points	
Age	_____
Total Cholesterol	_____
HDL Cholesterol	_____
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point Total	_____

Step 8 (determine CHD risk from point total)

CHD Risk	
Point Total	10 Yr CHD Risk
≤-1	2%
0	3%
1	3%
2	4%
3	5%
4	7%
5	8%
6	10%
7	13%
8	16%
9	20%
10	25%
11	31%
12	37%
13	45%
≥14	≥53%

Step 9 (compare to man of the same age)

Comparative Risk		
Age (years)	Average 10 Yr CHD Risk	Low* 10 Yr CHD Risk
30-34	3%	2%
35-39	5%	3%
40-44	7%	4%
45-49	11%	4%
50-54	14%	6%
55-59	16%	7%
60-64	21%	9%
65-69	25%	11%
70-74	30%	14%

*Low risk was calculated for a man the same age, normal blood pressure, total cholesterol 160-199 mg/dL, HDL cholesterol 45 mg/dL, non-smoker, no diabetes

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Coronary Disease Risk Prediction Score Sheet for Women Based on Total Cholesterol Level

Step 1

Age	
Years	Points
30-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	7
60-64	8
65-69	8
70-74	8

Step 2

Total Cholesterol		
(mg/dl)	(mmol/L)	Points
<160	<4.14	-2
160-199	4.16-5.17	0
200-239	5.18-6.21	1
240-279	6.22-7.24	1
≥280	≥7.25	3

Key	
Color	Risk
green	Very low
white	Low
yellow	Moderate
rose	High
red	Very high

Step 3

HDL - Cholesterol		
(mg/dl)	(mmol/L)	Points
<35	<0.90	5
35-44	0.91-1.16	2
45-49	1.17-1.29	1
50-59	1.30-1.55	0
≥60	≥1.56	-3

Step 4

Blood Pressure					
Systolic	Diastolic (mmHg)				
(mmHg)	<80	80-84	85-89	90-99	≥100
<120	-3 pts				
120-129		0 pts			
130-139			0 pts		
140-159				2 pts	
≥160					3 pts

Note: When systolic and diastolic pressures provide different estimates for point scores, use the higher number

Step 5

Diabetes	
	Points
No	0
Yes	4

Step 6

Smoker	
	Points
No	0
Yes	2

Risk estimates were derived from the experience of the NHLBI's Framingham Heart Study, a predominantly Caucasian population in Massachusetts, USA

Step 7 (sum from steps 1-6)

Adding up the points	
Age	_____
Total Cholesterol	_____
HDL Cholesterol	_____
Blood Pressure	_____
Diabetes	_____
Smoker	_____
Point Total	_____

Step 8 (determine CHD risk from point total)

CHD Risk	
Point Total	10 Yr CHD Risk
≤-2	1%
-1	2%
0	2%
1	2%
2	3%
3	3%
4	4%
5	4%
6	5%
7	6%
8	7%
9	8%
10	10%
11	11%
12	13%
13	15%
14	18%
15	20%
16	24%
≥17	≥27%

Step 9 (compare to women of the same age)

Comparative Risk		
Age (years)	Average 10 Yr CHD Risk	Low* 10 Yr CHD Risk
30-34	<1%	<1%
35-39	1%	<1%
40-44	2%	2%
45-49	5%	3%
50-54	8%	5%
55-59	12%	7%
60-64	12%	8%
65-69	13%	8%
70-74	14%	8%

*Low risk was calculated for a woman the same age, normal blood pressure, total cholesterol 160-199 mg/dL, HDL cholesterol 55 mg/dL, non-smoker, no diabetes

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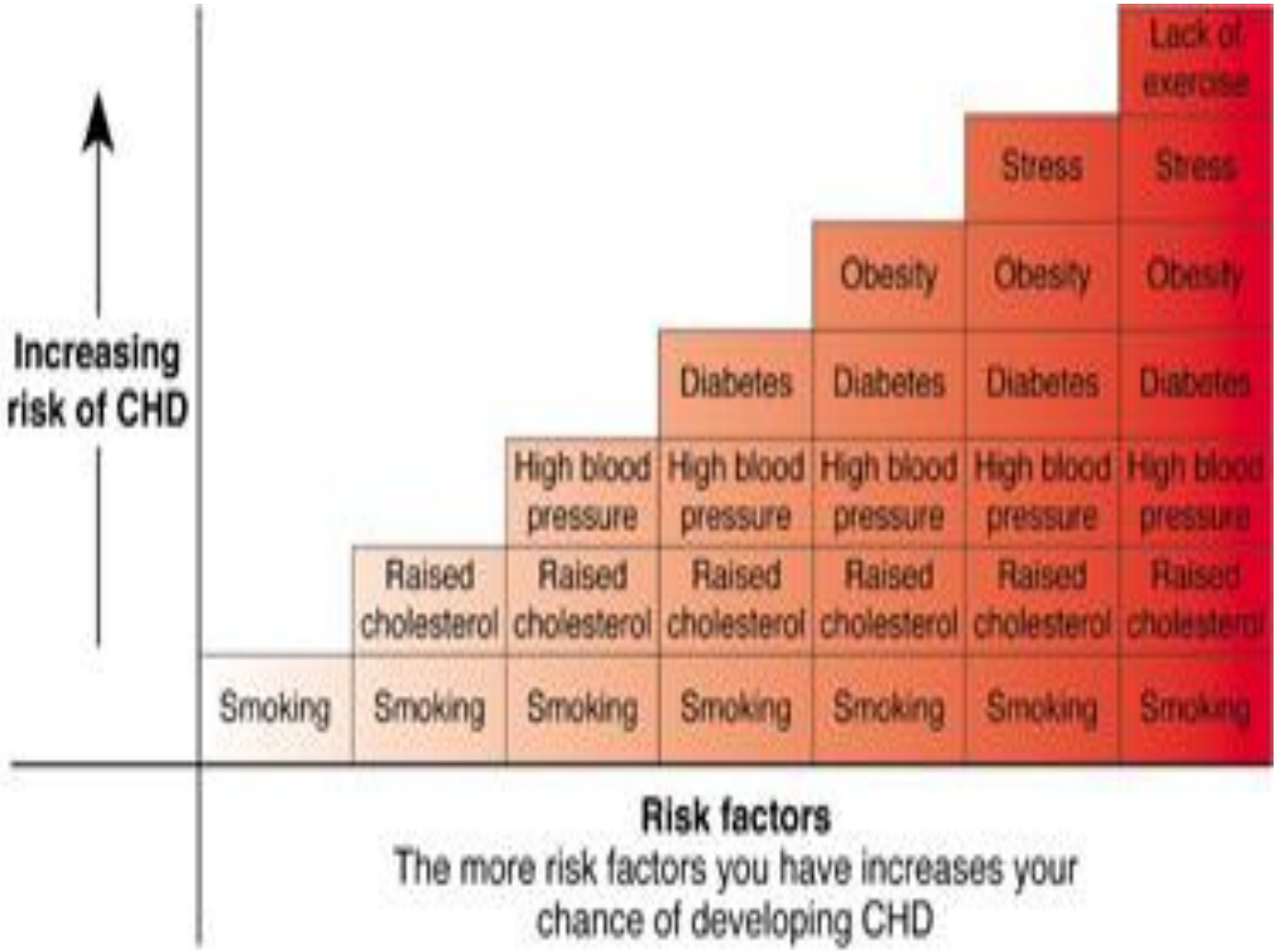
Compounding of Key CVD Risk Factors



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Male Age:60 - Case Study 2008

	Parameter Measured	Initial Assessment Sept 8/08	3-4 Month Follow-up Assessment
1.	Weight – 4 months	**210 lbs**	**184 lbs (-26 lbs)**
2.	Waist Circumference 4 mths -	**45 inches**	**41.5 inches**
3.	Hip Circumference 4 mths -	**45 inches**	**41.5 inches**
4.	Total Cholesterol 3 mths -	**178.8mg/dl (4.65mmol/L)**	**154mg/dl (4.0mmol/L)**
5.	**LDL-Cholesterol 3 mths -**	**119.6mg/dL (3.11mmol/L)**	**99.2mg/dL (2.5 mmol/L)**
6.	**HDL-Cholesterol 3 mths –**	**40.76 mg/dL (1.06mmol/L)**	**44.23 dL (1.14 mmol/L)**
7.	**TC:HDL Ratio 3 mths**	**4:39:1**	**3.5:1**

Interventions – low fat diet, high fiber (with flaxseed powder), 40 mins elliptical exercise daily, Adeeva MV, NEO, Cardio Essentials, Prostate 40 Plus

History of Childhood and Adolescent Obesity

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Endothelial Dysfunction

Decreased release of nitric oxide by endothelial cells

Causes:
Saturated fat and high LDL-C
Cigarette smoking
Hypertension
Diabetes

Reversal:
Folic acid
Antioxidants (vits C,E)
Exercise
Improved glucose tolerance (exercise and weight loss)
Hawthorn
CoQ10 (diabetics)
Tribulus terrestris (40% saponins) – also helps erectile dysfunction

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Part 3. Other Important Cardiac Drugs

1. Digitalis (Digoxin)

Overview:

- Digitalis discovered in the foxglove shrubs
- The term digitalis is also used for preparations containing cardiac glycosides, particularly digoxin, extracted from plants of this genus
- The use of Digitalis purpurea extract containing cardiac glycosides for the treatment of heart conditions dates back to 1785

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Digitalis

Mechanism Of Action: inhibits sodium-potassium ATPase, an enzyme that drives the sodium-calcium exchanger pump.

Result: increased intracellular calcium by passively decreasing the action of the sodium-calcium exchanger in the sarcolemma (muscle cell membrane)

Increased intracellular calcium gives a positive inotropic effect.

Useful in **Congestive Heart Failure** and other
Cardiomyopathies when heart muscle is weak

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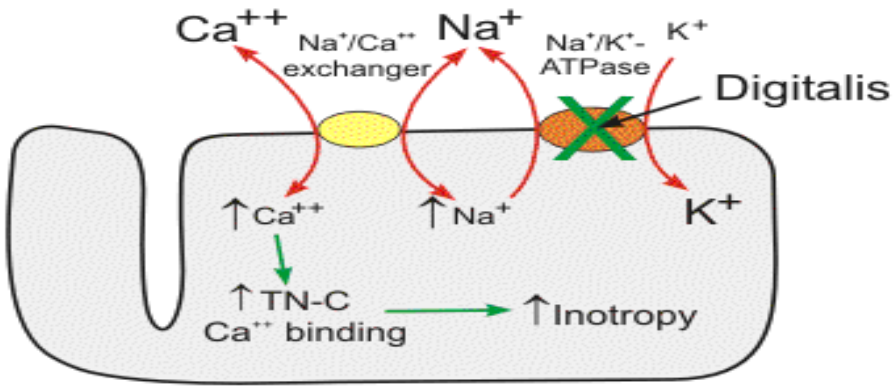
The Sodium Calcium Exchanger (NCX)

- The Sodium Calcium Exchanger (NCX) is a pump that removes a single calcium ion in exchange for import of three sodium ions.
- The NCX is a most important cellular mechanism for removing Ca2+. (but not the only one)
- The NCX exchanger is found in plasma membranes, mitochondria, endoplasmic reticulum & sarcoplasmic reticulum of excitable cells (e.g. muscles)
- The NCX is a different pump than the sodium-potassium pump.



- The NCX is most highly activated after cell depolarization, to pump calcium back out of the cell

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Other Effects Of Digitalis

Digitalis and Re-entrant Arrhythmias:

- Digitalis also increases vagal effect on heart
- Therefore, used to treat **reentrant cardiac arrhythmias** and to slowing the ventricular rate during **atrial fibrillation.**

Reentrant arrhythmias occur when an electrical impulse recurrently travels in a tight circle within the heart, rather than moving from one end of the heart to the other and then stopping.

Re-entry circuits are responsible for **atrial flutter**, most **paroxysmal supraventricular tachycardia**, and dangerous **ventricular tachycardia**.

*The dependence on the vagal effect means that digitalis is not effective when a patient has a high sympathetic nervous system drive, which is the case with acutely ill persons, and also during exercise

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Clinical Applications:

1. Heart Failure, especially when atrial fibrillation is present (Anti-arrhythmic)

- It is therefore often prescribed for patients in **atrial fibrillation**, especially if they have been diagnosed with **heart failure.**

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Adverse Side Effects of Digitalis:

- *Heart Block and bradycardia
- *Tachycardia
- Nausea, Vomiting, Diarrhea
- Hallucinations
- Blurred Vision

Narrow therapeuctic safety index

- **Note:** Do not recommend hawthorn-containing (and Ginseng) supplements to patients taking digitalis or digoxin (or Lanoxin injections)

2. Nitroglycerin: Nitroglycerin is converted to nitric oxide in the body, which is a natural vasodilator.

Clinical Application – Angina - Nitroglycerin dilates veins more than arteries, decreasing cardiac preload and leading to the following therapeutic effects during episodes of angina pectoris:

1. subsiding of chest pain
2. decreased blood pressure
3. increased heart rate.
4. orthostatic hypotension

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Administration Of Nitroglycerin:

- Tablets
- Ointment
- Solution for intravenous use
- Transdermal patches
- Sprays administered sublingually

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Adverse Side Effects:

- Lack of sexual desire
- * Headache
- Painful urination
- Increased bowel movements

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Complementary Management Of Congestive Heart Failure And Arrhythmias

Reviewed in the Cardiovascular Section

1. Co-enyzme Q10 (Ubiquinone)
2. L-Taurine
3. D-Ribose
4. L-Carnitine
5. Hawthorn
6. Magnesium

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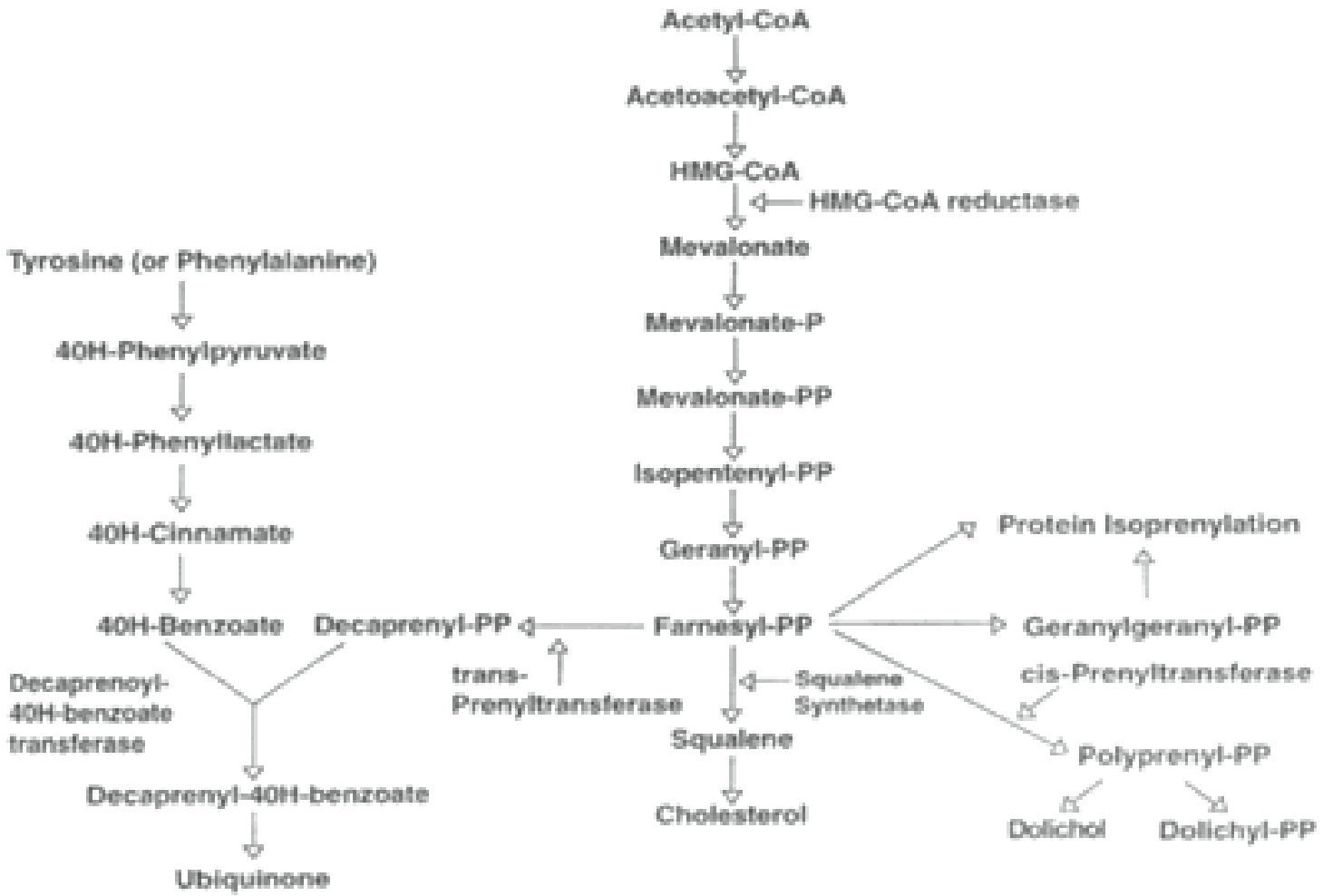
CoQ10 Synthesis - note that statin drugs inhibit HMG-CoA Reductase Enzyme and thus CoQ10 production



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Drugs That Decrease CoQ10 Status

- Orlistat: reduces CoQ10 absorption. (Don't take CoQ10 supplements within 90 minutes of ingesting Orlistat – a fat absorption blocker)
- Beta blockers: decreases CoQ10 synthesis.
- Biguanides: decreases CoQ10 synthesis.
- Cloindine: decreases CoQ10 synthesis.
- Gemfibrozil: (cholesterol-lowering drug).
- Haloperidol: decreases CoQ10 synthesis.
- HMG-CoA Reductase inhibitors: decreases CoQ10 synthesis.
- Hydralazine: decreases CoQ10 synthesis.
- Methydopa: decreases CoQ10 synthesis.
- Phenothiazines: decreases CoQ10 synthesis.
- Sulfonylureas: some of these drugs decrease CoQ10 synthesis (acetohexamide, glyburide, tolazamide).
- Thiazide Diuretics: decrease CoQ10 synthesis.
- Tricyclic Antidepressants: decrease CoQ10 synthesis.

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3. Anti-coagulants (Warfarin, Coumadin, Plavix)

Warfarin - a synthetic derivative of coumarin, found naturally in many plants, notably woodruff (*Galium odoratum*, Rubiaceae)

Coumadin: (crystalline warfarin sodium)

Mechanism of Action - Warfarin and Coumadin are anticoagulants which act by inhibiting vitamin K-dependent coagulation factors

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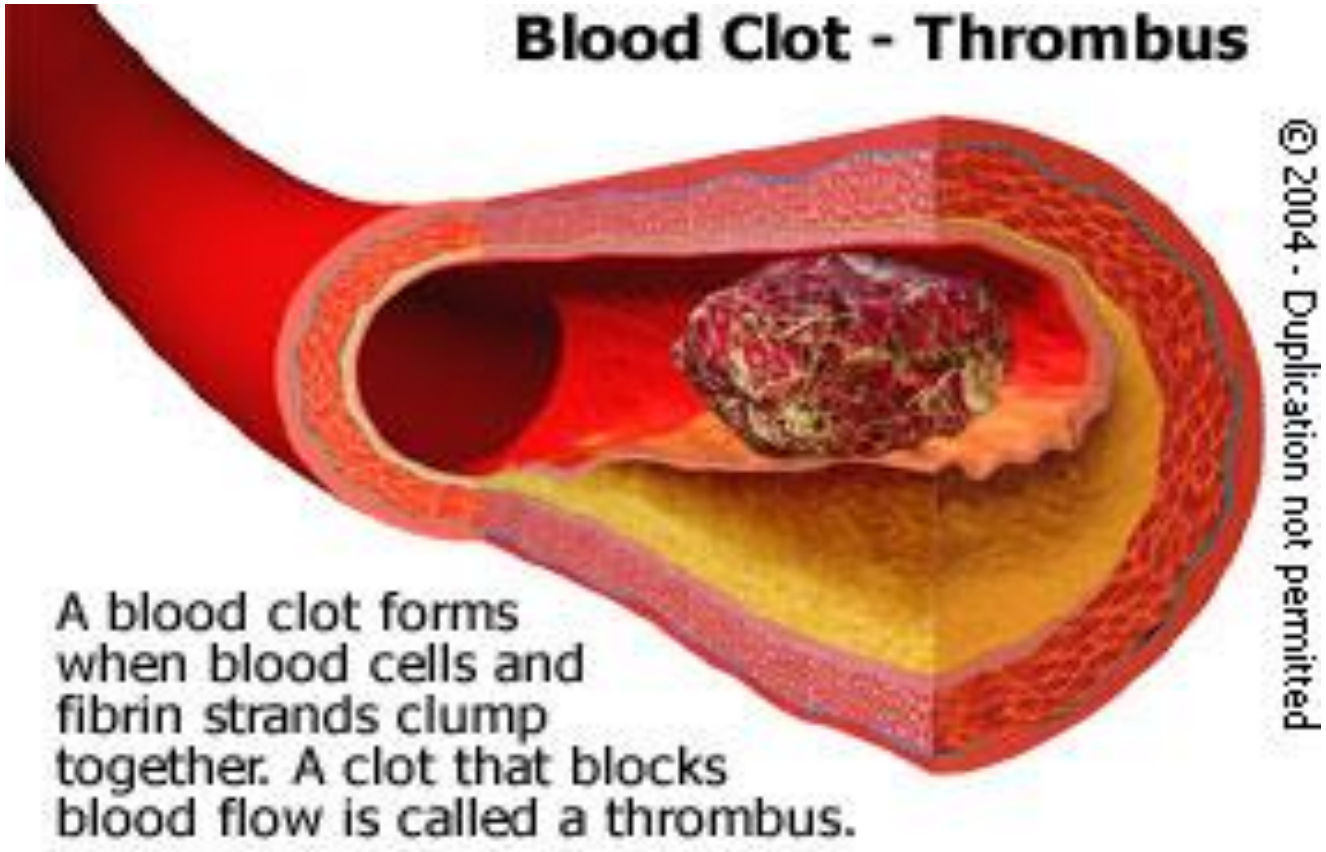
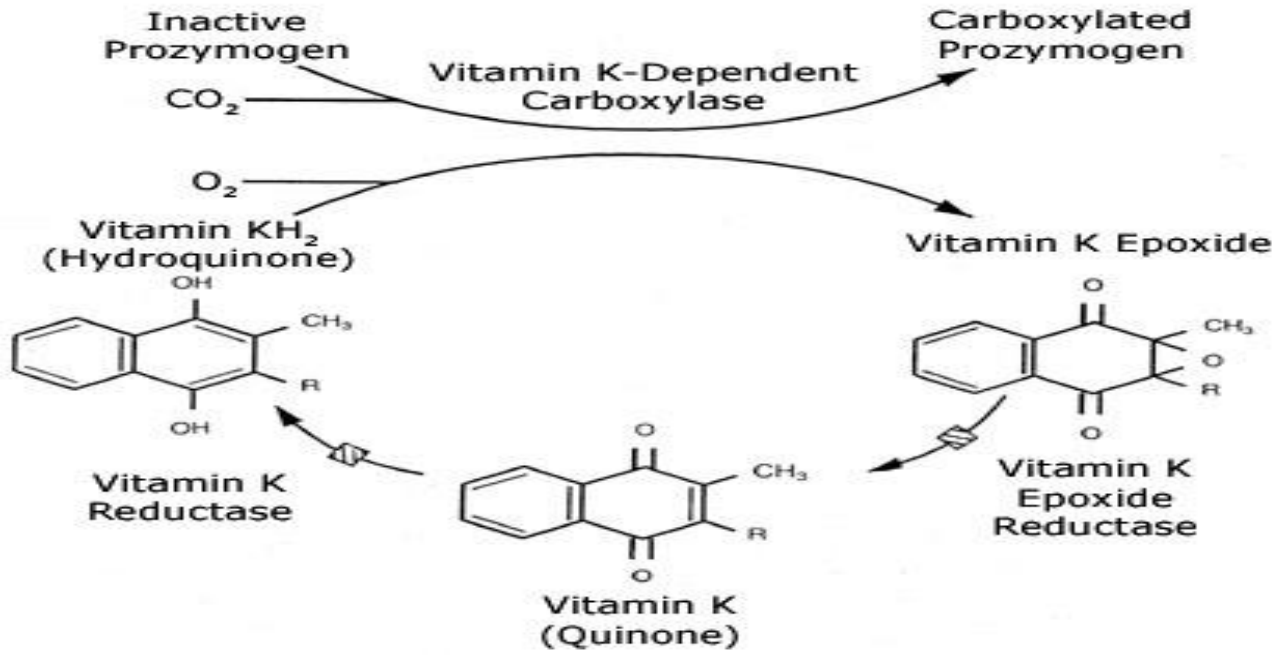
Purpose of drugs is to prevent thrombus formation



Warfarin and Coumadin Inhibit vitamin K epoxide reductase, which recycles oxidized vitamin K to its reduced form, after it has participated in the carboxylation of several blood coagulation proteins,

mainly prothrombin and factor VI . Vitamin K is also an essential cofactor in the post-ribosomal carboxylation of clotting factors II, VII, IX, and X by a vitamin K-dependent carboxylase that is

synthesized in the liver



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Clotting Events

1. Normally, coagulation begins almost instantly after an injury to the blood vessel has damaged the endothelium (a small cut for instance)

2. However, a **high fat diet**, **lack of aerobic fitness**, being **overweight** and **cigarette smoking** increase clotting behaviour, increasing risk of thrombus and emobolism

3. **Intrinsic Pathway Response**: Platelets immediately form a plug at the site of injury; this is called primary hemostasis.

4. **Extrinsic Pathway Response**: Secondary hemostasis occurs simultaneously whereby proteins in the blood plasma (coagulation factors or clotting factors) respond in a complex cascade to form **fibrin strands**, which strengthen the platelet plug.

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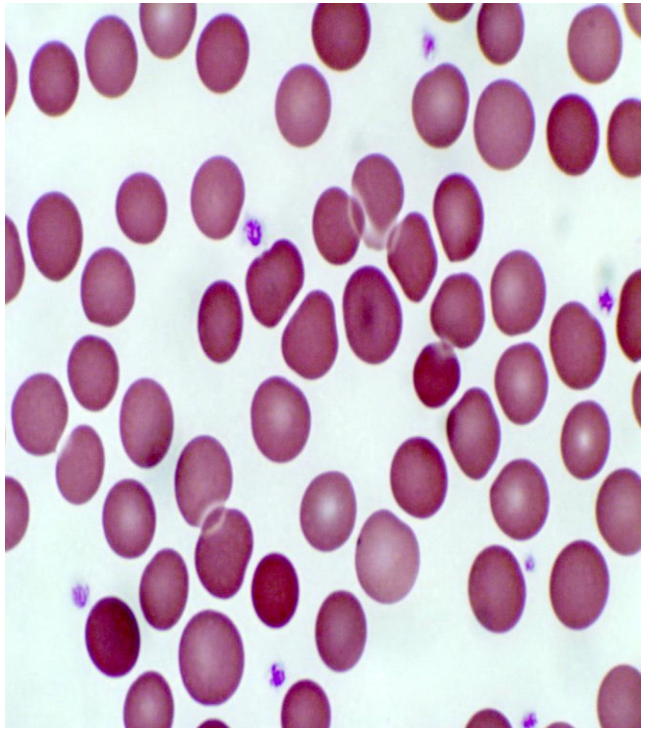
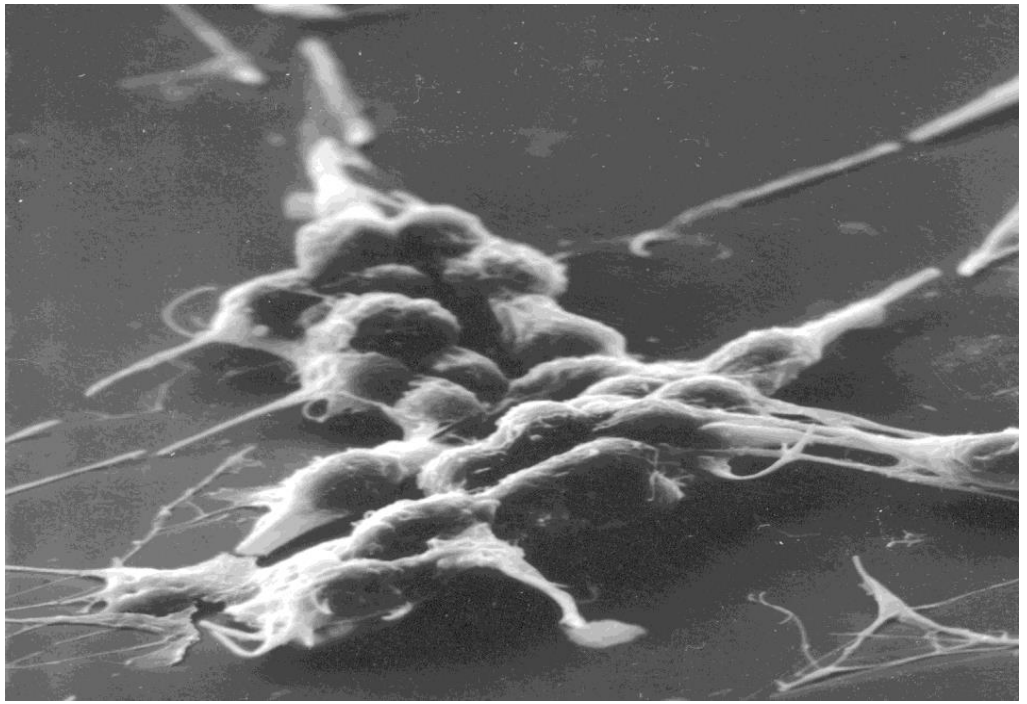
Scanning electron microscope on right shows group of platelets which have begun to initiate a clot. The stringy material covering them is fibrin. The left slide are inactivated

platelets.





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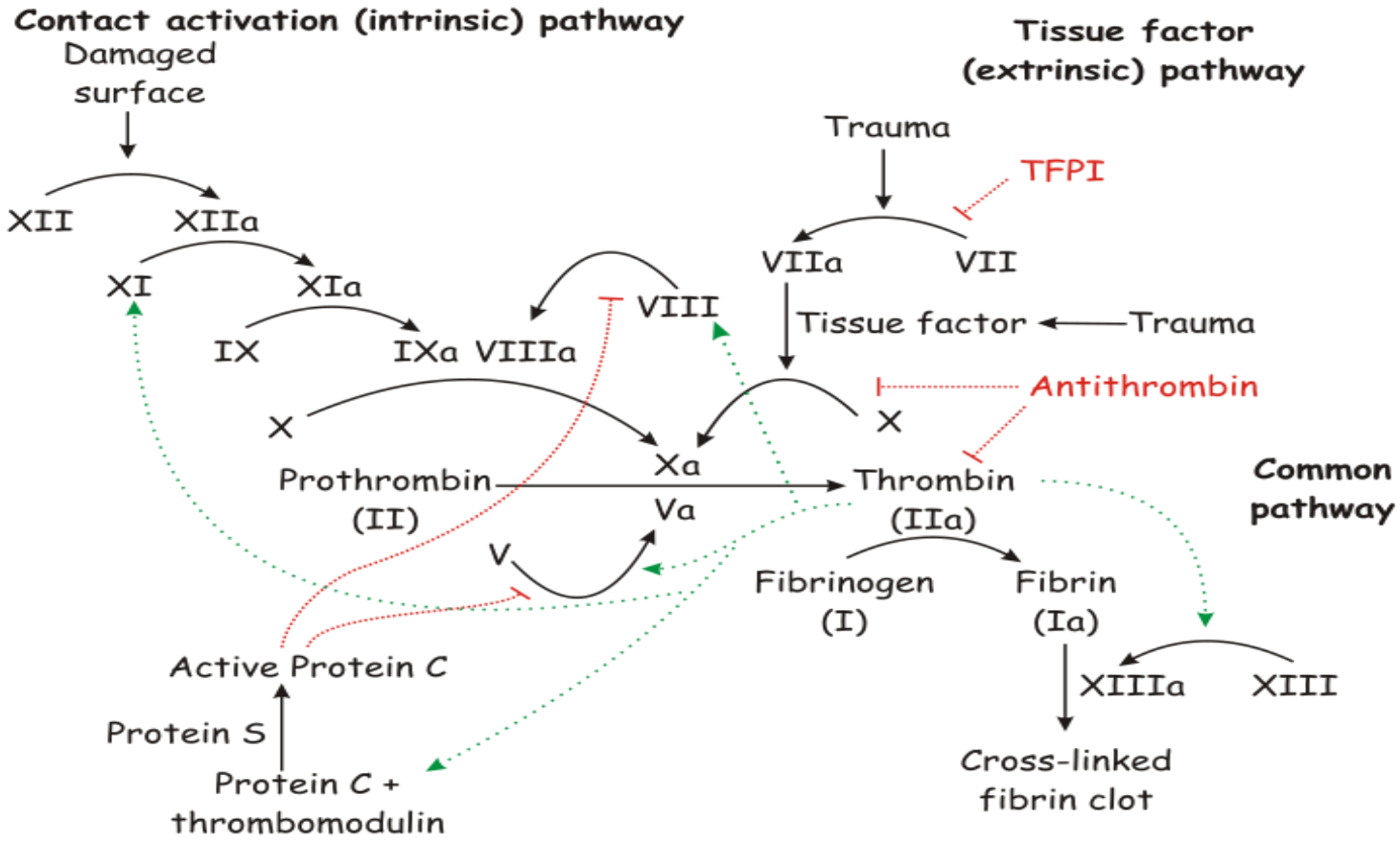
Clotting Cascade



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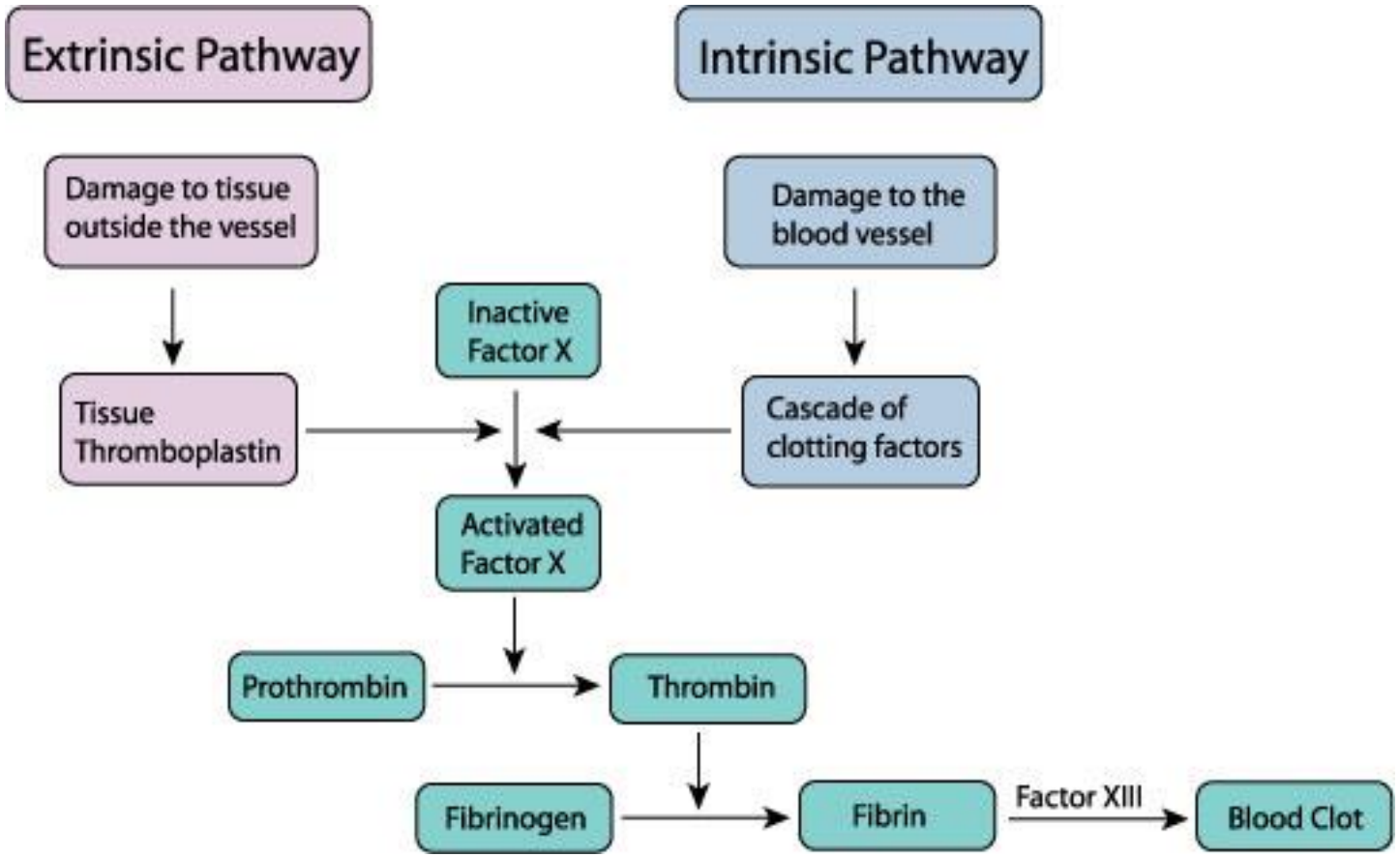
Warfarin prevents synthesis of prothrombin by preventing recycling of Vitamin K to its reduced state



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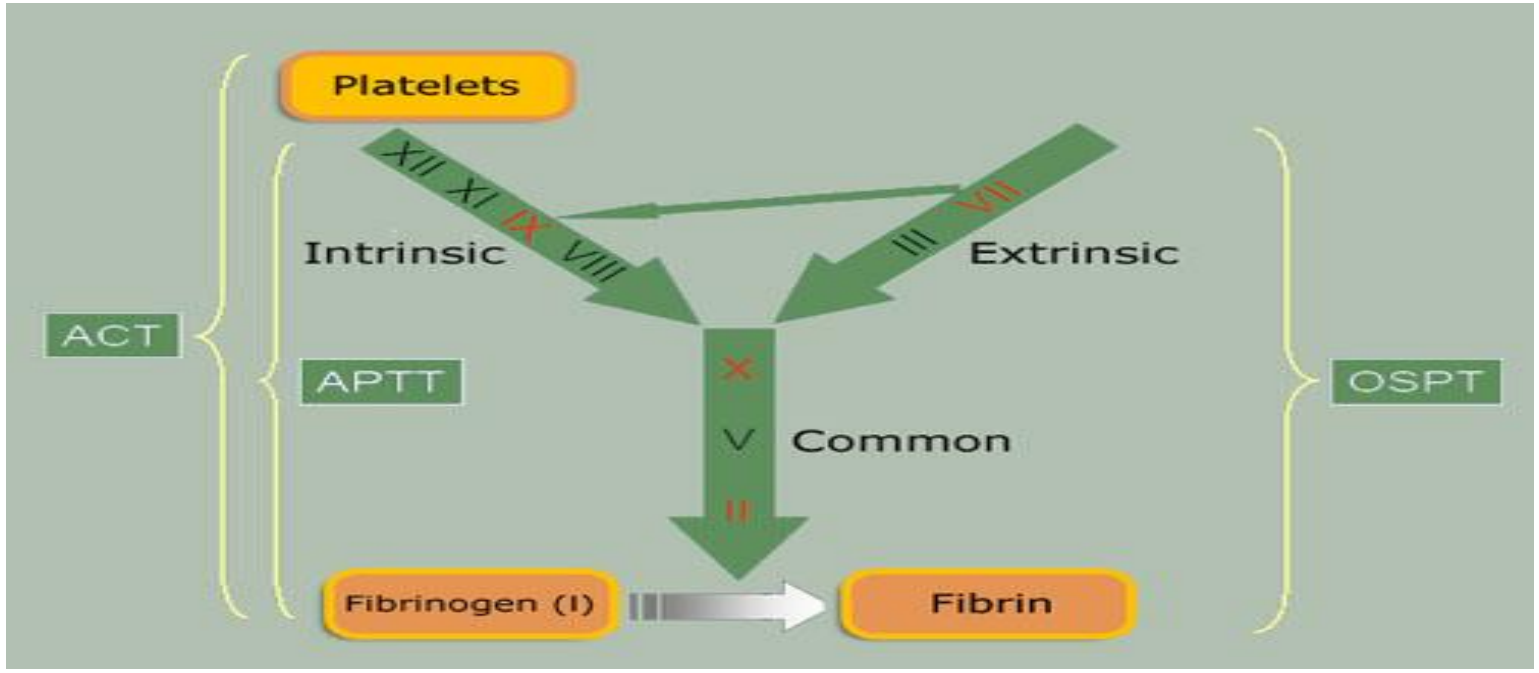
Vitamin K-dependent Clotting Factors

Vitamin K is responsible for the carboxylation or activation of clotting factors II, VII, IX, and X in the liver. Vitamin K reductase enzymes keep the vitamin in an active (reduced) state. These four clotting factors are not activated if the function of vitamin K is inhibited (**coumarin, warfarin, vitamin K deficiency**). **Note that factor VII increases with high fat diet, leading to increased fibrin synthesis and abnormal clots**.



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Clinical Application Of Anti-coagulants:

Used to prevent thrombosis and embolism in many disorders (some examples):

1. Prophylaxis and/or treatment of **venous thrombosis** (e.g. DVT) and its extension, and **pulmonary embolism**

2. Prophylaxis and/or treatment of the thromboembolic complications associated with **atrial fibrillation** and/or **cardiac valve replacement**

3. To reduce the risk of death due to recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization **after myocardial infarction**

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Interactions and Dosing Problems:

Dosing of warfarin is complicated by fact that it interacts with many commonly-used:

- **medications**
- **supplements**
- **vitamin K containing foods**

- In order to optimize the therapeutic effect without risking dangerous side effects such as bleeding, **close monitoring** of the degree of anticoagulation is required by blood testing **(INR).**

- During the initial stage of treatment, checking may be **required daily**; intervals between tests can be lengthened if the patient manages stable therapeutic INR levels on an unchanged warfarin dose

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Prothrombin Time And INR

- The reference range for prothrombin time is usually around 12–15 seconds; the normal range for the INR is 0.9–1.3. (International Normal Ratio)

- A high INR level such as INR=5 indicates that there is a high chance of bleeding, whereas if the INR=0.5 then there is a high chance of having a clot.

- Normal range for a healthy person is 0.9–1.3, and for people on warfarin therapy, 2.0–3.0, although the target INR may be higher in particular situations, such as mechanical heart valves.

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* **Major Adverse Side Effect** - Fatal or nonfatal hemorrhage from any tissue or organ.

Therefore, must be careful what supplements and dietary advice you give an individual on these medications.

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Drug-Nutrient Interactions With Coumadin (Warfarin)

Supplements With Reported Bleeding Disorders In Human Cases (GGGDC)

Garlic

Ginkgo biloba

Ginseng

Dong quai *(Angelica sinensis)*

Cranberry products

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Other Natural Health Products – that can potentially affect prothrombin time (no human cases yet reported)

1. Feverfew – parthenolide exhibits anti-clotting properties
2. White Willow Bark Extract – contains salicylic acid. At low concentration (15% std grade) studies do not demonstrate an anti-platelet clotting tendency
3. Turmeric – curcumin affects prostaglandin synthesis
4. Essential oils (Borage, Flaxseed, Fish oil) – Omega-3 fats decrease platelet clotting behavior via effects PG-3
5. Vitamin E - Safe up to 400 I.U. per day in conjunction with warfarin or aspirin. Testing at 800 I.U. and 1,200 I.U. per day yield equivocal results on safety with respect to altering the INR
6. Bromelain enzymes – may decrease platelet clotting tendency and increases fibrinolysis
7. Papain enzymes – these proteolytic enzymes may also potentiate the effect of warfarin
8. Saw Palmetto

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Supplements That May Counter Effects of Coumarin (Warfarin) – require INR monitoring

1. Coenzyme Q10 – may mimic vitamin K
2. Ginseng – may up-regulate warfarin detox
3. St. John's wort – may up-regulate warfarin detox
4. Grapefruit juice – can up-regulate detox of many drugs

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Foods To Limit

Reduce Intake Of Vitamin K Foods:

- Kale
- Spinach
- Turnip greens
- Collards
- Swiss chard
- Parsley
- Mustard greens

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Nutritional Medicine Coaching

Lifestyle and Blood Clotting Behavior:

Increased platelet stickiness and abnormal clotting is associated with:

1. Overweight
2. High Saturated fat diet (and cholesterol, transfats and fried foods), especially Factor VII, which ultimately increases fibrin formation – the main component of blood clots.
3. Decreased aerobic fitness
4. Cigarette smoking
5. PG-2 from Arachidonic acid increases thromboxane-A2 & constricts blood vessels via prostacyclin and endothelial dysfunction

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Lifestyle Counseling: Counsel patients on how to improve their own **hemostatic dynamics**, which in some cases results in decreased requirement or elimination for need of anticoagulants (e.g. deep vein thrombosis survivors).

Helping patients lower dosage of anti-coagulants lowers their risk of sudden death from internal bleeding.

Gentle Anti-coagulant Supplements For Consideration (INR monitoring):

- Fish, Flaxseed and Borage Seed Oil
- Vitamin E – 400 IU

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Plavix (Clopidogrel) – also a popular anticoagulant

Mechanism of Action - blocks receptor (P2Y12) on platelets, which in turn blocks

final common pathway in platelet aggregation & cross-linking of platelets by fibrin

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Adverse Side Effects Of Plavix:

1. **Severe neutropenia** (Incidence: 1/2,000)

2. **Thrombotic thrombocytopenic purpura** (TTP) (Incidence: 4/1,000,000)

3. **Hemorrhage** - The incidence of hemorrhage may be increased by the co-administration of aspirin
   - Gastrointestinal Hemorrhage (Incidence: 2.0%)
   - Cerebral Hemorrhage (Incidence: 0.1 to 0.4%)

   - Use of non-steroidal anti-inflammatory drugs is discouraged in those taking clopidogrel due to increased risk of digestive tract hemorrhage

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- Plavix - 2nd top selling drug in the world in recent years and was still growing by over 20% in 2007.

- In 2005 it had sales of $5.9 billion US.

- The same supplements that potentiate the effects of warfarin also potentiate the anti-coagulant effects of Plavix and COX-inhibitors such as Aspirin (ibuprofen, voltaren etc) – Same Precautions Apply

Common COX-inhibitors with Anti-coagulant Effects:

1. Aspirin (ASA, bufferin, anacin, entrophen, robaxisal)
2. Diclofenac (voltaren)
3. Ibuprofen (advil and motrin)
4. Naproxen (aleve)
5. Indomethacin (indocin)
6. Celebrex (celecoxib)

- However, vitamin K foods are fine with these anti-coagulants

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Part 4. Analgesics, Anti-Inflammatories And Sedatives

1. Paracetamol (acetaminophen)
2. Non-steroidal anti-inflammatory drugs (NSAIDs) such as ASA, Ibuprofen
3. TNF- alpha, methotrexate and purine metabolism inhibitors
4. Narcotic such as morphine, codeine
5. Synthetic drugs with narcotic properties such as Tramadol and others

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1 and 2. Acetaminophen and NSAID's

- **Acetaminophen** - Exact mechanism of action is uncertain, but appears to act centrally.

- **Aspirin** and the other non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen etc., inhibit cyclooxygenases, leading to a decrease in prostaglandin production.

- This reduces pain and inflammation (in contrast to paracetamol and the opioids, which do not reduce inflammation, but do reduce pain)

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Side Effects:

- Excessive acetaminophen can lead to kidney & liver damage (application for supplements that boost glutathione levels)

- NSAIDs predispose to peptic ulcers, renal failure, allergic reactions, and occasionally hearing loss, and they can increase the risk of hemorrhage by affecting platelet function.

- GI bleeds from NSAIDS causes many deaths and morbidity issues each year. Anything you can do to reduce reliance on these drugs is beneficial in cases of acute or chronic pain (Example - Adeeva Nature's Relief)

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3. Tumor Necrosis Factor-alpha Inhibitors, Methotrexate and Purine Synthesis Inhibitors

Overview: TNF-alpha (mostly from macrophages) activates release of NF-kb, which up-regulates synthesis and release of pro-inflammatory cytokines and interleukins in chronic inflammation and increases risk of cancer via sustained cell division.

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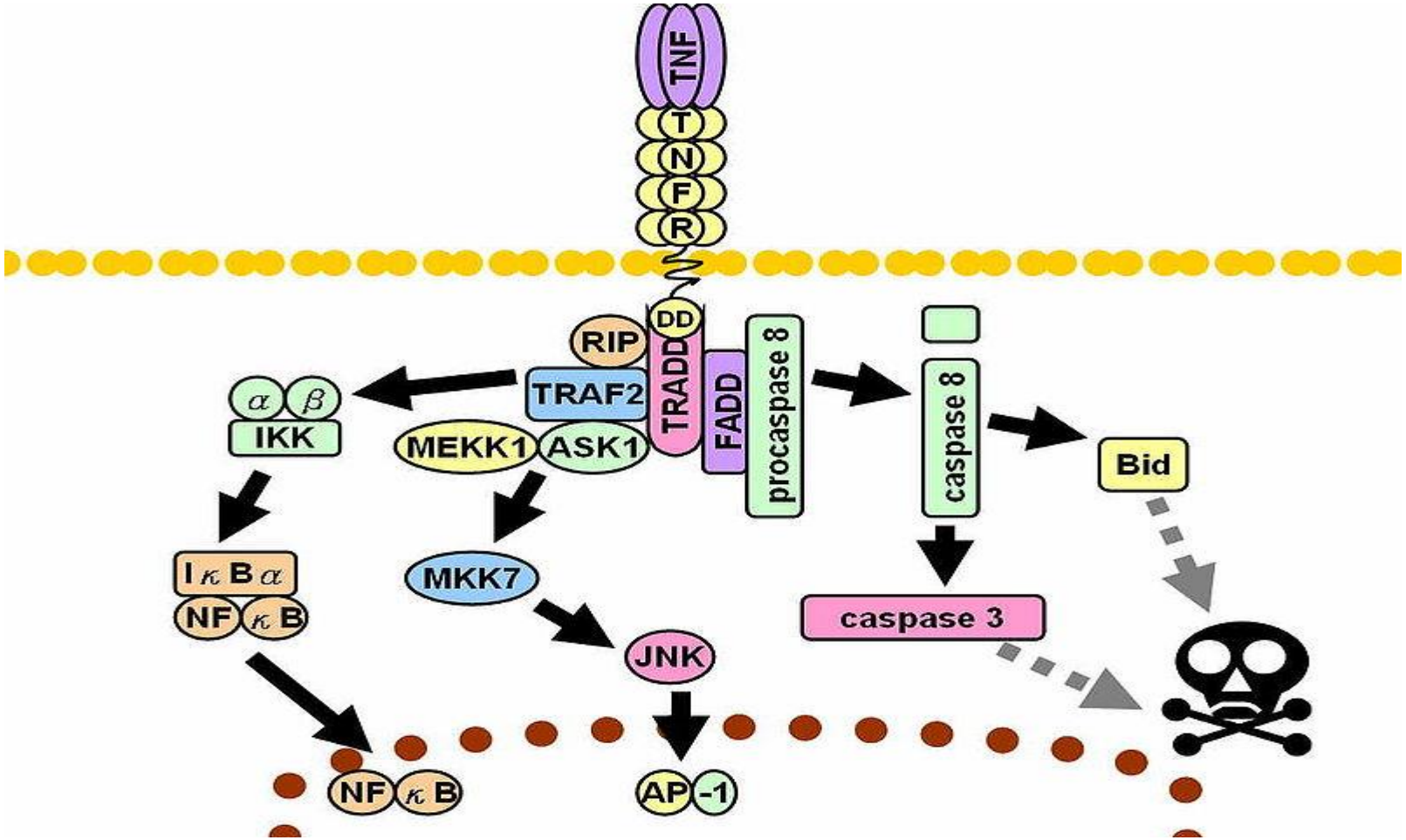
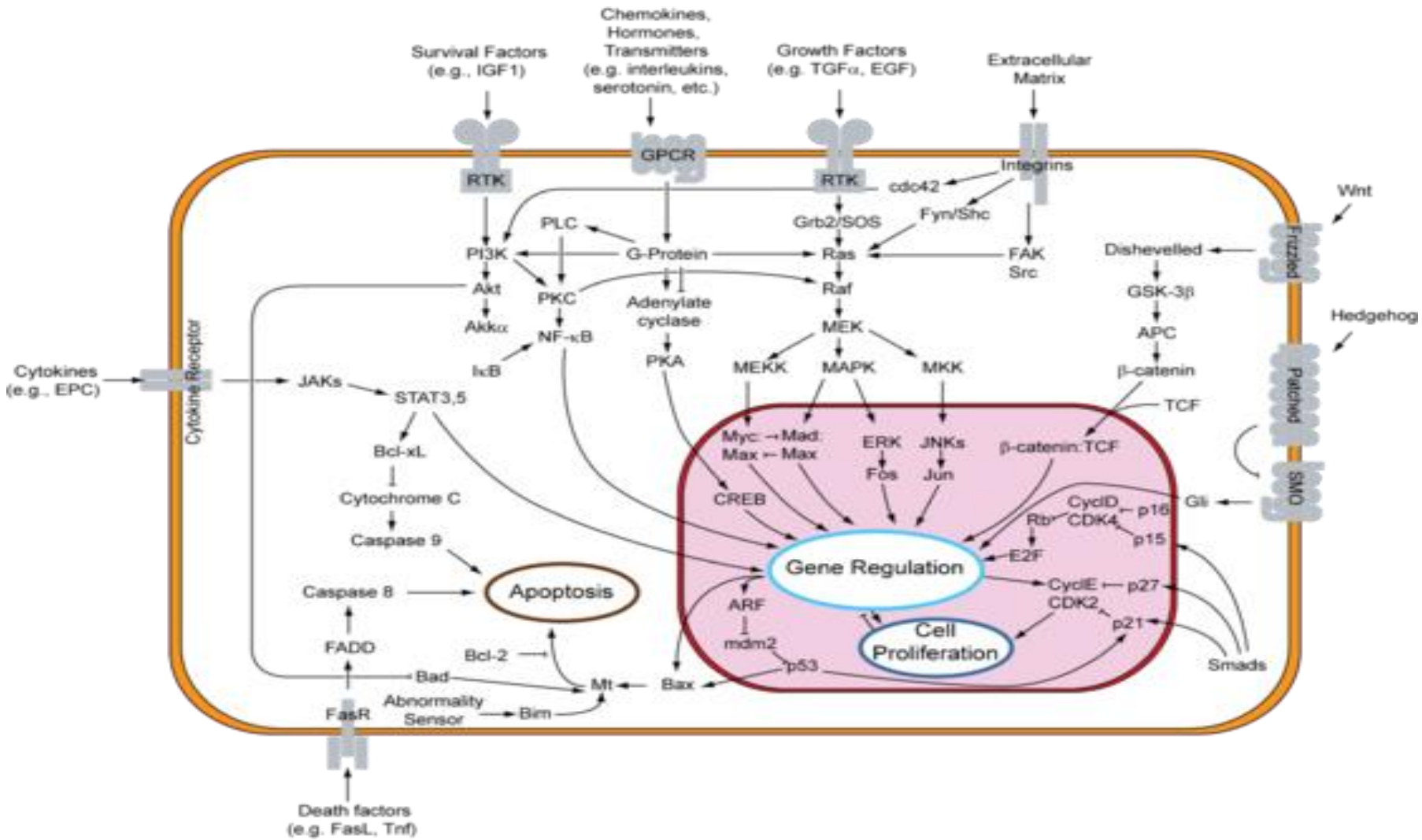
Three Pathways Activated By TNF-alpha




Survival Factors
(e.g., IGF1)
Chemokines,
Hormones,
Transmitters
(e.g. interleukins,
serotonin, etc.)
Growth Factors
(e.g. TGFα, EGF)
Extracellular
Matrix
RTK
GPCR
RTK
Integrins
cdc42
Fyn/Shc
Grb2/SOS
PLC
PI3K
G-Protein
Ras
FAK
Src
Akt
PKC
Raf
Adenylate
cyclase
Akkα
NF-κB
IκB
PKA
MEK
MEKK
MAPK
MKK
Cytokines
(e.g., EPC)
Cytokine Receptor
JAKs
STAT3,5
Bcl-xL
Cytochrome C
Caspase 9
Caspase 8
Apoptosis
FADD
Bcl-2
Bad
Mt
Bax
FasR
Abnormality
Sensor
Bim
Death factors
(e.g. FasL, Tnf)
Myc
Max
Mad
Max
ERK
JNKs
Fos
Jun
β-catenin:TCF
CREB
Gene Regulation
ARF
mdm2
p53
Cell
Proliferation
CyclD
CDK4
p16
p15
Rb
E2F
CyclE
CDK2
p27
p21
Smads
Gli
Wnt
Frizzled
Dishevelled
GSK-3β
APC
β-catenin
TCF
Hedgehog
Patched
SMO

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- **Chronic Inflammation:** In presence of higher levels of **oxidative stress**, TNF preferentially up-regulates **NF-kb,** which promotes inflammation by up-regulating the transcription of various pro-inflammatory interleukins. Chronic inflammation is also linked to increased risk of cancer.

- NF-kb can also be over-expressed via gene dysregulation, heat shock protein induction and loss of Inhibitor of NF-kb (INF-kb).

- Thus, factors that reduce the activation of NF-kb can suppress inflammation and help fight cancer.

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TNF And Chronic Inflammation

Dysregulation Of Tumor Necrosis Factor- Alpha:
Over expression of Tumor necrosis factor promotes the inflammatory response, which, in turn, causes many of the clinical problems associated with autoimmune disorders such as rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, psoriasis, hidradenitis suppurativa and refractory asthma.

Medical Treatment: These disorders are sometimes treated by using a TNF inhibitor. This inhibition can be achieved with a monoclonal antibody such as infliximab (Remicade), adalimumab (Humira) or certolizumab pegol (Cimzia), or with a circulating receptor fusion protein such as etanercept (Enbrel).

- The important side effects of TNFalpha inhibitors include: lymphoma, infections, congestive heart failure, demyelinating disease, a lupus-like syndrome, induction of auto-antibodies, injection site reactions, systemic side effects and opportunistic infections.

- **Other Novel Medical Treatments** – involves anti-metabolite drugs that inhibit the replication of immune cells (e.g. methotrexate and purine metabolism inhibitors)

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Methotrexate – folic acid antagonist (inhibits Dihydrofolate reductase).

Thus – decreases DNA synthesis, blocking cell division and proliferation of fibrotic tissue and immune cell replication and cytokine production in autoimmune disease (e.g. RA) and cancer

Side Effects: Most Common:

Acne; chills and fever; dizziness; flushing; general body discomfort; hair loss; headache; infertility; irregular periods; itching; loss of appetite; **lowered resistance to infection;** miscarriage; nausea; sensitivity to sunlight; sore throat; speech impairment; stomach pain; swelling of the breast; unusual tiredness; vaginal discharge; vomiting.

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Purine Synthesis Inhibitors

- Inhibit the proliferation of cells, especially leukocytes. (e.g. azathioprine)

Concerns:

Listed as a human carcinogen in the 11th Report on Carcinogens of the U.S. Department of Health and Human Services

Common Side Effects:

- nausea, fatigue, hair loss, and rash
- **Increased risk of infection**

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Sequence Of Events In Inflammation

TNF- alpha – up-regulates activity of NF-kb in Peripheral Blood Mononuclear Cells (PMNC cells), which acts a transcription factor to up-regulate pro-inflammatory cytokines affecting other immune cells and immune cell behaviour

Factors that inhibit NF-kb shown to suppress inflammation such as quercetin (see reference below), curcumin, catechins and others.

Reference

Madhavan P. Nair,* Supriya Mahajan, Jessica L. Reynolds, Ravikumar Aalinkeel, Harikrishnan Nair, Stanley A. Schwartz, and Chithan Kandaswami. The Flavonoid Quercetin Inhibits Proinflammatory Cytokine (Tumor Necrosis Factor Alpha) Gene Expression in Normal Peripheral Blood Mononuclear Cells via Modulation of the NF-κβ System. *Clin Vaccine Immunol.* 2006 March; 13(3): **319–328.** 2006, American Society for Microbiology

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Natural Bio-Regulation Of TNF: TNF or the effects of TNF are also inhibited by a number of natural compounds, including curcumin (a compound present in turmeric), quercetin, and catechins (in green tea). These agents are not associated with side effects.

Curcumin Refernces:

- Siddiqui AM, Cui X, Wu R, *et al.* (July 2006). "The anti-inflammatory effect of curcumin in an experimental model of sepsis is mediated by up-regulation of peroxisome proliferator-activated receptor-gamma". *Crit. Care Med.* **34** (7): 1874–82.
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- Gulcubuk A, Altunatmaz K, Sonmez K, *et al.* (February 2006). "Effects of curcumin on tumour necrosis factor-alpha and interleukin-6 in the late phase of experimental acute pancreatitis". *J Vet Med a Physiol Pathol Clin Med* **53** (1): 49–54.
- Lantz RC, Chen GJ, Solyom AM, Jolad SD, Timmermann BN (June 2005). "The effect of turmeric extracts on inflammatory mediator production". *Phytomedicine* **12** (6-7): 445–52..

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- NF-kb is activated by oxidative stress and pro-inflammatory stimuli and controls the expression of numerous genes involved in the inflammatory response (IL 1, 6, 8)

- Sustained elevated levels of pro-inflammatory cytokines and acute phase proteins have been associated with increased risk of disease and poor outcome of chronic inflammatory diseases and cancer

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- Dampening NF-B activation, thereby limits the inflammatory response

- Many natural products (including anti-oxidants) that have been promoted to have anti-cancer and anti-inflammatory activity, have also been shown to inhibit NF-κB.

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Natural Inhibitors of Inhibit NF-kb:

Curcumin (plus LOX, COX, Her-2 inhibition)
Ginger
Reishi mushroom extract
Quercetin
Antioxidants (Vitamin C, Vitamin E)
Anthocyanidins (berrries)
EPA and DHA
N-acetyl cysteine (NAC)
Isoflavones
Pomegranate
Baicalein
Parthenolide

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Reducing Inflammation Naturally

1. Low Arachidonic and Linoleic Acid Diet
2. Nature's Essential Oils – 3 - 6 caps/d
3. Nature's Relief – up to 3 caps, 3 times/d
4. Multiple Vitamin and Mineral (B-vits, antioxidants, magnesium)
5. Additional – Quercetin – up to 2000 mg/d
6. Vitamin D – 5,000 – 10,000 IU daily (increased IL-4, which is an anti-inflammatory cytokine)
7. Additional Antioxidants (vitamin C – 5000 mg, Vitamin E – 1000 – 2000 IU, Selenium – 200-400 mcg
8. Avoid Alcohol, trans fats
9. More alkaline diet
10. Probiotics – especially autoimmune disease
11. Maybe Digestive Enzymes and Prebiotics
12. Maybe Immuno-Detox Prime – 4 caps/d

3. Barbiturates - act as central nervous system depressants, producing a wide spectrum of effects **(phenobarbital, pentobarbital):**

- Mild sedation
- Anesthesia
- Anxiolytics
- Hypnotics
- Anticonvulsants

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Barbiturates have addiction potential, both physical and psychological.

- Barbiturates largely replaced by **benzodiazepines**, which are significantly less dangerous in overdose

- Barbiturates are thought to work by potentiating the inhibitory effects of GABA, by binding to certain GABA receptors

- Fiorinal contains barbiturates – will see shortly

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4. Benzodiazepines

Mechanism of action - potentiate action of GABA on GABAA receptor, the most prevalent inhibitory receptor within the brain. This leads to sedation, decreased anxiety and decreased sensitivity to seizure activity and pain.

Clinical Application: used more as **anxiolytics**, for **insomnia** and as **anti-convulsants** than for **pain control**.

Side Effects:

Dependency – mainly high levels of anxiety, insomnia, tension, tremors, and fatigue – also depression

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Some common Drugs (often include suffix “pam”):

- clorazepate (Tranxene)
- **diazepam (Valium)**
- estazolam (ProSom)
- flurazepam (Dalmane)
- **lorazepam (Ativan)**
- midazolam (Versed)
- nitrazepam (Mogadon)
- oxazepam (Serax)
- temazepam (Restoril)
- **triazolam (Halcion)**
- quazepam (Doral)

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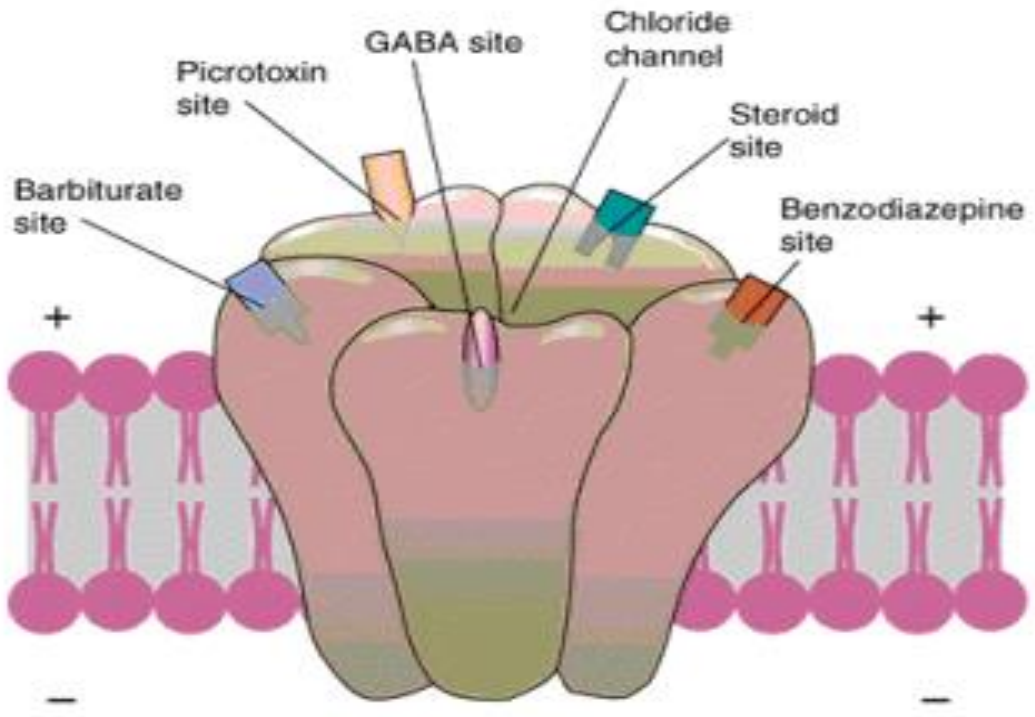
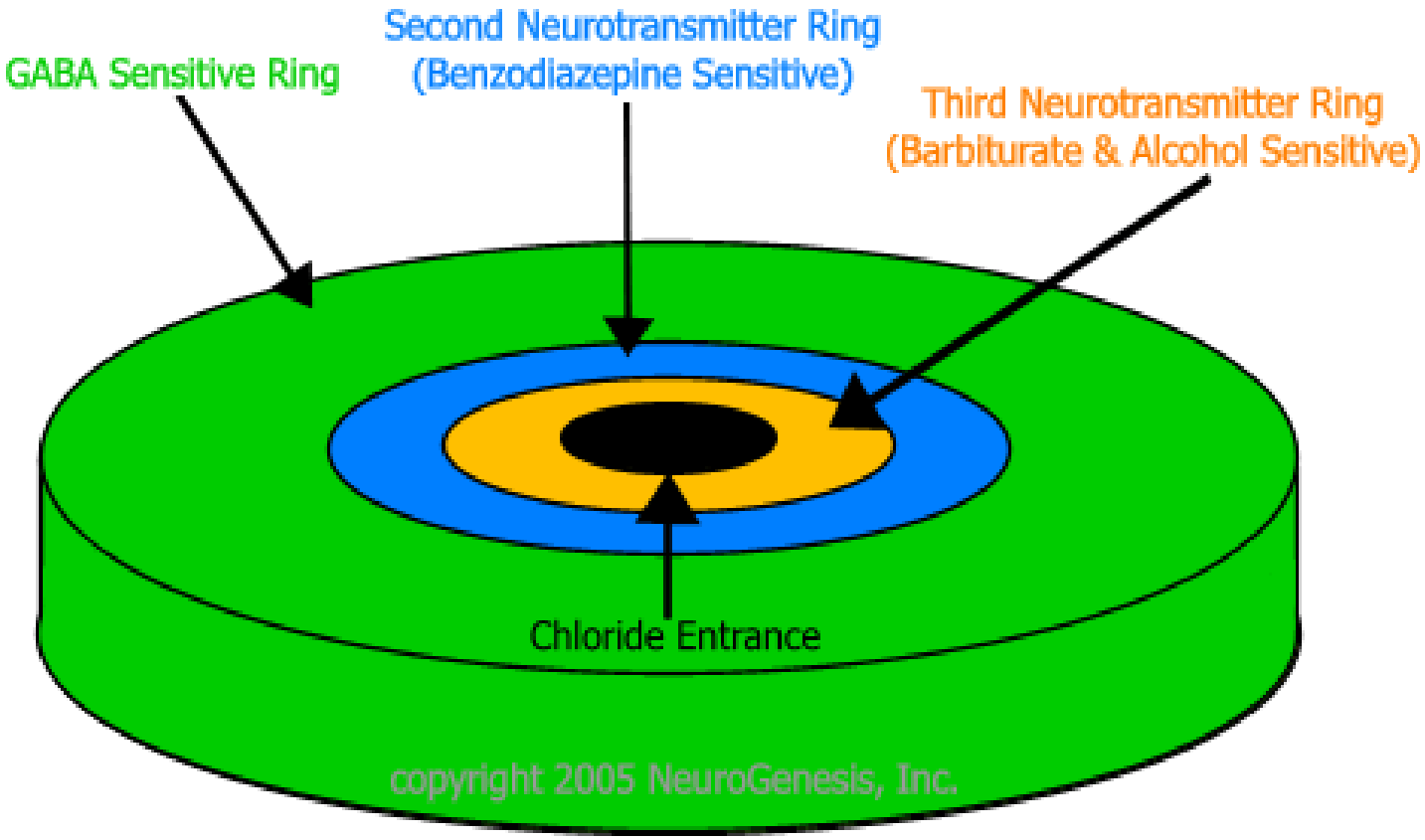
GABA Receptor

Note: Picrotoxin found in the *Cocculus indicus* and *Anamirta cocculus plants* inhibits chloride channels, producing convulsions

► **Schematic Illustration of a $GABA_A$ Receptor, with Its Binding Sites**




GABA Sensitive Ring
Second Neurotransmitter Ring
(Benzodiazepine Sensitive)
Third Neurotransmitter Ring
(Barbiturate & Alcohol Sensitive)
Chloride Entrance
copyright 2005 NeuroGenesis, Inc.

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GABA Receptor Function

- When brain experiences an abundance of nervous tension and stress, it can be caused by a surplus of norepinephrine or epinephrine (adrenaline). To neutralize this extra adrenaline, the brain produces neurotransmitters, one of which is **GABA**, that have inhibitory effects upon the nervous system.

  Please Note: The two inner rings are receptors for other neurotransmitters that have not yet been scientifically identified. But scientists have discovered that the **two inner rings** are sensitive to external source substances or chemicals, such as **benzodiazepines, barbiturates and alcohol.**

- These external substances attach to the GABA receptor site like neurotransmitters, and can have an effect on the brain similarly to their respective neurotransmitters.
-

  L-Glutamine is an amino acid that in a precursor to GABA. Using a nutritional supplement that contains L-Glutamine along with a balanced diet can support the natural replenishment of GABA, as well as other neurotransmitters. GABA supplementation can also have a direct effect

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Chloride Neutralizes Norepinephrine Producing Calming Effect

- As the GABA Sensitive Ring and either the Second or Third Neurotransmitter rings begin to fill with their respective molecules, they tighten the whole GABA complex, thereby widening the chloride channel to allow more chloride to enter. Since **chloride neutralizes norepinephrine**, this process can **calm excessive nervousness, tension, and stress**.

- Since the Second and Third Neurotransmitter Rings are sensitive to external source substances such as benzodiazepines, barbiturates and alcohol, these external substances can cause the Chloride Channel to open, thereby assisting in the neutralizing of additional adrenaline.

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- However, **prolonged use of any external substances that cause the GABA complex to widen without the natural production of GABA, can eventually send the message to the brain that GABA is no longer needed**. This can lead to dependency as the body shuts down production of its own GABA

- This is how valium dependency and addiction occurs

- Supplements containing L-Glutamine can nutritionally support the natural production of GABA.

- GABA supplementation is also available and can be used in moderate dosages

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Fiorinal For Migraines

Fiorinal and Firoinal-type drugs are a 3-in-1 analgesics consisting of:

1. aspirin or acetaminophen
2. the **barbiturate** - butalbital
3. caffeine.

- Some formulations Fiorinal #3) contain the opioid codeine.

- Most often used for tension headaches and migraines.

  Mechanism of action is not well understood. Since butalbital is habit-forming, using fiorinal daily can lead to dependency.

Fiorinal #3 contains: **30 mg codeine**
50 mg butalbital
40 mg caffeine
and 325 mg aspirin.

Other brand names include Fiormor, Fiortal, Fortabs, and Laniroif.

Natural Alternatives – Fever few and Butterbur

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5. Opiates and Morphinomimetics

- Morphine and related opiates(e.g. codeine, oxycodone, hydrocodone, diamorphine, pethidine) exert similar influence on **cerebral opioid receptor system**.

- **Synthetic Analogues:** Tramadol and buprenorphine are thought to be partial agonists of the opioid receptors - Tramadol is a synthetic analog of codeine

- Dosing opioids limited by opioid toxicity (confusion, respiratory depression, myoclonic jerks and pinpoint pupils), but no dose ceiling in patients who tolerate these drugs

- **Codeine** (methylmorphine**)** is an opiate used in many pain medications and often included in cough syrups (antitussives), as it elevates the cough threshold at the level of the medulla.

- **Codeine -** most widely used opiate in the world and very likely most commonly used drug overall

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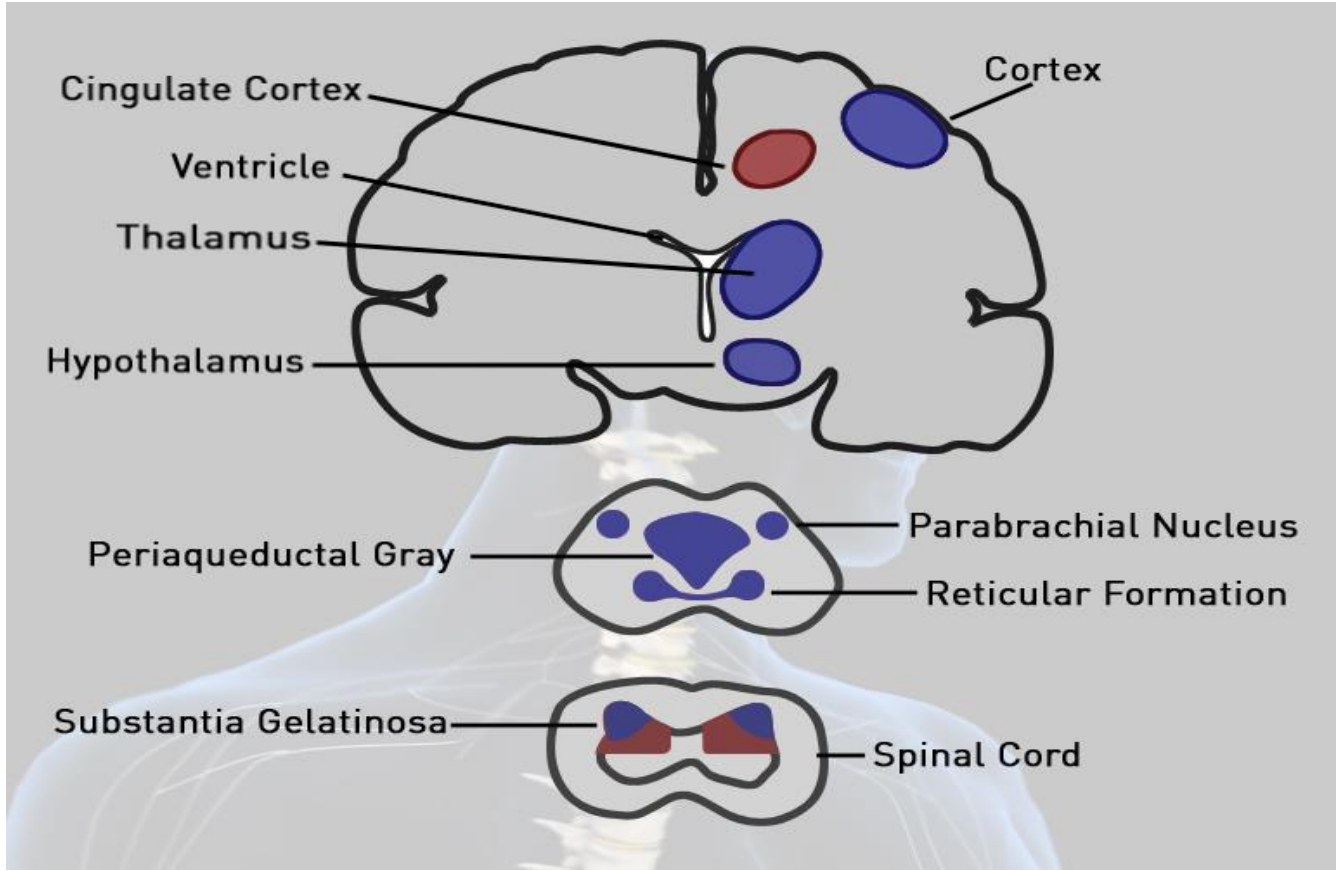
Location Of Opioid Receptors: stimulation by enkephalins and opioid-drugs block pain via dopamine release



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Electro-Acupuncture (with and without needles) can silence pain central sensitization via release of natural endorphins and reduce area of chronic hyperactivity pain modulation in periaquaductal grey matter, the brachial nucleus and other pain modulation centres.

It is the only method shown to change physiology of pain in chronic pain syndromes

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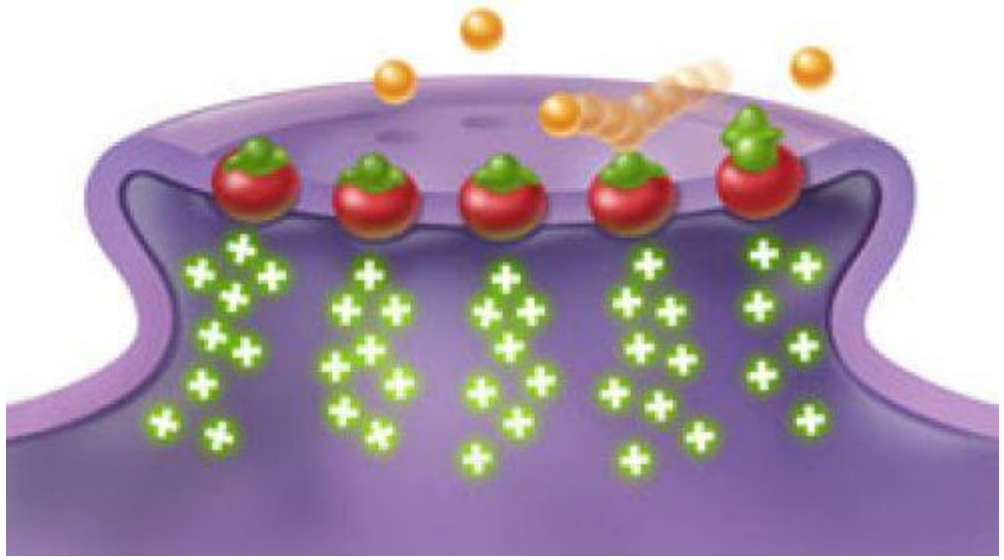
Opioid Addiction



- When opiates are taken into the body, **dopamine is released** which produces a feeling of pleasure and euphoria. As the drugs wear off, the receptors which received the opiates are left empty, causing withdrawal symptoms to begin.

- In Addiction Treatment : Methadone or Buprenorphine in drug Suboxone attaches to the empty receptors and stops them from feeling the pangs of craving and withdrawal.
- They are partial opioid agonists, which means it completely halts withdrawal without producing the euphoria and unconsciousness. At its best, buprenorphine also blocks other opiates from attaching to the empty receptors and does not allow a high to be felt.

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Oxycodone - a semi-synthetic opioid synthesized from opium-derived thebaine

Percodan – contains oxycodone and aspirin

Percocet – contains oxycodone and acetominophen

Combunox – contain oxycodone and ibuprofen

Oxycodone is a narcotic and, even if taken only in prescribed amounts, can cause physical and psychological dependence when taken for a long time.

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Narcotic Dependency (morphine, cocaine, heroine etc):

- Physical dependence refers to continued need of drug in order to prevent the withdrawal or abstinence syndrome. And higher doses become required to achieve same pain control.

- The withdrawal symptoms occur shortly before the time of the next scheduled dose. Early symptoms include watery eyes, runny nose, yawning and sweating.

- **Followed by**: Restlessness, irritability, loss of appetite, tremors and severe sneezing appear as the syndrome progresses.

- **Followed by**: Severe depression and vomiting are not uncommon. The heart rate and blood pressure are often elevated.

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- **Kick The Habit -** Chills alternating with flushing, pains in the bones and muscles of the back and extremities occur as do muscle spasms and kicking movements, which may be the source of the expression "kicking the habit."

- At any point during this process, a suitable dose of any opioid can be administered that will dramatically reverse the withdrawal symptoms.

- Without intervention, the syndrome will run its course and most of the overt physical symptoms will disappear within **5 to 15 days**, depending on the opioid used.

Common side effects Of Opiates:

Dizziness

Light-headedness

Nausea

Sedation

Vomiting

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Analgesic Decision-Making

- In choosing analgesia, the severity and response to other medication determines the choice of agent. The WHO pain ladder, originally developed in cancer-related pain, is widely applied to find suitable drugs in a stepwise manner.

- The choice of analgesia is also determined by the type of pain:

  - for neuropathic pain, traditional analgesia is less effective, and there is often benefit from classes of drugs that are not normally considered analgesics, such as **tricyclic antidepressants and anticonvulsants.**

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Anti-Inflammatory Drugs – block COX enzymes not LO

NSAIDS:

1. 10-30% GI ulcers in long-term users

2. GI erosion in 30-50% users

3. 10,000-20,000 deaths annually (US) from GI bleeds due to NSAIDS use

4. COX-2 Inhibitors reduce GI effects by 50%

5. Liver and kidney damage (including acetaminophen)

6. Hasten further cartilage erosion

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Side Effects From Prednisone and Corticosteroid Drugs

1. Weight Gain – and redistribution of body fat (Buffalo hump)
2. Glucose Intolerance
3. Hypertension
4. Increased Susceptibility to Infections – immune suppression and risk of cancer and fungal infections
5. Bone Thinning – demineralization
6. Easy Bruising
7. Mood Swings/Insomnia – including depression (sometimes upon withdrawl)
8. Avascular Necrosis of bone
9. Abdominal Striae
10. Cataracts
11. Acne

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Natural Management Of Inflammatory Diseases And Chronic Pain

Goals:

1. Decrease synthesis of PG-2
2. Decrease synthesis of TNF-alpha
3. Inhibit activity of NF-kb
4. Bioregulation of Immune System
5. Glucosamine Sulfate if cartilage erosion concerns (after 40 yrs old)
6. Electroacupuncture if chronic pain
7. California poppy for night pain and related insomnia

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Implementation

Diet and Lifestyle:

- Low animal fat diet (except fish)
- Minimize intake of transfats and alcohol
- Replace vegetable oils with olive oil, flaxseed oil, grape seed oil (canola oil)
- Reduce Body Fat
- Endurance Exercise
- No smoking
- Deep breathing, visualization (mind-body work)

Therapies:

- Electromodalities, including electroacupuncture
- Chiropractic
- Massage – soft tissue etc

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Supplementation

- Essential Fatty Acid
- High-Potency Multiple Vitamin and Mineral
- Natural Anti-inflammatories (Curcumin, Bowellia, White willow extract, Ginger)
- Glucosamine Sulphate (cartilage concerns)
- Quercetin – 1000-2000 mg/day
- If under stress – Adrenal Adaptogen Herbs
- Additional antioxidants if required (e.g. Vitamin E- 2000 IU, Vitamin C – 5000 mg etc)
- Vitamin D – 5,000 – 10,000 IU (increase IL-4 – anti-inflammatory)
- Zadaxin – requires medical administration
- Immune Modulation (medicinal mushrooms, astragalus, probiotic, prebiotics, sterolin etc.)

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Acupuncture For Pain Control

Homeostatic Points (HA) – affect major nerve branches (endorphin and calming of neurological circuitry responsible for tissue hyperalgesia)

Symptomatic Points (SA) – neighboring trigger points to HA points

Paravertebral Points (PA) – stimulation of spinal nerves related to the dermatome region of pain

5 hertz stimulation produces endorphin blockade at spinal cord level

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Part 5. Sleep/Anxiety Drugs

1. **Benzodiazepines** - class of psychoactive drugs with varying hypnotic, sedative, anxiolytic (anti-anxiety), anticonvulsant, muscle relaxant and amnesic properties, which are mediated by slowing down the central nervous system.

2. The **nonbenzodiazepines** are comparatively new drugs whose actions are somewhat similar to those of the benzodiazepines, but are structurally unrelated to the Benzodiazepines

Sleep Aid - Benzodiazepines - All benzodiazepines are effective in the short-term management of insomnia. They decrease the time taken to fall asleep, decrease the number and duration of nighttime awakenings, and increase total sleep time and sleep efficiency.

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Common Benzodiazepines:

- clorazepate (Tranxene)
- diazepam (Valium)
- estazolam (ProSom)
- flurazepam (Dalmane)
- lorazepam (Ativan)
- midazolam (Versed)
- nitrazepam (Mogadon)
- oxazepam (Serax)
- temazepam (Restoril)
- triazolam (Halcion)
- quazepam (Doral)

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Non Benzodiazepine Sleeping Aids:

Zolpidem (Ambien) - rapid onset of action and short duration. Therefore less daytime grogginess

Zaleplon (Sonata) – approved in 1999 - new chemical class of nonbenzodiazepines called the pyrazolopyrimidines – effects last only 4 hours, so can take it if night time awakening occurs

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Natural Sleep Aids

1. **Melatonin** – made in the pineal gland from serotonin, melatonin required for sleep, brain antioxidant and immune system modulator (low melatonin associated with breast and prostate cancers)

Dosage: 0.5 to 3 mg one hour before bedtime

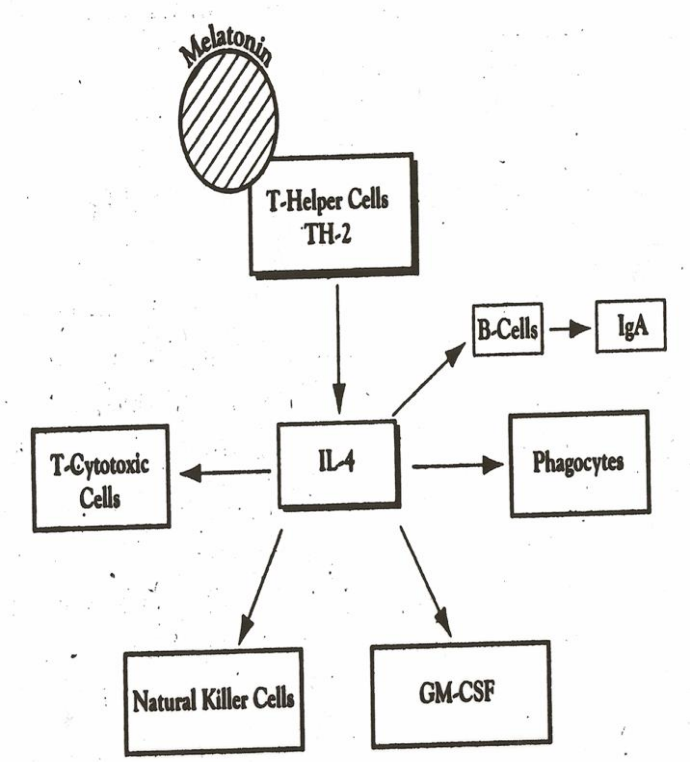

Figure 7. Melatonin Stimulates T-Helper Cells

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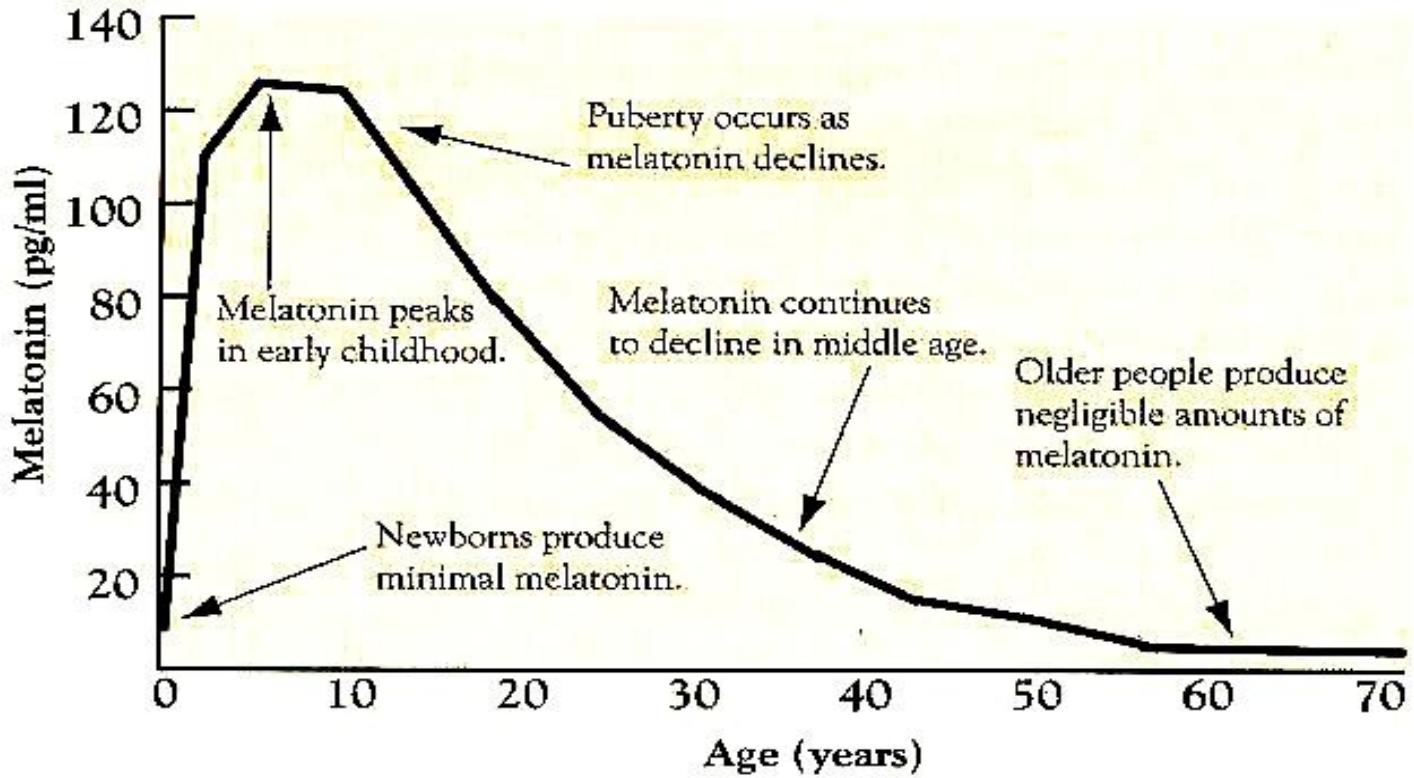
Decline In Melatonin With Age



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2. 5-Hydroxytryptophan – crosses blood-brain barrier better than tryptophan (70% vs 3%) and is converted to serotonin in brain (see next slide)

Serotonin helps improve sleep

Serotonin can also be converted to melatonin, although decreased conversion with age,

Dosage: 12.5 – 50 mg

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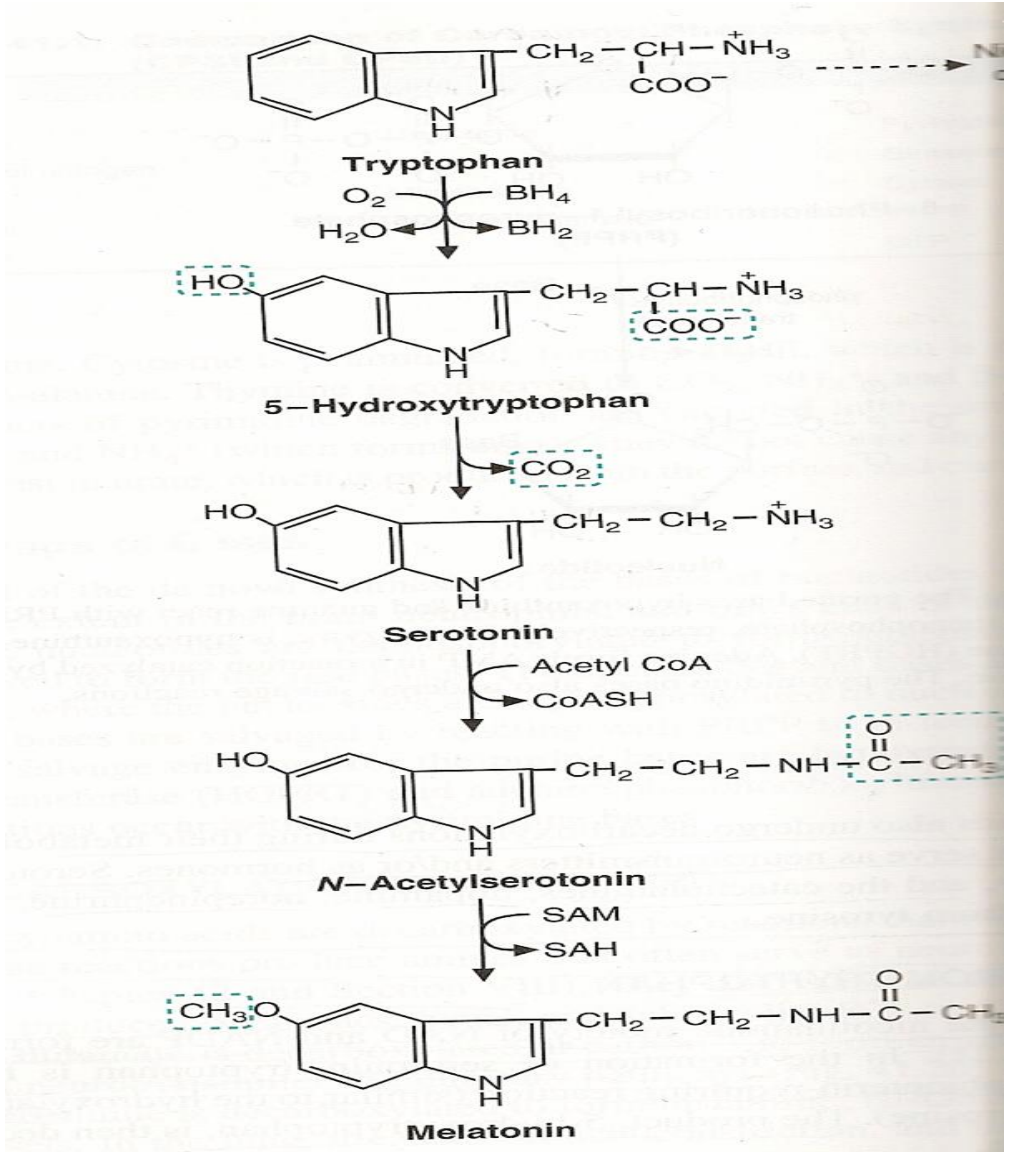
Synthesis of Serotonin and Melatonin



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Example Supplement

One Capsule Contains:

- Melatonin – 0.5 mg (500 mcg)
- 5-HTP (5-hydroxytryptophan) – 10 mg
- GABA (Gamma-amino butyric acid) – 25 mg
- Bacopa Monnieri – (std to 20% bacosides) – 15 mg

Clinical Applications:

- Sleep Aid
- Brain Antioxidant
- Immune Modulator
- Breast and Prostate Protection
- Mild Anti-anxiety Effects

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Dosage Considerations

- Age 40-50 – one capsule, one hour before bedtime
- Age 50-60 - two capsules, one hour before bedtime
- Age 60-70 - three capsules, one hour before bedtime
- Over 70 - four capsules, one hour before bedtime

Advantages Over Valium:

1. No dependency
2. Brain Antioxidant
3. Slows Cell Division Of Breast and Prostate Cells (used in cancer treatment – Lissoni)
4. Preserved Immune Modulation with age – linked to CA prevention
5. Can support Serotonin levels (appetite suppression, mood elevation)
6. Memory preservation

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Part 6. Muscle Relaxant Drugs

Robaxin, Robaxisal, Robaxacet - do not affect the neuromuscular junction, but rather produce a sedation effect of the CNS at the level of the **brainstem.**

The exact mode as to how they produce muscular relaxation is unclear.

Common Drugs:

1. Robaxin (Methocarbamol)
2. Robaxacet (contains Methocarbamol and Acetaminophen)
3. Robaxisal (contain Methocarbamol and Aspirin)
4. Robax Platinum (Methocarbamol and Ibuprofen)

Side Effects:

1. Drowsiness
2. GI upset
3. Light Rash
4. May enhance effects of alcohol, barbituates and other CNS depressants

Note: **Valium (Diazepam)** is the one benzodiazepine that has direct skeletal muscle relaxant action at the spinal level.

Other benzodiazepines do not act as muscle relaxants.

However, Diazepam has abuse potential and should be prescribed judiciously and for short-term use only.

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Flexeril – looks like GABA, producing inhibitory effects on nerves at the spinal cord level, thereby reducing spasm.

Primarily used to treat CNS diseases that produce spasm (MS, ALS, spinal cord injury, trigeminal neuralgia)

Muscle Relaxants Used During Surgery

Act on neuromuscular junction inhibiting depolarization effects of acetylcholine, which are used to prevent movement of the patient during surgery while under anesthesia.

Example is tubocurarine.

Historical Note

- European explorers encountered natives of the Amazon Basin in South America using poison-tipped arrows that produced death by skeletal muscle paralysis. The poison was an extract of Chondrodendron tomentosum, a plant found in South American jungles.

- Its active ingredient **tubocurarine**, as well as many synthetic derivatives, played a significant role in scientific experiments to determine the function of acetylcholine in neuromuscular transmission.

- By 1943, neuromuscular blocking drugs became established as muscle relaxants in the practice of anesthesia and surgery.

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Natural Muscle Relaxants

There are no proven muscle-relaxant drugs, although some people use valerian root for:

1. Anti-anxiety
2. Relaxation
3. Sleep Aid

Active constituents in Valerian appear to weakly bind to GABA-A receptors in the brain, producing a sedation effect.

Human trials suggest that Valerian tends not to impair mental function or produce a morning hangover, and dependency has not been reported with its use.

Studies have demonstrated improved sleep quality and insomnia relief.

Dosage: Anxiety and Stress Reduction: 200 mg, twice per day (standardized to 0.8% valerenic acids content)

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Side Effects (rare)

- GI upset
- Drowsiness

Drug-Nutrient Interactions

Valerian may potentiate the actions of the following medications and thus, it is considered prudent to not take Valerian concurrently with these drugs:

- Barbiturates or Sedatives
- Antidepressants
- Anti-anxiety medications
- Hypnotic drugs

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New Science:

Night Time Pain With Sleep Impairment: **California Poppy** – contains molecules that stimulate opioid receptors to decrease pain **and** creates sedation.

Result: Patient feels less pain and falls asleep more easily (enteric coated product)

- It has no addictive properties and no “high” is experienced

- The perfect alternative to Percadan, Oxycodone etc in patients with pain that keeps them awake at night

Very common – as pain reaches consciousness more easily between 2:00 – 6:00 AM

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Part 7. Hormone Replacement Therapy and Menopause

Applications:

1. Menopausal Symptoms

2. Bilateral Oophorectomy in a younger woman

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Menopause And Hormone Replacement Therapy

The Menopause Story:

At menopause ovulation stops, but the pituitary gland over secretes FSH and LH hormones to try to induce another menstrual cycle. The over secretion of hormones cause hot flashes, sweats and other menopausal symptoms.

The drop in estrogen & progesterone promotes:

- calcium loss from bone (osteoporosis)
- decreases LDL clearance and HDL synthesis (CVD risk)
- skin and vaginal atrophy
- breast changes (less density).

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HRT Treatment

HRT re-introduces estrogen and progesterone to block over secretion of FSH and LH to minimize menopausal symptoms and helps support bone density, and the integrity of skin and reproductive tissue.

The problem is that HRT has been shown to increase risk of heart attack, stroke and breast cancer. Therefore, HRT is no longer routinely recommended and reserved for special cases only.

Common Drugs:

- Premarin
- Prempro
- Provera

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HRT

Indications

1. Short-term relief (often one or two years, usually less than five) from menopausal symptoms (hot flashes, irregular menstruation, fat redistribution etc.).

2. Younger women with premature ovarian failure or surgical menopause may use hormone replacement therapy for many years, until the age that natural menopause would be expected to occur

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Change In HRT Use Due To Recent Studies

- The **Women's Health Initiative Study** of the National Institutes of Health showed that the treatment (Prempro), used in the main part of their study, coincided with a larger incidence of **breast cancer**, **heart attacks** and **strokes.**

- Findings reconfirmed in a national study done in the UK (Million Women Study).

- As a result of these findings, the number of women taking hormone treatment dropped by almost half.

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- Later, a warning that followed in the Journal of the American Medical Association and elsewhere, suggested that women with normal rather than surgical menopause should take any prescribed HRT treatment at the lowest feasible dose, for the shortest possible time

- In January 2003, the FDA required Wyeth to affix a "black box" warning to Prempro, stating:

- **"WARNING”**: Estrogens and progestins should not be used for the prevention of cardiovascular disease. The Women’s Health Initiative (WHI) reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women during 5 years of treatment with conjugated equine estrogens (0.625 mg) combined with medroxyprogesterone acetate (2.5 mg) relative to placebo.

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Available Forms:

HRT is available in various forms. It generally provides low dosages of one or more estrogens, and often also provides either progesterone or a chemical analogue, called a progestin. Testosterone may also be included.

1. **CEE:** Conjugated equine estrogens are produced from the urine of pregnant mares, hence the product name Premarin, the most-prescribed form. In the sister product, Prempro, Premarin is combined with a synthetic progestin, medroxyprogesterone acetate.

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2. Bioidentical Hormones: Hormones and steroids taken from plants and animals and altered to be identical to human hormones (estradiol, estrone, estriol, progesterone, and testosterone). The plants that the hormones are extracted from are **soy and yams, and the animals are pigs or horses.**

- Treatment with bioidentical hormones is theoretically based on creating a unique cocktail of hormones for the individual patient, based on hormone deficiencies identified via saliva samples, an approach that is in direct contradiction to medical guidelines which support tailoring hormonal therapy individually, according to symptoms.

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- Bioidentical hormones are delivered via cream, oral, suppository or injection route, but oral route is rarely used due to insufficient bioavailability.

- Advantages include, a lower risk for thromboembolic disease compared to CEE and the inclusion of estriol, which binds to beta-estrogen receptors and decreases breast cell proliferation, which may help counter the breast cancer-promoting effects of estradiol and estrone.

- BHRT may present risks for breast cancer similar to those posed by conventional HRT (*Bardin, A; Boulle N, Lazennec G, Vignon F, Pujol P (2004). "Loss of ERbeta expression as a common step in estrogen-dependent tumor progression". Endocrine-Related Cancer **11**: 537–51).*

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FDA Warnings

1. Compounding pharmacies were warned by the FDA to stop using the "non-scientific" term "bio-identical" in 2008, a warning supported by The Endocrine Society and the American Association of Clinical Endocrinologists. **Individually-compounded mixtures of hormones**, is the allowable term.

2. In early 2008 the U.S. FDA sent letters warning seven pharmacies that the claims they make about the safety and effectiveness of the BHRT products they sold are unsupported by medical evidence, and are considered false and misleading by the agency. The FDA expressed concern that unfounded claims made about BHRT mislead women and health care professionals

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Delivery System Of HRT In General:

1. Patches, tablets, creams, troches, IUDs, vaginal rings, gels or, more rarely, by injection.

2. Dosage is often varied cyclically, with estrogens taken daily and progesterone or progestins taken for about two weeks every month or two; a method called "sequentially combined HRT" or scHRT.

3. An alternate method, a constant dosage with both types of hormones taken daily, is called "continuous combined HRT" or ccHRT, and is a more recent innovation.

4. **Sometimes an androgen, generally testosterone**, is added to treat reduced sexual desire /(libido). It may also treat reduced energy and help reduce osteoporosis after menopause

5. **In women who have had a hysterectomy,** an estrogen compound is usually given without any progesterone, a therapy referred to as "unopposed estrogen therapy".

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Important Side effects of CEE

1. headache
2. weight changes
3. changes in sex drive or performance
4. nervousness
5. acne
6. swelling of hands, feet, or lower legs due to fluid retention
7. changes in menstrual flow
8. breast tenderness, enlargement, or discharge
9. sudden difficulty wearing contact lenses

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Less Common Side Effects Of CEE

1. double vision
2. yellowing of skin or eyes
3. severe mental depression
4. extreme tiredness or lack of energy
5. dark-colored urine
6. light colored stool
7. chorea – involuntary jerky movements

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Contraindications of HRT

Absolute Contraindications:

1. undiagnosed vaginal bleeding
2. severe liver disease
3. pregnancy
4. coronary artery disease (CAD)
5. venous thrombosis
6. endometrial cancer

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Relative Contraindications:

1. migraine headaches
2. personal history of breast cancer
3. history of uterine fibroids
4. atypical ductal hyperplasia of the breast
5. active gallbladder disease (cholangitis, cholecystitis)

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Natural Management Of Menopause

- We will see this in Womens' Health Course

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Part 8. Erectile Dysfunction Drugs

Common Drug: Viagra, Cialis, Levitra

Primary Use: Erectile Dysfunction

Secondary Use: Arterial Pulmonary Hypertension

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How An Erection Occurs

Biochemistry Of Erection:

1. Release of nitric oxide by endothelial and nerve cells (NO) in the corpus cavernosum of the penis.

2. NO binds to enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP)

3. Increased cGMP causes vasodilation of helicine arteries, results in increased blood flow and erection.

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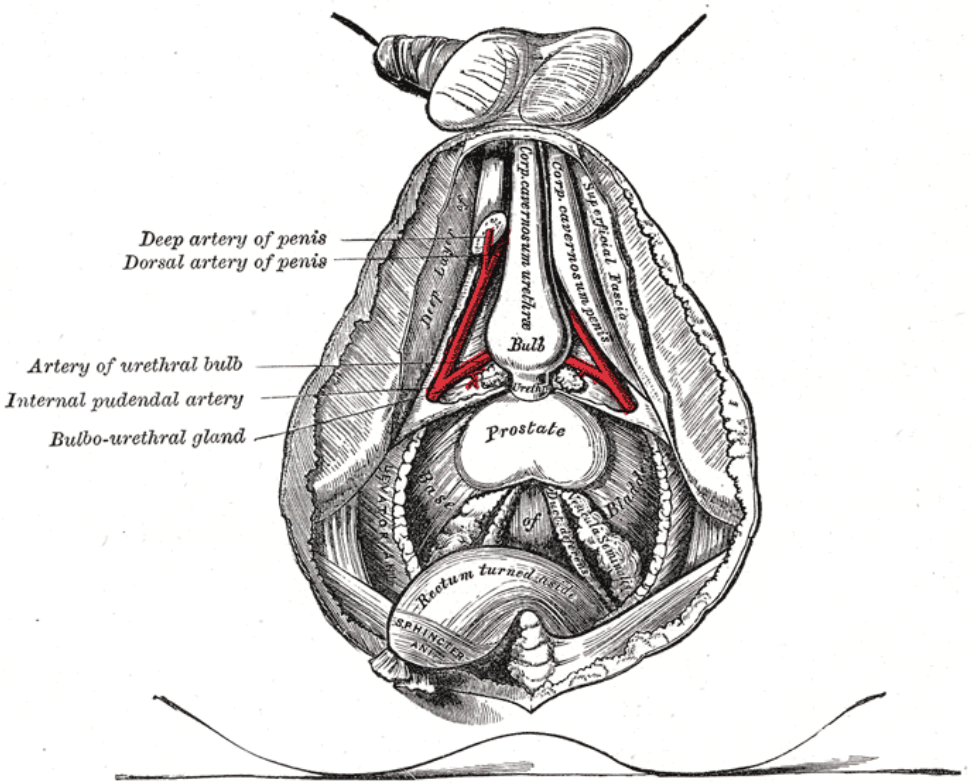
The deep artery of the penis (artery to the corpus cavernosum), is a terminal branch of the internal pudendal artery.

It runs forward in the center of the corpus cavernosum of the penis, to which its branches are distributed



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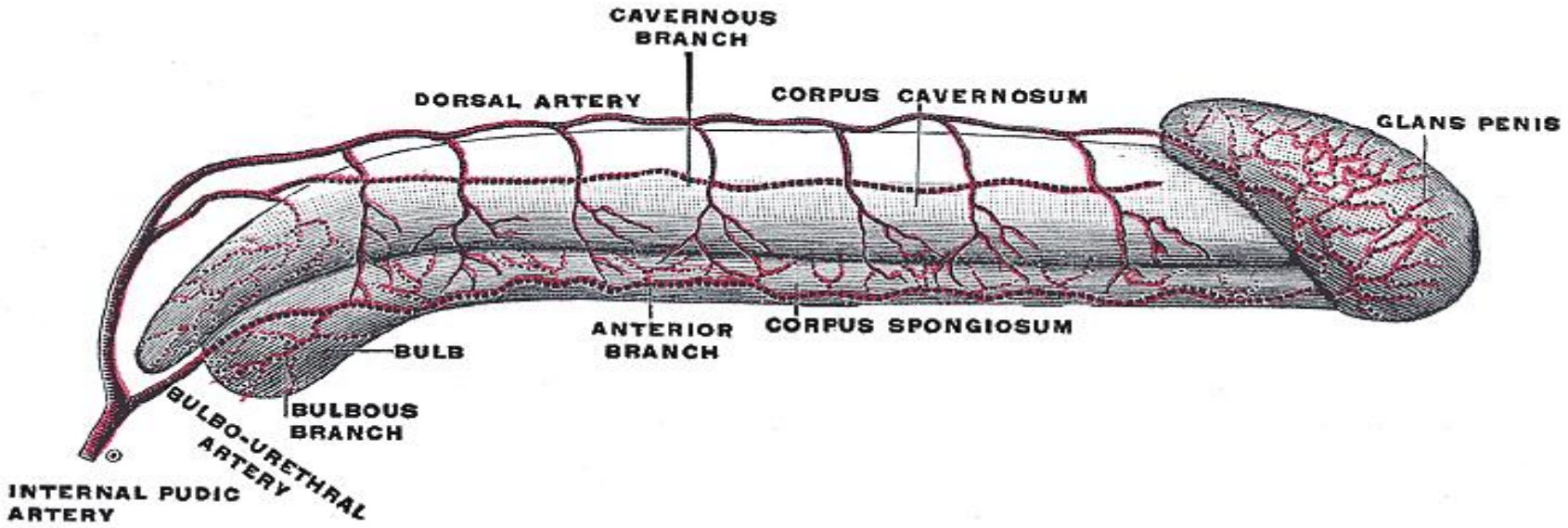
Neurovascular Aspects of an Erection:

Sympathetic stimulation maintains a tonic contractile state of the intimal cushion smooth muscle lying in the center of the artery. This keeps the artery coiled and little blood flow occurs, instead routing to arteriovenous shunts to the deep dorsal vein.

Parasympathetic stimulation removes the tonic state and allows vasodilation of the intimal cushion. Blood now pools in the corpus cavernosa, resulting in erection. The valves prevent backflow in the now-tortuous route through the cavernosa.

This parasympathetic relaxation response is mediated by a release of Nitric Oxide (NO). NO binds to the receptors of the enzyme guanylate cyclase, which results in increased levels of cGMP. cGMP causes vasodilation to occur, enabling an erection to develop. cGMP has a very short half-life. Viagra and related drugs block the enzyme the degrades cGMP, known as PDE5. These drugs result in vasodilation even with small amounts or no stimulation



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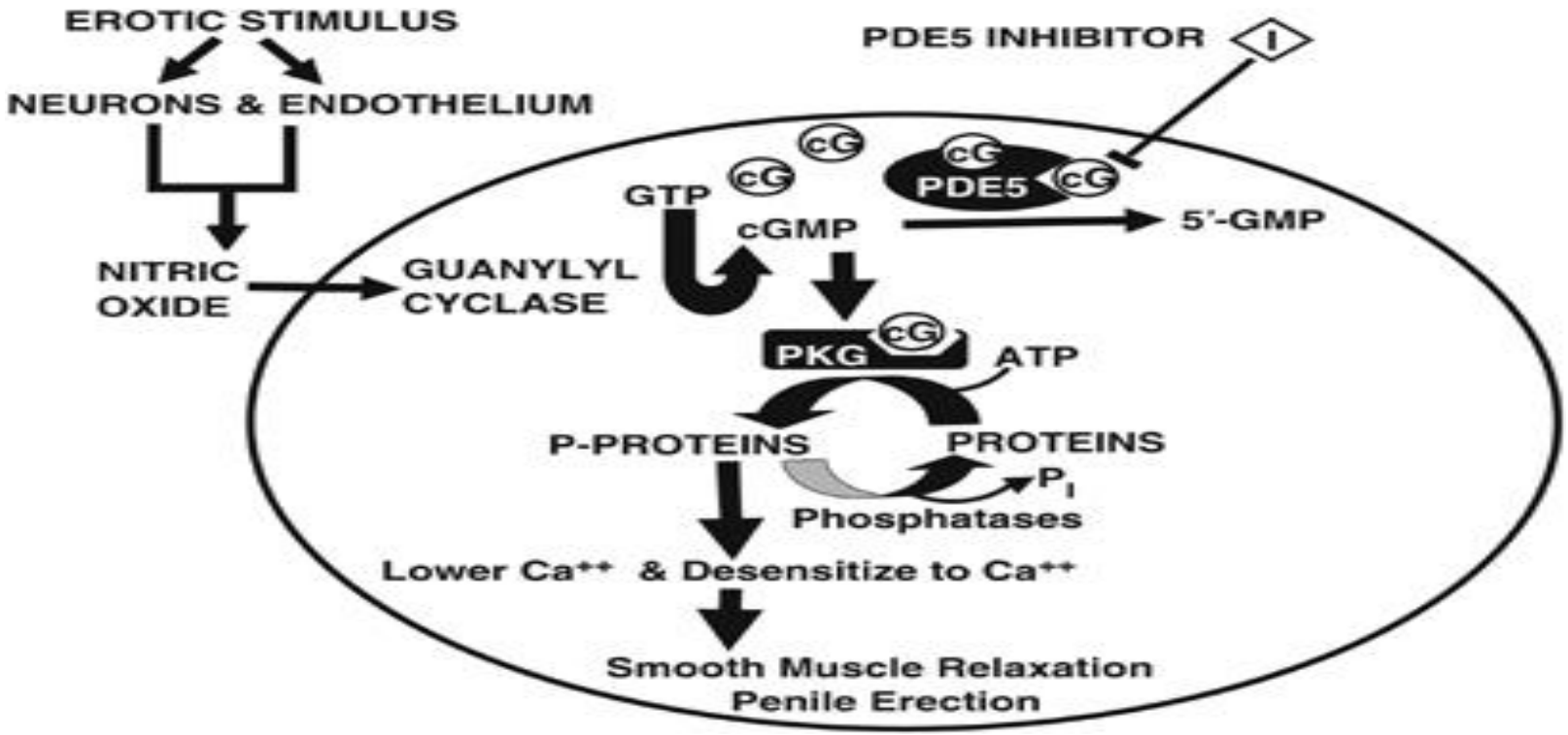
Smooth Muscle Relaxation via cGMP



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Mechanism Of Action Of Drugs:

- **Sildenafil (Viagra)** - first drug developed, is a potent and selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5), which is responsible for degradation of cGMP in the corpus cavernosum.

- Inhibiting the break down of cGMP leads to sustained vasodilation of the helicine arteries.

- Without sexual stimulation, and therefore lack of activation of the NO/cGMP system, sildenafil should not cause an erection. Stimulation requires both sympathetic and parasympathetic action, initially, then parasympathetic relaxation of blood vessels (via NO system) allows erection to occur. Tactile, visual, emotional, memory, and other stimulation can also trigger these responses.

- Cialis and Levitra operate by the same mechanism.

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Drugs block PDE5 with different chemicals, however, there are some important differences between the three drugs:

1. Only Viagra causes color-vision problems.

2. Cialis causes muscle aches in about 5 percent of patients.

3. Viagra and Levitra last about four hours in the bloodstream. Cialis stays in the bloodstream much longer (it has a 17.5-hour half life) and can therefore be effective for a longer period.

4. If Viagra is taken with a high-fat meal, absorption of the drug is reduced; the time taken to reach the maximum plasma concentration is around one hour. The total effect lasts 4 hours.

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Side Effects:

Most Common:

- Headache
- Facial flushing
- Upset stomach

Less Common:

- Temporary bluish vision or blurred vision, or sensitivity to light.

Rare Side Effects:

- Loss of vision
- Loss of hearing
- *Sudden Death from cardiovascular causes and related cardiovascular events

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Cardiovascular Events

***Viagra: Cardiovascular Concerns, Including Sudden Death** - Researchers from Cedars-Sinai Hospital in Los Angeles, California analyzed post-marketing adverse events reports submitted to the FDA between 4/15/98 until 5/21/99.

1,473 serious adverse events included death, myocardial infarction (heart attack), heart arrhythmia, congestive heart failure, strokes and sudden low blood pressure and fainting. Of these, there were:

- 517 Heart attacks
- 255 Cases of sudden death/arrhythmia (abnormal heart rhythm)
- 53 Cases of congestive heart failure
- 119 Strokes
- 271 Episodes of sudden low blood pressure (dizziness, fainting, etc.)
- 522 Deaths

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- Majority of deaths due to cardiovascular events, mostly occurring in patients younger than 65 (with an average age of 61), the majority (67%) of whom had no previous evidence of heart disease or risk factors for heart disease.

- 70% of deaths associated with 50 mg dose, and 2/3 of the deaths occurred within 45 hours of taking drug.

- Most deaths occurred in men who were NOT taking nitrates at the same time.

- The initial warning that patients taking nitrates and Viagra at the same time had an increased risk of adverse cardiovascular events has not been the only problem with Viagra, since only 12% of these deaths occurred in men who were taking nitrates.

- However, in patients who regularly took nitrates with Viagra, death occurred in 68% and death or heart attack in 88%.

Source: Supplement to Journal of the American College of Cardiology February 2000, Vol. 35, Issue 2, Suppl. A, Page 553

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Contraindications:

1. Individuals taking nitric oxide donors (e.g. nitroglycerin), usually for angina. Concurrent use of Viagra and nitrates enhances the effect of both medications and can drastically lower a patient's blood pressure. This effect can cause heart attacks and lead to death
2. In men for whom sexual intercourse is inadvisable due to cardiovascular risk factors
3. Severe hepatic impairment (decreased liver function)
4. Severe renal function
5. Hypotension (low blood pressure)
6. Recent stroke or heart attack
7. Hereditary degenerative retinal disorders
8. Men on alpha-adrenergic blocker for enlarged prostate and men on beta-blockers for high blood pressure (or other conditions) require a lower dose of Viagra

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Jan 10, 2003 Publication

- Incidents of heart attack and stroke, some fatal events, in a small number of men taking the drug Viagra have remained a puzzle.

- After all, Viagra, commonly prescribed for erectile dysfunction, was originally developed to prevent these conditions -- not only by dilating blood vessels but also by stopping platelets in the blood from clumping

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- In fact, the drug does just the opposite, according to researchers at the University of Illinois at Chicago College of Medicine.

- They found that Viagra, by elevating levels of a compound in cells called cyclic guanosine monophosphate, or cGMP, actually encourages platelets to aggregate.

- Abnormal clots can block a blood vessel -- a life-threatening condition called thrombosis that can cause heart attack and stroke.

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- If a person were at risk of thrombosis -- if, for instance, a damaged blood vessel were already narrowed -- even the initial accumulation of platelets could be sufficient to cause a problem.

- Researchers discovered that men with some arterial injury (plaque and related inflammatory cytokines) were more likely to experience thrombosis upon use of Viagra, than were men with healthy arteries.

- An estimated 16 million men worldwide have taken Viagra. According to data in the Journal of the American Medical Association, 564 deaths were reported as of July 1999.

Reference: University Of Illinois At Chicago (2003, January 10). Viagra Deaths Explained By New Understanding Of Platelet Clumping. http://www.sciencedaily.com/releases/2003/01/030110193129.htm

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Other Medical Treatments For ED

DHEA (from adrenals; travels to testes and ovaries and can become testosterone or estrogen via testosterone)

DHEA peaks in 20's, with progressive decline in thirties and beyond, by age 70 there is a 75% decline in DHEA (vs 20 yr old)

Supplementation with 50 mg per day may increase libido, may stimulate growth of latent prostate CA

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DHEA

Prostate cells shown to convert DHEA into Testosterone and DHT

Experimental Studies – prostate CA cells convert DHEA into androstenedione, testosterone and DHT, promoting cellular replication

Case study – flaring of prostate cancer with DHEA

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Medical Rx For SD

Testosterone Replacement Therapy – highly effective, but may increase growth of latent CA of prostate

Dr. Rouzier – gives testosterone to block effects of estrogen, along with aromatase inhibitors to prevent conversion of testosterone to estrogen

Gives DHT, which can’t convert to estrogen

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Medical Rx For SD

GH Injections or GH Secretagogues

Potential Side Effects:

1. Colon CA
2. Cancer cells increase IGF-1 production to promote their growth

Safe – under 275-300 ng/ml (IGF-1)

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Natural Approach To Sexual Dysfunction

- 50% of males experience some degree of erectile dysfunction by age 50
- By age 60, 75% have ED
- ED defined as consistent inability to obtain and/or maintain an erection for satisfactory sexual relations, or Complete ED - inability to have penetrative relations at any stage

We will examine Nutritional Medicine approach to SD in Men's Health Section on this platform.

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SD Causes

1. 1% per year decline in testosterone between ages 40 and 70 yrs is considered major contributing factor (30% decline by age 70) – explained by drop off in DHEA synthesis
2. Atherosclerosis and diabetes
3. High Blood Pressure – via endothelial dysfunction
4. Anti-depressant and beta-blocker drugs (excess serotonin from SSRI inhibits PNS activity in sexual arousal in men and women)
5. Alcohol
6. Psycho-social factors
7. BPH (also increased risk of ejaculatory loss and painful ejaculation

7. Decreased vibrotactile sensitivity of the penis (Reduced mechano-receptors)

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Part 9. Prostate Drugs For Benign Prostatic Hyperplasia (BPH)

1. Alpha-blockers - α1-adrenergic receptor antagonists provide symptomatic relief of BPH symptoms by inhibiting adrenaline and norepinephrine from stimulating the alpha-1 adrenergic receptors on the prostate gland.

In turn, this relaxes smooth muscle in the prostate and the bladder neck, and decrease the degree of blockage of urine flow.

- **Common Drugs:**
- Doxazosin
- Terazosin
- Alfuzosin
- Tamsulosin (Flomax)

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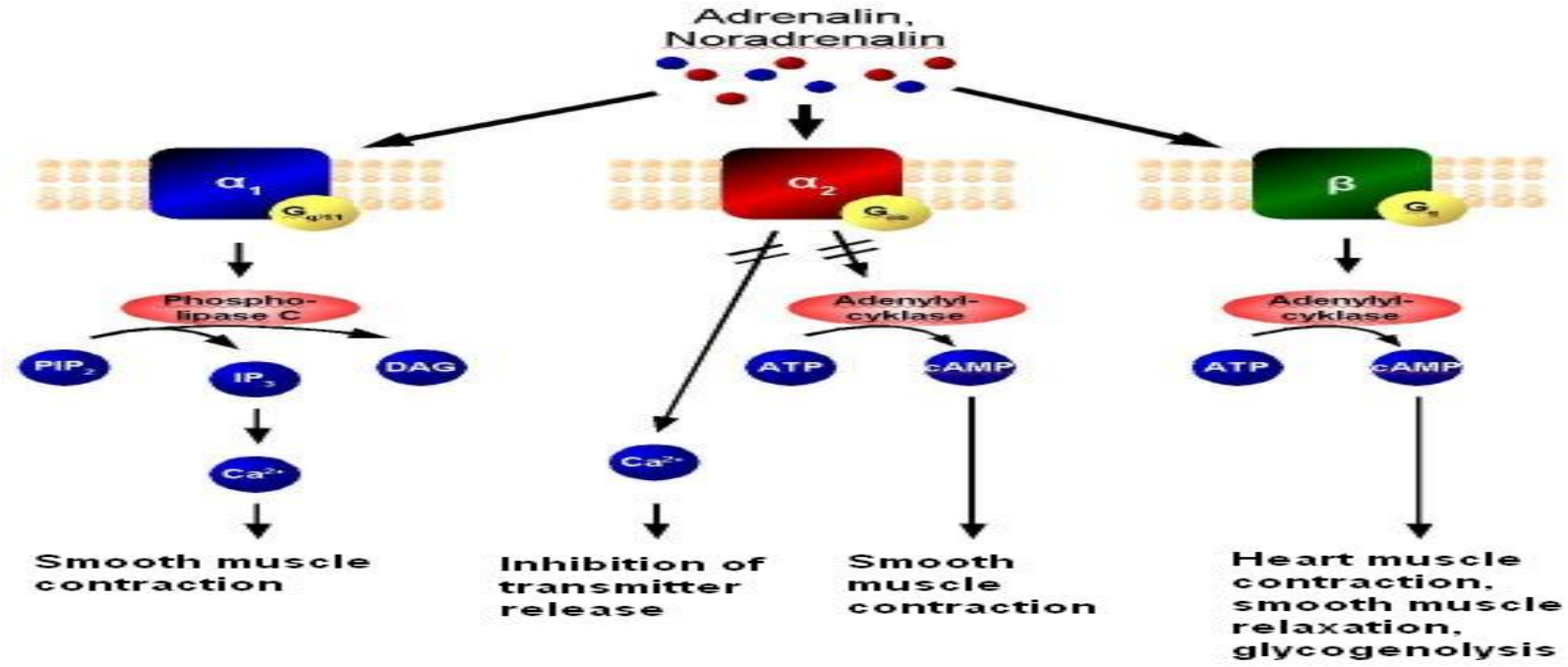
Inhibition of Alpha -1 Adrenergic Receptors: relax smooth muscle around prostate and neck of the bladder by blocking effects of epinephrine and norepinephrine from sympathetic nervous system and adrenal glands.

Note: Alpha 1 & 2 receptors are G-coupled proteins that are slightly different amino acid sequence than Beta 1,2,3 receptors. Beta-receptors generate cAMP from ATP, to act as second messenger. Both Alpha and Beta Adrenergic Receptors Respond to epinephrine & norepinephrine



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Side Effects Of Alpha-blockers:

- *Ejaculation back into the bladder (retrograde ejaculation)
- *Orthostatic hypotension (dizziness)
- *Fatigue, sleepiness
- Rhinitis, diarrhea

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2. 5- Alpha-Reductase Inhibitors – inhibit the conversion of testosterone to dihydrotestosterone (a hormone responsible for enlarging the prostate via upregulation of cellular proliferation of prostate cells)

Common Drugs:

- Finesteride (Proscar)
- Dutasteride (Avodart)

Side Effects:

- Impotence (most common – 1% of cases)
- Decreased libido
- Breast disorders (including gynecomastia)
- Ejaculation disorders.

We will see Nutritional Medicine Approaches to Male Reproductive Health Issues in Male and Female Health Sections on Global Integrative Medicine Academy Platform.

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Part 10. Common Gastro-Intestinal Drugs

A. Antacids

B. H2 Receptor Antagonists

C. Proton Pump Inhibitors

D. Ulcer Treatment

E. Laxatives

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A. Antacids

Definition: An antacid is any substance, generally a base or basic salt, which counteracts stomach acidity (buffering gastric acid, raising the pH)

Clinical Application:

Dyspepsia - Treatment with antacids alone is symptomatic and only justified for minor symptoms.

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Adverse Side Effects:

1. Milk-Alkali Syndrome - Too high an intake of calcium, coupled with dehydration can lead to a life-threatening condition known as Milk-Alkali Syndrome, which can occur with abuse of antacids containing calcium (e.g. Tums)

Milk-Alkali Syndrome

- Vomiting
- Intense pain
- Renal failure
- Alkalosis
- Hypercalcemia

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Milk-Alkali Syndrome

- In recent years, Milk-Alkali Syndrome has been reported in women taking calcium supplements above the recommended range of 1200 to 1500 mg daily, for prevention and treatment of osteoporosis, and is exacerbated by dehydration.

- Calcium has been added to over-the-counter products, which contributes to inadvertent excessive intake.

2. Aluminum, Magnesium, and Sodium-containing antacids are dangerous to take in renal disease.

Calcium-containing antacids are most popular (Tum, Rolaids)

In any degree of compromised kidney function magnesium and sodium antacids are contra-indicated (calcium antacids are best choice in this circumstance due to decreased calcitriol synthesis in kidney with increased risk of osteoporosis) – unless hypercalcemia of malignancy is present (about 10% of cancer pts)

These supplements also block absorption of phosphorous – an important factor in the management of advancing renal disease

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Some Common Antacids:

- Aluminum hydroxide (Amphojel, AlternaGEL)
- ***Magnesium hydroxide (Phillips' Milk of Magnesia**)
- ***Aluminum hydroxide with magnesium hydroxide (Maalox, Mylanta)**
- Aluminum carbonate gel (Basaljel)
- ***Calcium carbonate** (Alcalak, **TUMS**, Quick-Eze, Rennie, Titralac, **Rolaids**)
- Sodium bicarbonate (Bicarbonate of soda, **Alka-Seltzer**)
- Hydrotalcite ($Mg_6Al_2(CO_3)(OH)_{16} \cdot 4(H_2O)$; Talcid)
- ***Bismuth subsalicylate** (**Pepto-Bismol**)
- Magaldrate with Simethicone (Pepsil)

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B. H2-Receptor Antagonists

Mechanism Of Action: block action of histamine on parietal cells in the stomach, decreasing the production of acid by these cells.

- Enterochromaffin-like cells (ECL cells) are found in the gastric glands of the gastric mucosa beneath the epithelium.

- In response to gastrin and other hormones secreted with a meal ECL cells synthesize and secrete histamine.

- Histamine and gastrin act synergistically as the most important stimulators of hydrochloric acid secretion from parietal cells.

Clinical Application:

1. Dyspepsia
2. Peptic ulcers

These drug have largely been surpassed in popularity by the more effective proton pump inhibitors.

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Common H2 Antagonist Drugs:

- Cimetidine
- Ranitidine **(Zantac)**
- Famotidine
- Nizatidine

- In the United States, all four FDA-approved members of the group are available over the counter in relatively low doses

Adverse Side Effects: The H2 antagonists are generally well-tolerated, except for cimetidine where all of the following adverse drug reactions are common:

- *Headache
- Tiredness
- *Dizziness
- *Confusion
- Diarrhea
- Constipation
- Rash
- *Additionally, cimetidine may also cause gynecomastia in males, loss of libido, and impotence, which are reversible upon discontinuation.
- Cimetidine is detoxified using common pathway thereby interfering with drug detoxification of many other drugs

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C. Proton Pump Inhibitors

Mechanism Of Action - irreversibly block the proton pump of the gastric parietal cell, thereby reducing release of stomach acids

- These drugs are significantly more effective than H2 antagonists and reduce gastric acid secretion by up to 99%.

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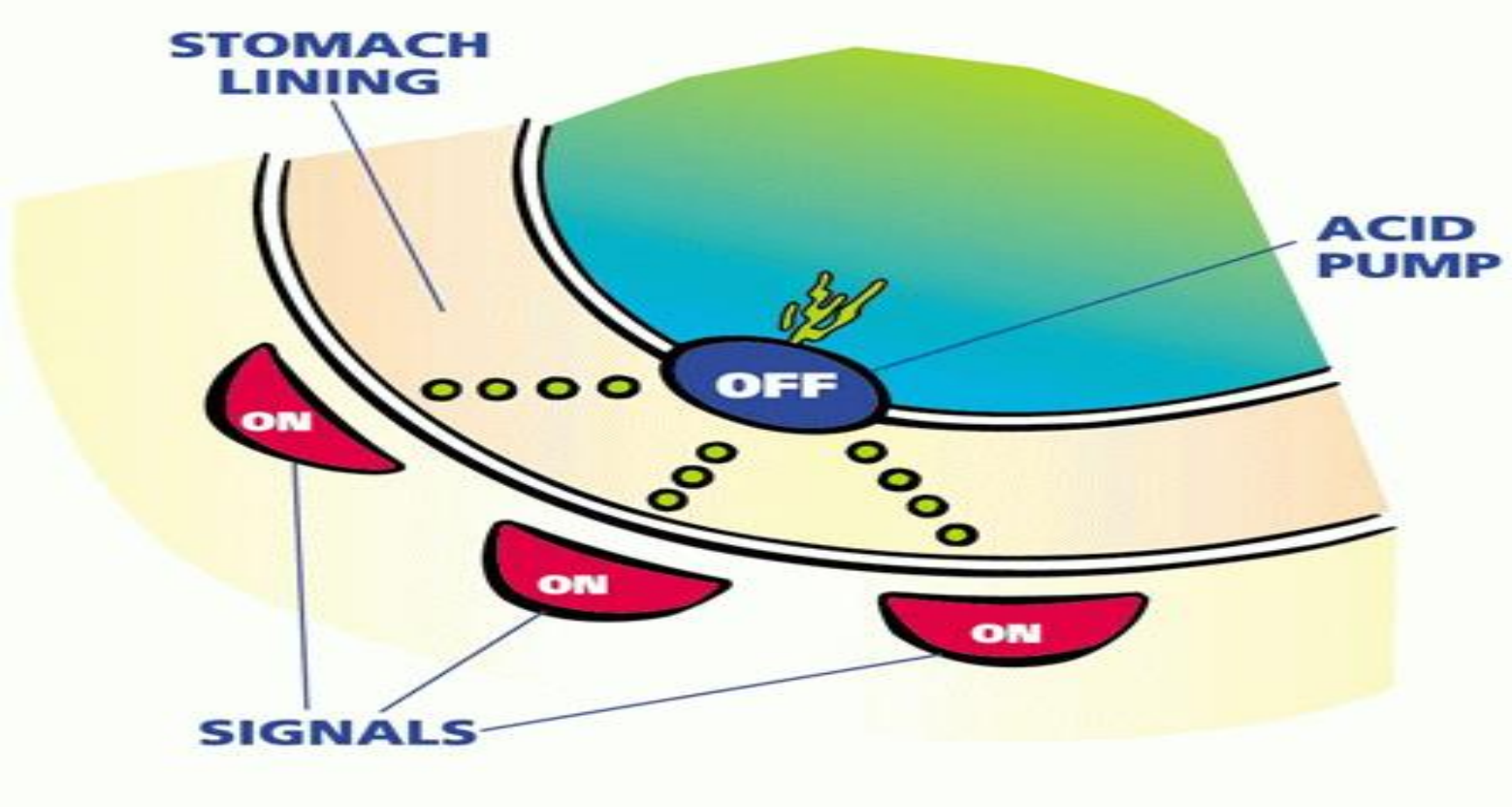
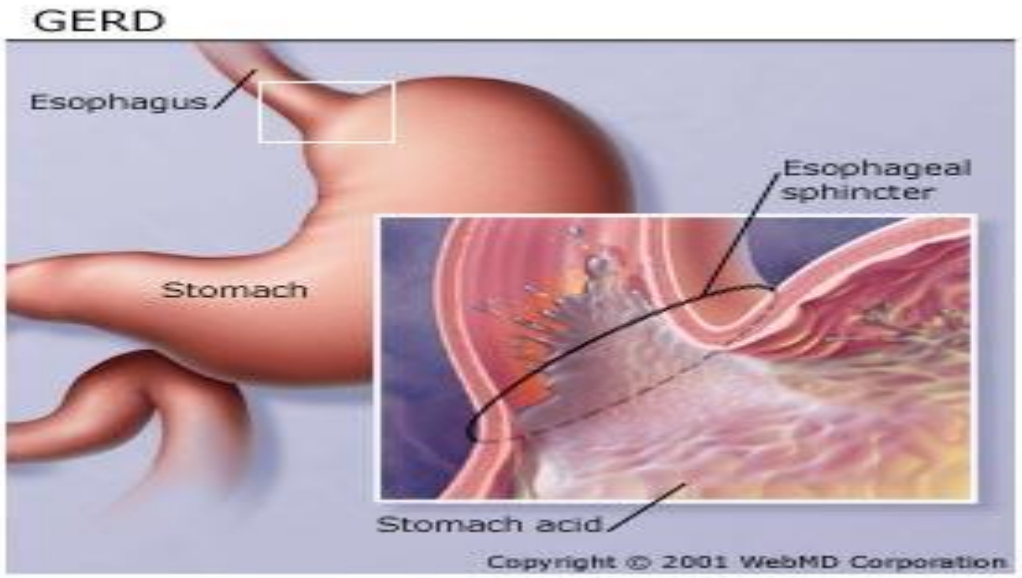
These drugs irreversibly binds to the gastric proton pump, deactivating it



Clinical Applications:

1. Duodenal ulcers (peptic ulcers)
2. Gastoesophageal reflux disease (GERD) (heartburn)



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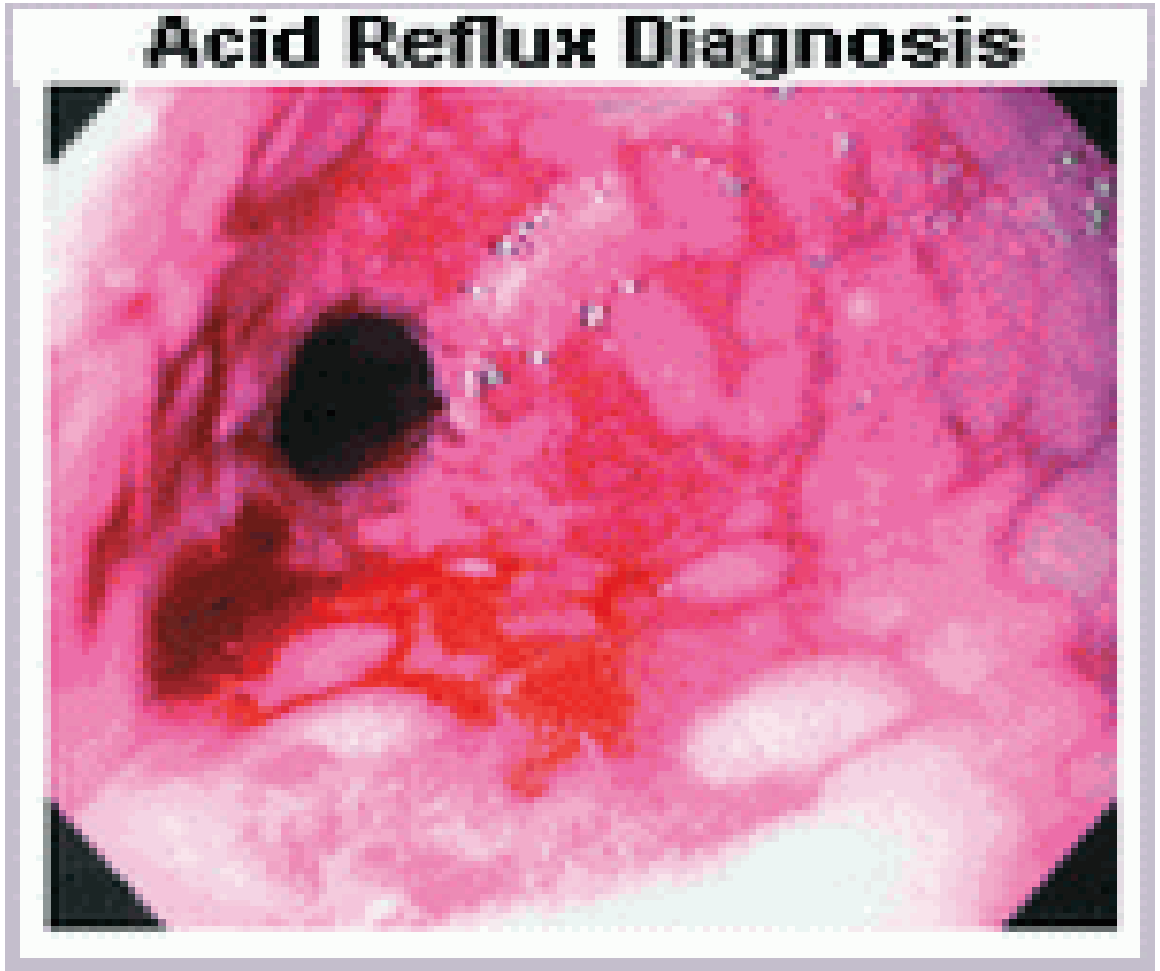
Endoscopy Image Of Acid Reflux Disease



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Precautionary Notes

- However, lack of stomach acid is also called hypochlorhydria.
- Hydrochloric acid is required for the digestion of proteins and for the absorption of nutrients, particularly vitamin B12 and of calcium.
- Some evidence suggests that taking these drugs for long-periods (1-4 years) in older subjects increases risk of hip fracture (likely due to decrease calcium absorption).
- Some authourites suggest concurrent supplementation with 100 mcg of vitamin B12 and 1500 mg of calcium per day, to mitigate against this potential side effect

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Common Proton Pump Inhibitor Drugs:

1. Omeprazole (brand names: **Losec,** Prilosec, Zegerid, ocid)
2. Lansoprazole (brand names: **Prevacid,** Zoton, Inhibitol)
3. Esomeprazole (brand names: **Nexium**)
4. Pantoprazole (brand names: Protonix, Somac, **Pantoloc**, Pantozol, **Zurcal**, Pan)
5. Rabeprazole (brand names: Rabecid, Aciphex, Pariet, Rabeloc)

- All five proton pump inhibitors have intravenous formulations.

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Adverse Side Effects

Proton pump inhibitors are generally well tolerated, and the incidence of short-term adverse effects is relatively uncommon.

The most common side effects:

- *Dizziness
- *Headache
- Nausea
- Diarrhea
- Abdominal pain
- Fatigue

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D. Ulcers and Antibiotics

- Approximately 80% of ulcers are associated with *Helicobacter pylori infection,* bacterium that lives in acidic environment of stomach

- Ulcers can also be caused or worsened by aspirin and other NSAIDs

Treatment:

1. When *H. pylori* infection is present, the most effective treatments are combinations of 2 antibiotics (e.g. Clarithromycin, Amoxicillin, Tetracycline, Metronidazole)
2. And 1 proton pump inhibitor (PPI),
3. Sometimes together with a bismuth compound (antacid and anti-inflammatory) e.g. Pepto-Mismol

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Natural Management Of Ulcers

1. **DGL Chewable Tablets** - demonstrate remarkable success in treating gastric and duodenal ulcers in clinical studies. Must mix with saliva to work

Results are comparable to treatment with cimetidine and ranitidine.

Prevent Recurrence – DGL shown to be equally, or more effective as standard ulcer drugs in preventing ulcer recurrence (one year follow-up).

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Mechanism Of Action

1. Improves and enhances quality and quantity of the protective coating that lines the intestinal tract
2. Increases the life span of the intestinal cells
3. Improves blood supply to the intestinal lining

- Active constituents (unknown) raise local concentration of prostaglandins that promote mucus secretion (through inhibition of 15- hydroxy-prostaglandin dehydrogenase and delta-13-prostaglandin reductase) in the stomach, leading to the healing of ulcers.

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Dosage: Peptic Ulcers: DGL chewable tablets (250 - 380 mg), two to four tablets between meals, or 20 minutes before meals.

Duration: Normally an 8-16 week course is utilized for therapeutic purposes.

Standardized Grade: DGL tablets should contain no more than 1 – 2% glycyrrhizin content.

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2. Aloe Vera Gel

Mechanism of Action:

1. Inactivates pepsin release when the stomach is empty.
2. Inhibits the release of hydrochloric acid by interfering with the binding of histamine to parietal cells (H2 inhibitory effect)

Dosage: a tablespoon of the gel in mineral oil taken once daily for the until ulcer heals

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E. Laxatives

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Clinical Applications:

1. Constipation
2. Preparation for colonoscopy, certain poisonings and preparing for colon surgery

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Different Types Of Laxatives:

1. Bulking Agents
2. Stool Softeners
3. Lubricants
4. Hydrating Agents
5. Stimulants (Castor Oil)
6. Hyperosmotic Agents

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1. **Bulking Agents** - dietary fiber, which cause stool to be bulkier and to retain more water, as well as forming an emollient gel, making it easier for peristaltic action to move it along.

Must drink plenty of water.

Have gentlest and most natural effects among laxatives and can be taken just for maintaining regular bowel movements.(e.g psyllium husk (Metamucil), methylcellulose (Citrucel)

2.Stool-Softeners - These cause water and fats to penetrate the stool, making it easier to move along. (e.g. Docusate - (Colace, Diocto, Dolculax)

3. Lubricants – make stool slippery, so that it slides through the intestine more easily.

An example is **mineral oil**, which also retards colonic absorption of water, softening the stool.

Mineral oil may decrease absorption of fat soluble vitamins and other nutrients.

4. Hydrating Agents - cause intestine to hold more water, softening the stool. (e.g. magnesium hydroxide - Milk of magnesia, magnesium sulfate - Epsom salt)

5. Stimulants (Senna-containing laxatives like Ex-Lax, and Castor Oil) – These stimulate peristaltic action and can be dangerous under certain circumstances. Long term use can lead to **'cathartic colon.**

Act on intestinal mucosa, or nerve plexus; they also alter water and electrolyte secretion. They are **the most severe among laxatives** and should be used only in extreme conditions.

Castor oil may be preferred when more complete evacuation is required.

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Senna Contra-indications: chronic gastrointestinal conditions such as:

- Hemorrhoids
- Ulcers
- Colitis (inflammatory bowel diseases)

Do not use Senna products for more than two weeks in any situation

6. Hyperosmotic Agents (e.g. Glycerin suppositories, Sorbitol, Lactulose, and Polyethylene glycol (PEG)

A. Lactulose works by the osmotic effect, which retains water in the colon, lowering the pH and increasing colonic peristalsis.

B. Glycerin suppositories work mostly by hyperosmotic action, but also the sodium stearate in the preparation causes local irritation to the colon.

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C. Preparing For Colonoscopy - Solutions of polyethylene glycol and electrolytes (sodium chloride, sodium bicarbonate, potassium chloride, and sometimes sodium sulfate) are used for whole bowel irrigation, a process designed to prepare the bowel for surgery or colonoscopy and to treat certain types of poisoning.

Some Brand names include:

GoLytely

GlycoLax

CoLyte

NuLytely

Side Effects

Other than bulking agents, Laxative abuse is potentially serious since it can lead to:

1. Intestinal paralysis
2. Irritable Bowel Syndrome (IBS)
3. Renal failure
4. Pancreatitis
5. Other problems

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Natural Laxatives

Natural Bulking Agents:

- Wheat bran, Corn bran, Rice bran -7-15 gms
- Peas and Beans -1/2 cup
- Ground Flaxseeds – 2 tablespoons
- Salba Grain- 2 tablespoons
- Psyllium Husk Fiber – 2-3 teaspoons

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Part 11. Antidepressants and Other Common Mental Health Drugs

In the United States, a 2005 independent report stated that **11% of women** and **5% of men** in the non-institutionalized population take antidepressants

The Three Most Common Types Of Anti-Depressants Include:

1. MAOIs (monoamine oxidase inhibitors)
2. Tricyclics
3. SSRIs

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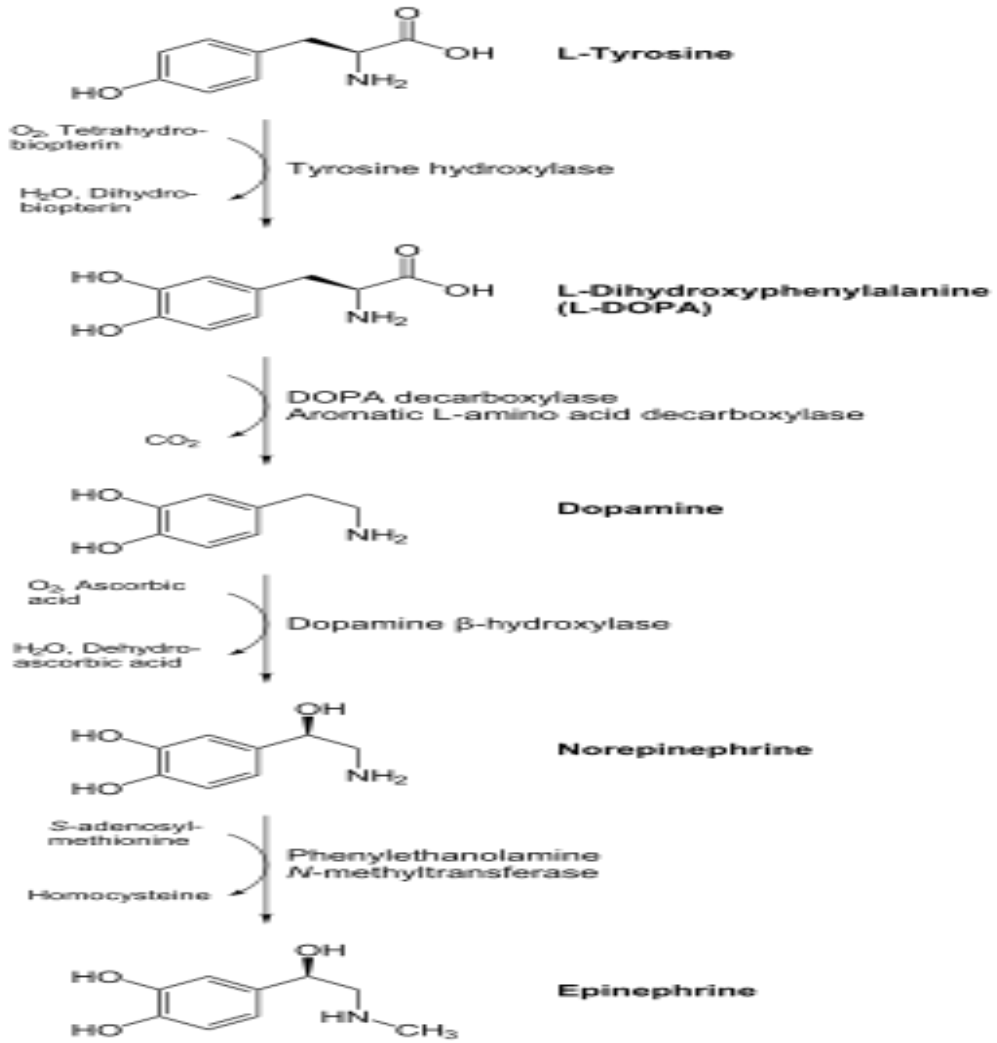
Synthesis of Catecholamines: Dopamine, Norepinephrine and Epinephrine



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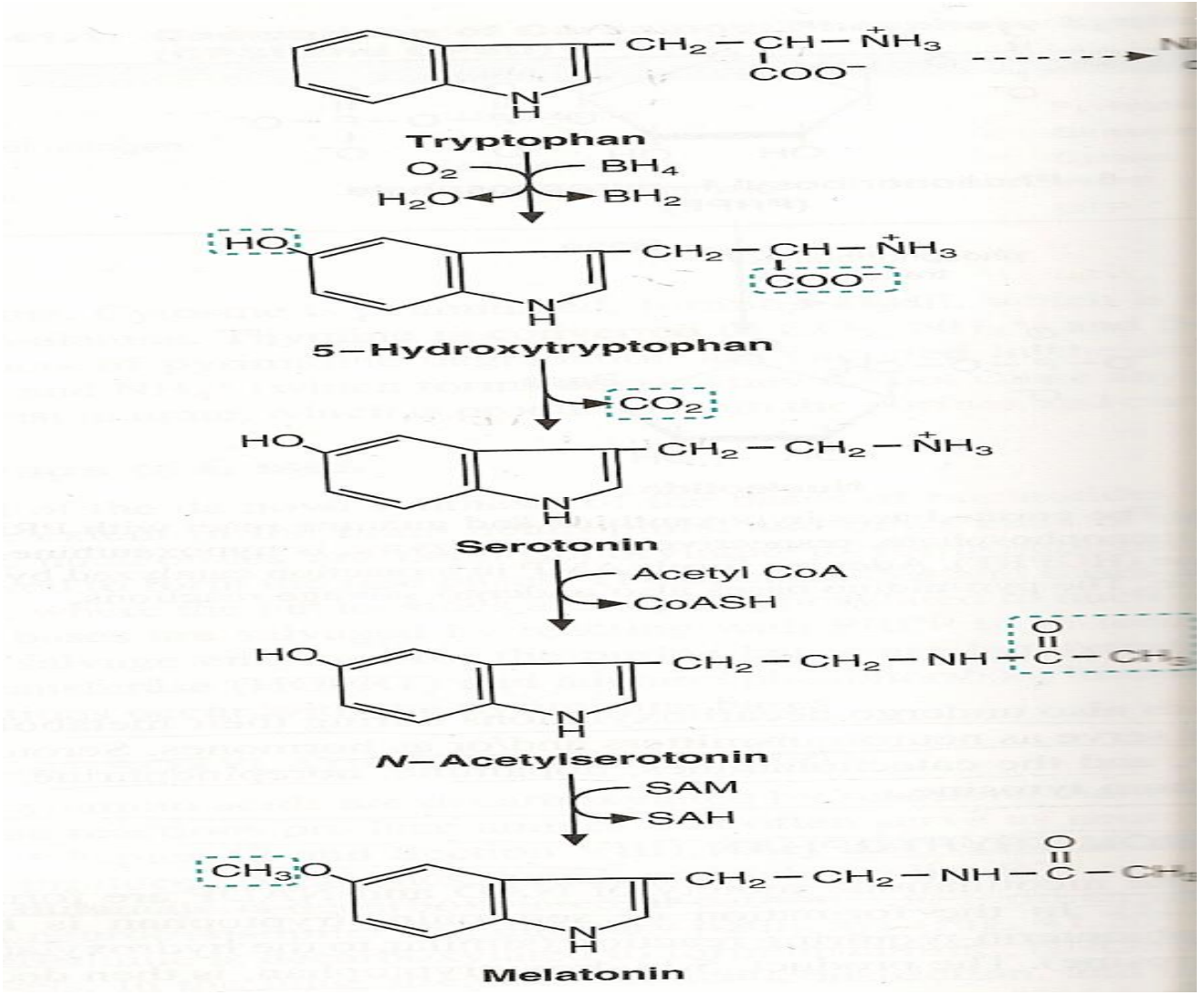
Synthesis of Serotonin and Melatonin



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1. **MAOI -** block monoamine oxidase enzyme breaks down dopamine, serotonin, and norepinephrine (noradrenaline). Inhibiting this enzyme raises neurotransmitter levels. As effective as tricyclic antidepressants.

- Potentially fatal interactions between MAOI and certain foods (particularly those containing Tyramine), like red wine, cheese, as well as certain drugs.

- For this reason MAOIs are rarely prescribed anymore.

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Why Are MAOI Dangerous?

MAO-A inhibition can lead to **hypertensive crisis**, when foods containing tyramine are consumed (so-called "cheese syndrome”), or **hyperserotonemia** if foods containing tryptophan are consumed.

The amount required to cause a reaction exhibits great individual variation.

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How Hypertensive Crises Occurs

- The amino acid tyrosine, found in many foods, is precursor to catecholamines, not tyramine. Tyramine is a breakdown product of tyrosine.
- In the gut and during fermentation (red wine & cheese) tyrosine is decarboxylated to tyramine.
- Ordinarily, tyramine is deaminated in the liver to an inactive metabolite, but when the hepatic MAO (primarily MAO-A) is inhibited by MAOI drugs, the "first-pass" clearance of tyramine is blocked and circulating tyramine levels can climb.
- In turn, elevated tyramine competes with tyrosine for transport across the blood-brain barrier where it can then enter adrenergic nerve terminals and displace norepinephrine in synaptic vesicles
- The mass transfer of norepinephrine (and other monoamines, dopamine and epinephrine) from their vesicular storage space into the extracellular space can precipitate the hypertensive crisis, which can result in stroke or cardiac arrhythmia if not treated.

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Tyramine From Foods

In foods, tyramine is often produced by the **decarboxylation of tyrosine** during fermentation or decay:

- Foods containing considerable amounts of tyramine include **meats that are potentially spoiled** or **pickled, aged**, **smoked**, **fermented**, or **marinated** (some fish, poultry, and beef); most pork (except cured ham); processed meat, **chocolate; alcoholic beverages (RED WINE)**

- **Fermented foods** - most cheeses (except ricotta, cottage cheese, cream cheese), sour cream, yogurt, shrimp paste, sauerkraut

- **Fermented Soy Products** - soy sauce, soy bean condiments, teriyaki sauce, tofu, tempeh, miso soup

- **Some Beans And Nuts-** broad (fava) beans, green bean pods, Italian flat (Romano) beans, Chinese (snow) pea pods, peanuts, Brazil nuts, coconuts

- **Some Fruits and Vegetables** - avocados, bananas, pineapple, eggplants, figs red plums, raspberries, yeast, and an array of cacti.

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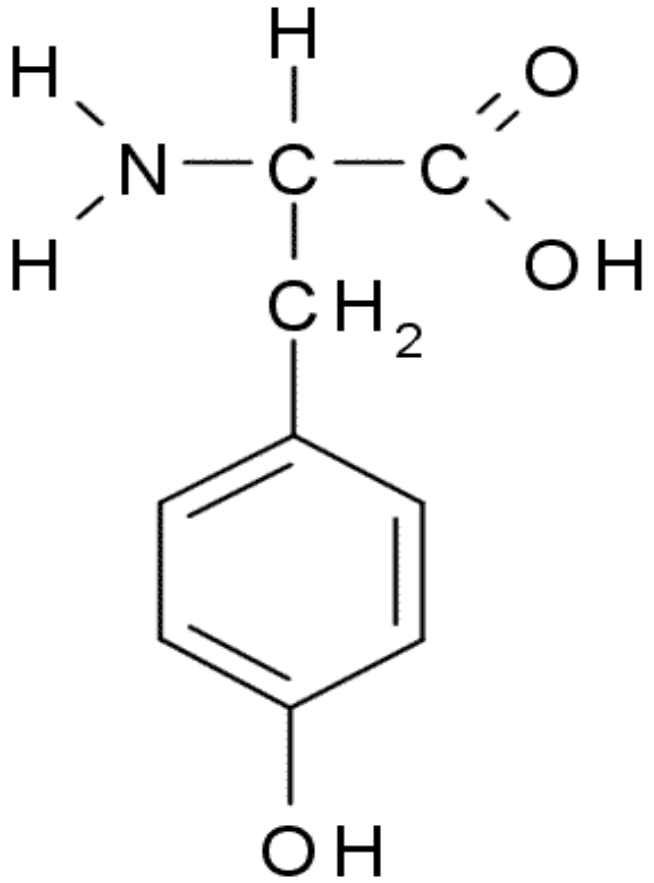
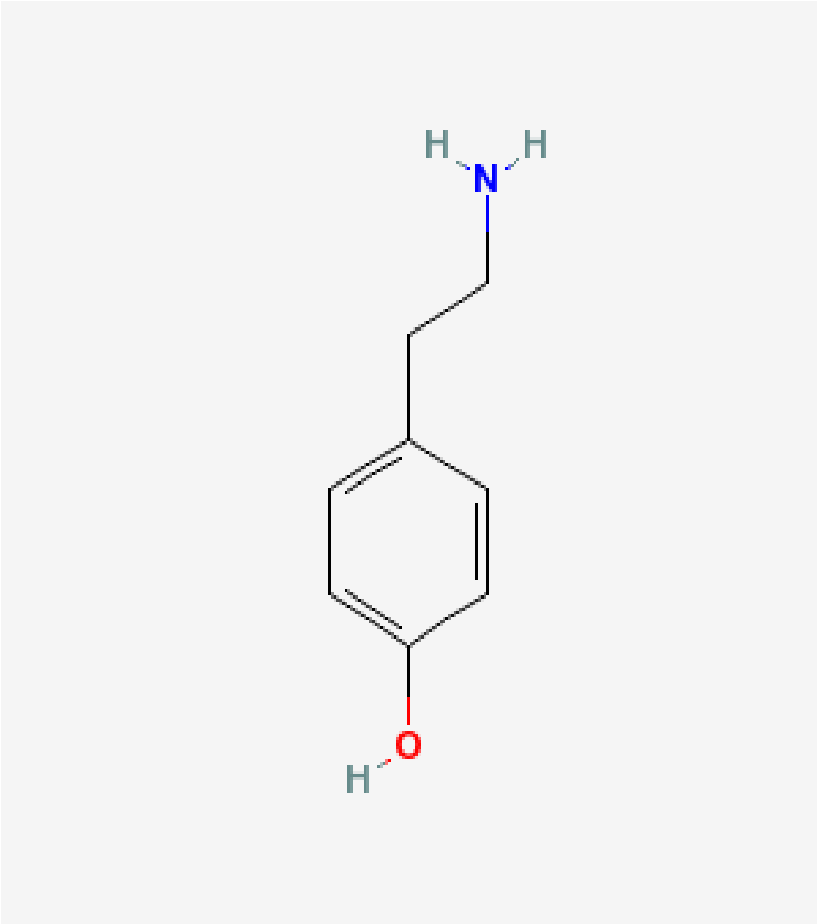
Tyrosine: Left
Tyramine: Right (decarboxylated)





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2. Tricyclic Antidepressants: oldest class of antidepressant drugs, e.g.:

- **Amitriptyline**
- **Desipramine**.

Block reuptake of certain neurotransmitters (norepinephrine, serotonin).

Largely replaced by Selective Serotonin Reuptake Inhibitors, which are safer and have fewer and/or less pronounced side effects

However, tricyclic antidepressants are still used because of their effectiveness, especially in **severe cases of major depression**.

Side Effects Of Tricyclic Anti-depressants:

- increased heart rate
- drowsiness
- dry mouth
- constipation
- urinary retention
- blurred vision
- dizziness
- confusion
- sexual dysfunction

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3. Selective Serotonin Reuptake Inhibitors (SSRIs): fluoxetine (**Prozac**), paroxetine (**Paxil**, Seroxat), escitalopram (**Lexapro**, Esipram), citalopram (**Celexa**), sertraline (**Zoloft**), and fluvoxamine (**Luvox**) – **inhibit breakdown of serotonin**

- Fewer adverse events & side effects than tricyclics or MAOIs.

Side Effects:

- drowsiness
- dry mouth
- nervousness
- anxiety
- insomnia
- decreased appetite
- sexual dysfunction

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4. Wellbutrin (Bupropion)

- Bupropion is used as an antidepressant and smoking cessation aid. It is marketed as Wellbutrin and Zyban among other trade names. It is an effective antidepressant on its own, but is also popular as an add-on medication in cases of incomplete response to first-line SSRI antidepressants

- It is a **norepinephrine-dopamine reuptake inhibitor (NDRI) and a nicotinic receptor antagonist**. It is an atypical antidepressant, different from most commonly prescribed antidepressants such as selective serotonin reuptake inhibitors (SSRIs).

- A nicotinic antagonist is a type of anticholinergic drug that inhibits the action of acetylcholine at nicotinic acetylcholine receptors. These compounds are mainly used for peripheral muscle paralysis in surgery, the classical agent of this type being tubocurarine, but some centrally acting compounds such as bupropion, mecamylamine, and 18-methoxycoronaridine block nicotinic acetylcholine receptors in the brain and have been proposed for treating nicotine addiction. Bupropion reduces the severity of nicotine cravings and withdrawal symptoms.

May also be prescribed for:

1. ADHD
2. Weight Loss
3. Fewer Sexual Dysfunction side effects than many SSRI, and thus a consideration for depressed patients experiencing sexual dysfunction (or weight gain) from use of SSRI drug(s).

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5. Lithium (Manic Depression and Bipolar)

- Lithium is used for the treatment of manic/depressive (bipolar) and depressive disorders. Lithium is a positively charged element or particle that is similar to sodium and potassium. Lithium can easily displace K+ and Na+ and even Ca+2, in spite of its greater charge, occupying their sites in several critical neuronal enzymes and neurotransmitter receptors.

- Lithium interferes with the production and uptake of chemical messengers by which nerves communicate with each other (neurotransmitters). Lithium also affects the concentrations of tryptophan and serotonin in the brain. In addition, lithium increases the production of white blood cells in the bone marrow.

- Lithium has been used since the 1950's.

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6. Adderall and Ritalin (ADHD – drugs)

- Both Adderall and Ritalin are CNS stimulants that work by increasing the availability of the neurotransmitters **norepinephrine and dopamine** in CNS connections. This speeds up brain activity.

- Ritalin works sooner and reaches peak performance more quickly than Adderall does.

- However, Adderall stays active in the body longer than Ritalin does. Adderall works for four to six hours. Ritalin is only active for two to three hours.

- This doesn’t necessarily mean that Adderall is a better choice, though. Some people prefer the shorter-acting Ritalin because they can better control the timing of side effects, such as loss of appetite and trouble sleeping.

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7. Anti-Psychotics

- Antipsychotic medications can reduce or relieve symptoms of psychosis, such as delusions (false beliefs) and hallucinations (seeing or hearing something that is not there). Formerly known as major tranquilizers and neuroleptics, antipsychotic medications are the main class of drugs used to treat patients with schizophrenia.

- They are also used to treat people with psychosis that occurs in bipolar disorder, depression and Alzheimer's disease. Other uses of antipsychotics include stabilizing moods in bipolar disorder, reducing anxiety in anxiety disorders and reducing tics in Tourette's syndrome.

- Psychosis is believed to be caused, at least in part, by overactivity of a brain chemical called dopamine, and antipsychotics are thought to work by blocking this dopamine effect. This blocking helps to make the symptoms of psychosis—such as voices and delusions—less commanding and preoccupying, but it does not always make them go away completely. People may still hear voices and have delusions, but they are more able to recognize what isn't real and to focus on other things, such as work, school or family.

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Second Generation (atypical) Antipsychotics?

- The second generation antipsychotics are usually the first choice for the treatment of schizophrenia. Although they may not be officially approved for these other uses, they are sometimes used in the treatment of mood and anxiety disorders, such as bipolar, posttraumatic stress and obsessive-compulsive disorders.

- Medications available in this class include risperidone (Risperdal)[*], quetiapine (Seroquel), olanzapine (Zyprexa), ziprasidone (Zeldox), paliperidone (Invega), **aripiprazole (Abilify)** and **clozapine (Clozaril).** Clozapine is exceptional in that it often works even when other medications have failed; however, because it requires monitoring of white blood cell counts, it is not the first choice for treatment.

- Some possible side-effects of this type of medication include dry mouth, dizziness, blurred vision and, rarely, seizures.

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First Generation (typical) Antipsychotics?

- These older medications include chlorpromazine (once marketed as Largactil), flupenthixol (Fluanxol), fluphenazine (Modecate), haloperidol (Haldol), loxapine (Loxapac), perphenazine (Trilafon), pimozide (Orap), trifluoperazine (Stelazine), thiothixene (Navane) and zuclopenthixol (Clopixol).

- Side-effects of this group of medications vary depending on the drug and may include drowsiness, agitation, dry mouth, constipation, blurred vision, emotional blunting, dizziness, stuffy nose, weight gain, breast tenderness, liquid discharge from breasts, missed periods, muscle stiffness or spasms

Reference:https://www.camh.ca/en/hospital/health_information/a_z_mental_health_and_addiction_information/antipsychotic_medication/Pages/antipsychotic_medication.aspx

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- Aripiprazole, sold under the brand name Abilify among others, is an atypical antipsychotic.

- Aripiprazole is primarily used for the treatment of schizophrenia or bipolar disorder.

- Aripiprazole rebalances dopamine and serotonin to improve thinking, mood, and behavior. Aripiprazole may help some or all of these symptoms.

Nutritional Medicine, as an adjunct in Depression, is covered in the Nutritional Medicine and Mental Health Section on the Global Integrative Medicine Platform

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Part 12 Hypothyroidism and Thyroxine

Hypothyroidism: Insufficient production of thyroid hormone.

Most common causes:

1. Hashimoto's thyroiditis (an autoimmune disease) – most common cause of hypothyroidism
2. Radioiodine therapy for hyperthyroidism (Grave's disease) and Thyroid Cancer
3. Age-Related Decline in Thyroid Function affects 3-16% of population causing clinical hypothyroidism. Higher percentage experience thyroid dysfunction (see later)

- Historically, iodine deficiency was the most common cause of hypothyroidism world wide. Iodize salt has helped to conquer this problem

- **Secondary hypothyroidism -** pituitary gland does not create enough thyroid stimulating hormone (TSH) to induce the thyroid gland to create a sufficient quantity of thyroxin. This is usually related to a pituitary damaged by a tumor, radiation, or surgery.

- **Tertiary hypothyroidism -** hypothalamus fails to instruct the pituitary to produce sufficient TSH.

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Diagnosis: High levels of TSH indicate thyroid is not producing sufficient levels of Thyroid hormone.

The normal medical range for **TSH** in most laboratories is 0.4 milliunits per liter (mU/L) to 4.0 mU/L (but anything over 2 is thyroid dysfunction).

However, measuring just TSH fails to diagnose secondary and tertiary forms of hypothyroidism, thus leading to the following suggested minimum blood testing:

* thyroid-stimulating hormone (TSH)
* free triiodothyronine (fT3)
* free levothyroxine (fT4)
* total T3
* total T4

Treatment - **Synthroid or Lexothyroxine:** Synthetically produced thyroid hormone (T4 or thyroxine).

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Clinical Applications:

1. Hypothyroidism
2. Goiter

Common Side Effects Of Thyroid Hormone Therapy:

- *Palpitations
- Nervousness
- *Headache
- Insomnia
- Swelling of the legs and ankles
- Weight loss and/or increased appetite

Note: in hyperthyroidism, often caused by Grave's Disease, the patient may be treated with radioiodine drugs, radiation or surgical removal of thyroid. In Grave's Disease auto-antibodies chronically stimulate thyroid receptors prompting them to continually produce thyroxin hormone

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Example of a Thyroid Support Supplement (to aid thyroxine or to treat thyroid dysfunction). Does not replace thyroid hormone drugs, however

2 Capsules Contain:

- L- Tyrosine- 500mg – key amino acid for thyroid hormone synthesis
- Coleus Forskolin – 200 mg – increases release of thyroxin from thyroid
- Guggul (Comniphora mukul) Extract) - 100 mg – converts T4 to T3 (more active form of thryoxin)
- Iodine (from kelp)150 mcg – required prosthetic group for thyroid hormone

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Contra-Indications – don't recommend Thyroid Support Formula or Kelp to patients undergoing Radio-iodine treatment or radiation treatment for hyperthyroidism or thyroid cancer – the iodine in these products competes with radioactive iodine for uptake into thyroid cells (undermining treatment)

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Part 13. Diabetes

Type 1 Diabetes - requires insulin – allowing glucose entry into Glut-4 transporter dependent cells (muscle and adipose – 2/3 of all body cells)

Type 2 Diabetes – a number of drugs either stimulate release of insulin from the pancreas helping to overcome insulin resistance, or act by increasing insulin sensitivity:

1. Sulfonylureas -increase insulin release **(insulin secretagogue)**

- **First-generation agents (suffix is "mide")**
- *Tolbutamide (Orinase)
- Acetohexamide (Dymelor)
- Tolazamide (Tolinase)
- Chlorpropamide (Diabinese)

Second-generation insulin secretagagues (suffix is “ide”)

- Glipizide (Glucotrol)
- *Glyburide (Diabeta, Micronase, Glynase)
- Glimepiride (Amaryl)
- Gliclazide (Diamicron)

2. Meglitinides help pancreas produce insulin and are often called "short-acting secretagogues." They are taken with meals to boost the insulin response to each meal.

- Repaglinide (Prandin)
- Nateglinide (Starlix)

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Drugs That Increase Insulin Sensitivity

1. Metformin (Glucophage) - usually the first-line medication for type-2 diabetes.

   Metformin increases insulin sensitivity of liver and peripheral cells and decreases hepatic glucose synthesis and intestinal absorption of glucose, and may decrease triglyceride and LDL-cholesterol levels and increase HDL-cholesterol.

2. Thiazolidinediones (TZDs), also known as "**glitazones”:**

- *Rosiglitazone (Avandia)
- Pioglitazone (Actos)

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Adverse Side Effects:

- *Main one is hypoglycemia
- *Migraine and Headache
- *Paresthesia with Sulfonylureas
- There are numerous other potential side effects depending on which class of drug used

- Nutritional Medicine in Diabetes is covered in the Diabetes Section on the Global Integrative Medicine Platform.

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Part 14. Antibiotics and Infections

Antibiotics are classified as either:
Bactericidal

Bacteriostatic

- Bactericidals kill bacteria directly
- Bacteriostatics prevent cell division

1. Bactericidals – target bacterial cell wall (penicillin, cephalosporins) or cell membrane (polymixins), or interfere with essential bacterial enzymes (quinolones, sulfonamides).

e.g. Cipro (Bayer) - Ciprofloxacin is a popular synthetic bactericidal antibiotic.

- Blocks bacterial DNA replication

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2. Bacteriostatics – inhibit protein synthesis such as the:

Aminoglycosides

Macrolides

Tetracyclines

- **Nutrition Note** – Do not combine antibiotics with alcohol intake (nausea, vomiting, shortness of breath)

- (See Article on Emerging Antibiotic Resistance)

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Natural Antibiotic

Oregano (wild P73 Blend) – volatile oils that kill many viruses, bacteria, candida etc

1. **Colds, Flu, Acute Bronchitis and Sinusitis** – 2 capsules every 4 hours at the earliest signs of a cold or flu-bug (as well as sinusitis
2. **Chronic Bronchitis and Chronic Asthma** – take 2 capsules twice per day until condition improves to a significant degree and then reduce or eliminate
3. **Chronic Mono and Chronic Fatigue** – 2 capsules twice per day along with other supplements to boost immune system (reishi mushroom extract and astragalus)

4. **Candida and yeast infections** – 2 capsules, three times per day until significant improvement is realized,
5. **Duodenal and Gastric (stomach) ulcers** – 3 capsules, twice per day (can be taken with antibiotics aimed at killing the H. pylori)
6. **Acne and Rosacea** – kills the bacteria and skin mite associated with acne and rosacea, respectively. Take 2 capsules, twice per day.

A topical oil of oregano cream applied at night can further assist in cases of acne and rosacea.

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Antifungal Medications – most work by interfering with synthesis of components of the fungal cell membrane (e.g. Nystatin)

The Problem – cells of the fungi similar to humans and animals (eukaryocytes – membrane encased cells with a nucleus and membrane-bound organelles, whereas bacteria are prokaryocytes, which have cell wall and no nucleus or membrane-bound organelles).

As such, its harder to make drugs that attack unique physiology of fungus, as fungi share many biochemical processes as human cells. Therefore, many antifungal drugs also affect human cells, producing untoward side effects

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Challenges:

1. Expensive drugs

2. Long Treatment Course (nail fungus – 6-12 months)

3. Many Side Effects:

- Nausea
- Headache
- Rash
- Vomiting
- Abdominal pain
- Diarrhea
- Dyspepsia
- Taste changes
- Dizziness
- **Possible Liver Toxicity**
- Possible seizures

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Anti-Viral Herpetic Drugs – primarily affect viral **enzyme thymidine kinase,** which interferes with DNA replication in virus.

This gives body's immune system an opportunity to intervene

Common Drugs:

Acyclovir (Zovirax)

Valaciclovir (Valtrex)

Famciclovir (Famvir)

Penciclovir

Anti-viral drugs for HIV/AIDS beyond scope of course

No anti-viral drugs to combat common cold (corona or rhino-viruses most often)

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Accutane And Acne

- High doses of vitamin A (100,000-500,000 IU per day) effective for acne in 1930's

But vitamin A toxicity occurred:

- Dry, peeling skin
- Liver damage etc.

Vitamin A – shrinks sebaceous glands and decreases sebum secretion, normally under hormonal control

Accutane (isotretinoin (13-*cis*-retinoic acid) – released in 1982 by Hoffman - La Roche is a safer form of vitamin A, and more effective than antibiotics for cystic acne

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Adverse Side Effects Of Accutane:

Common:

- **Skin and Integument:** Mild acne flare, dryness of skin, lips and mucous membranes, infection of the cuticles, cheilitis, itch, rosacea, skin fragility, skin peeling, rash, flushing, nose bleeds, dry eyes, diffuse alopecia areata, eye irritation, conjunctivitis, reduced tolerance to contact lenses

- **Systemic: Hyperlipidemia, raised liver enzymes,** permanent thin skin, **headaches**, permanent hair thinning, myalgia and/or **arthralgia,** back pain.

Infrequent: severe acne flare, raised blood glucose level, increased erythrocyte sedimentation rate, fatigue.

- **Rare:** impaired night vision; cataracts; optic neuritis; menstrual disturbances; inflammatory bowel disease; pancreatitis; hepatitis; corneal opacities; papilloedema; idiopathic intracranial hypertension; skeletal hyperostosis; extraosseous calcification; psychosis; and it is believed that severe depression can occur, although there is no conclusive evidence for this.

- **Residual Side Effects:** may persist after discontinuing therapy: alopecia (hair loss), arthralgias, decreased night vision, inflammatory bowel disease, degenerative disc disease, keloids, bone disease, rosacea.

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- **Do Not Take If Pregnant:** Isotretinoin is **a teratogen** and is highly likely to cause birth defects if taken during pregnancy.

Other Considerations:

- **Depression -** Several studies have suggested a possible link between isotretinoin and clinical depression. (Many lawsuits pending)

- **Crohn's Disease and Ulcerative Colitis -** Several scientific studies have posited that isotretinoin is a probable cause of Crohn's Disease and Ulcerative colitis in some individuals. (Lawsuits pending)

- **Drug-Nutrient Interactions** - Concurrent intake of Vitamin A supplementation increases the risk of vitamin A toxicity. Thus, should not give a patient more than 2500 IU per day of vitamin A from a multiple vitamin supplement.

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Consider: Oil of Oregano capsules and Cream (oil) for:

1. Acne/Rosacea
2. Skin, nail and internal fungal infections
3. Combat flus and colds (chronic mono)

Herpetic Lesions:

1. Reishi Mushroom Extract
2. Tribulus Terrestris
3. L-lysine

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Part 15. Asthma

Many people with asthma or some form of COPD use inhalers that dilate the bronchial passages.

These drugs are usually Beta-2-Adrenergic Receptor Agonists.

Beta-2- Adrenergic Receptor Agonist Drugs: act on Beta-2 receptors causing smooth muscle relaxation, resulting in dilation of bronchial passages.

Also cause vasodilation in muscle and liver, relaxation of uterine muscle and release of insulin

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Common Drug Forms:

- **Inhalers:** Salbutamol - (trade name **Ventolin**), and Terbutaline – (trade names Brethine, Bricanyl, or Brethaire)

- **Solution Form For Nebulization:** Salbutamol (known as albuterol in the US) also comes in a solution form for nebulization (mist form), which is commonly used in emergency rooms and under certain medical circumstances (unconscious patient)

- **Oral Form**: Salbutamol and Terbutaline are also both available in oral forms.

- **Intravenous Form:** These are used in severe cases of asthma, but more commonly it is used to **suppress premature labor** because it also relaxes uterine muscle, thereby inhibiting contractions.

Side Effects:

- Insomnia
- Anxiety
- Tremor

In acute asthmatic attacks or anaphylactic reaction the patient may be instructed to use an **EpiPen**, which is an autoinjector (spring-loaded syringe) of epinephrine.

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Natural Management Of Asthma

Oil of Oregano – has helped to improve these conditions in some cases

Take 2 capsules twice per day until condition improves to a significant degree and then reduce or eliminate

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Part 16. Allergic Reaction

Activation of pre-sensitized mast cells release histamine and other inflammatory mediators upon exposure to an allergin. In turn, see systemic vasodilation, along with increased cell permeability due to histamine's action on H1 receptors on various tissues.

Recruitment and degranulation of eosinophils also results from histamine release from mast cells.

Anti-histamine drugs block the effect of histamine on the Histamine-1 Receptors. They **do not** block the release of histamine itself, only its effects.

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Anti-Histamines

Mechanism Of Action – block effect of histamine on H1 histamine receptor, which are expressed in:

1. Smooth muscles,
2. Vascular endothelial cells
3. Heart
4. Central nervous system

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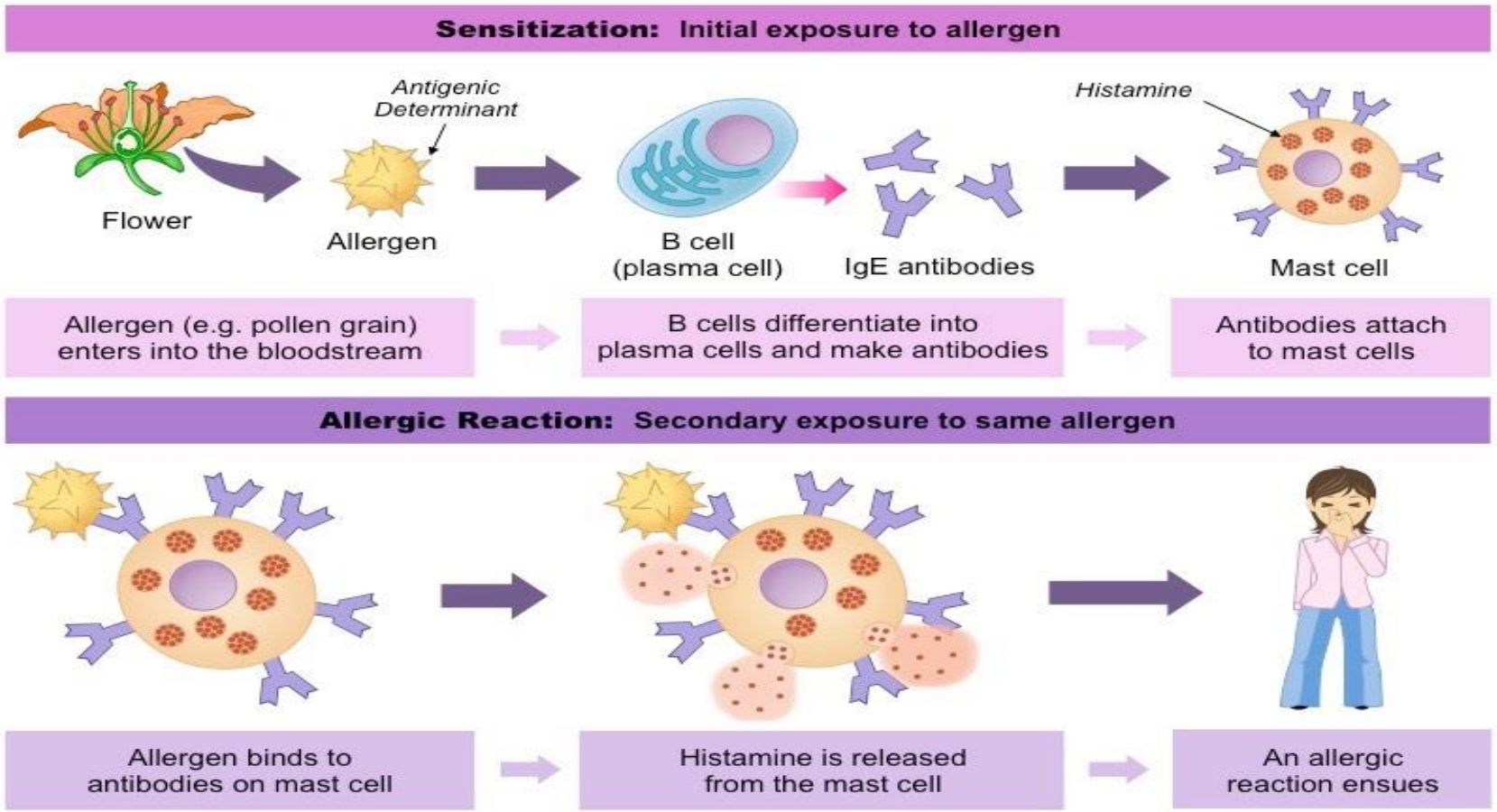
Steps in Allergy and Mast Senstization



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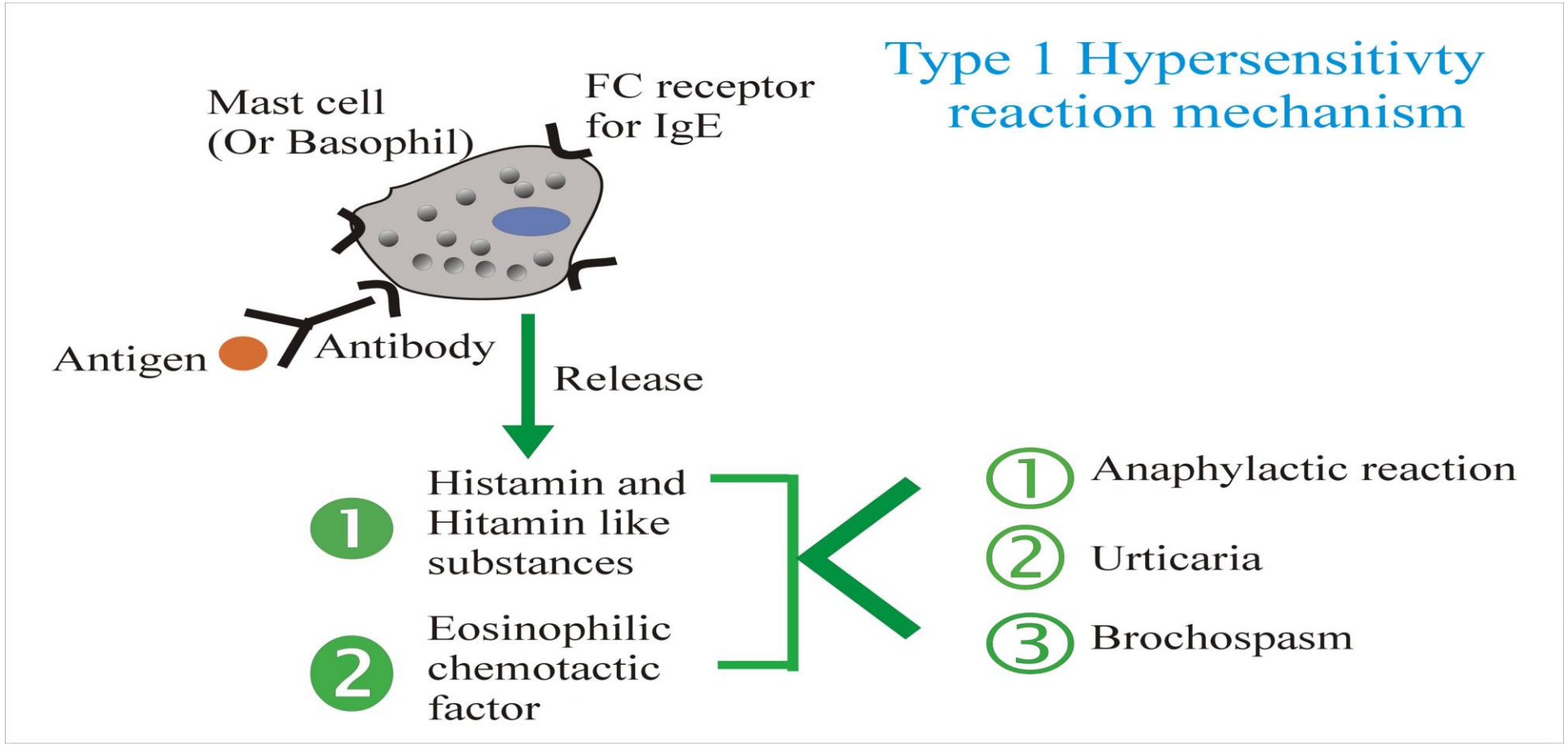
Involvement of Mast Cells and Eosinophils



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Clinical Applications For Anti-Histamine Drugs:

1. Allergic Rhinitis (especially seasonal allergies)
2. Hives
3. Insect Bites

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Common Anti-Histamine Drugs:

1. Benadryl (Diphenhydramine)
2. Claratin (Loratadine**)**

Common Side Effects:

- Drowsiness
- CNS depression (sedation properties)
- Dry Mouth (due to their additional anticholinergic effects)
- Headache

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Natural Anti-Histamine

Quercetin - inhibits histamine release at therapeutic doses (also anti-inflammatory)

Dosage: 200-400 mg, three time daily

No drowsiness

Excellent for seasonal allergies

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Part 17. Osteoporosis and Bisphosphonate Drugs

Mechanism of Action - inhibit osteoclast action and thus, resorption of bone. (e.g. Fosamax)

Clinical Applications:

1. Osteoporosis
2. Osteitis deformans ("Paget's disease of bone")
3. Bone metastasis (osteoclastic nature)
4. Multiple myeloma
5. Osteogenesis imperfecta and other conditions that feature bone fragility

Common Drugs

- Alendronate (Fosamax)
- Ibandronate (Bonviva)
- Risedronate (Actonel)
- Zoledronate (Zometa, Aclasta)
- Etidronate (Didronel, Didrocal)

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Side Effects

1. Stomach upset and inflammation and erosions of the esophagus. This can be prevented by remaining seated upright for 30 to 60 minutes after taking the medication

2. Osteonecrosis of the jaw; with the mandible twice as frequently affected as the maxilla.

Most, but not all cases have occurred following high-dose intravenous administration used for some cancer patients.

Some 60% of cases are preceded by a dental surgical procedure (that involve the bone) and it has been suggested that bisphosphonate treatment should be postponed until after any dental work to eliminate potential sites of infection.

Nutritional Medicine in Osteoporosis covered in Osteoporosis Section on this platform.

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Part 18. Parkinson's Drugs

Levodopa - the most widely used drug.

Mechanism of Action - L-dopa is transformed into dopamine in the dopaminergic neurons (decarboxylation). However, only 1-5% of L-DOPA enters the dopaminergic neurons.

The remaining L-DOPA is often metabolized to dopamine elsewhere, causing a wide variety of side effects.

2. Carbidopa and Benserazide - dopa decarboxylase inhibitors.

Mechanism Of Action - prevent metabolism of L-dopa before it reaches the dopaminergic neurons.

Are generally given as combination preparations of carbidopa/levodopa

(e.g. Sinemet, Parcopa) and benserazide/levodopa (e.g. Madopar).

3. Selegiline and Rasagiline - reduce symptoms of Parkinson's by inhibiting monoamine oxidase-B (MAO-B), which inhibits the breakdown of dopamine in brain

Note – these are different than MAO-A-Inhibitors, as they don't block breakdown of tyramine in the liver (no hypertensive crises)

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Side Effects:

Involuntary movements -most common serious side effects of levodopa-carbidopa therapy.

These may include chewing, gnawing, twisting, tongue or mouth movements, head bobbing, or movements of the feet, hands, or shoulder.

Nutritional Medicine in the management of Parkinson's disease is presented in the Nutritional Medicine and Neurology Part 1 Section on the Global Integrative Medicine Platform

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Part 19. Alzheimer's Disease And Age-Related Memory Loss

Causes (Three Hypotheses)

1. **Cholinergic Hypothesis** - AD caused by reduced synthesis of the neurotransmitter acetylcholine.

However, medications that boost acetylcholine levels are not effective in the long-run.

Most popular AD drugs act on this pathway

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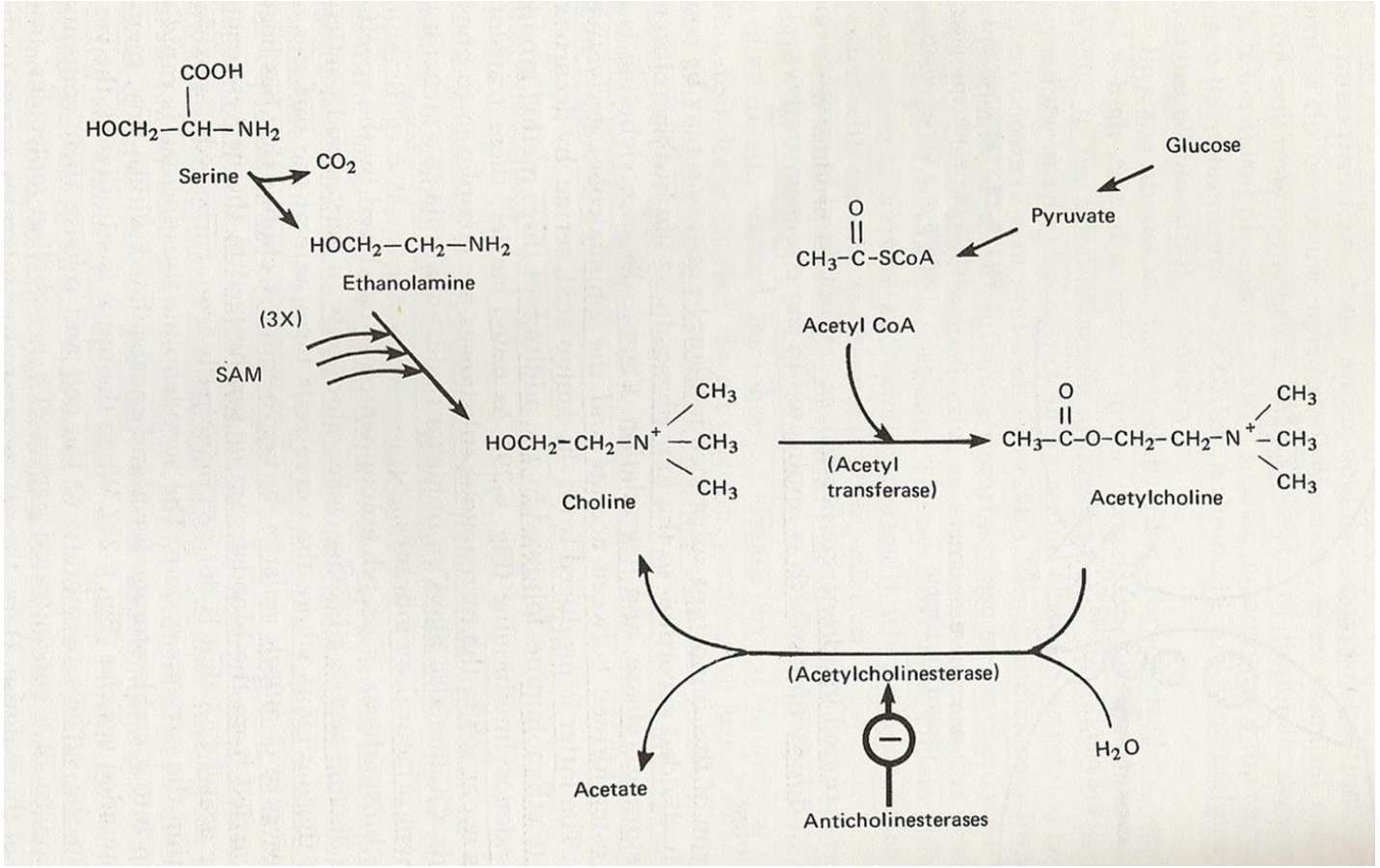
Synthesis of The Memory Neurotransmitter Acetylcholine



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2. Amyloid Hypothesis - amyloid beta deposits are fundamental cause of AD in that the gene for the amyloid beta precursor (APP) is located on chromosome 21, and people with trisomy 21 (Down Syndrome), who have an extra gene copy, invariably exhibit AD by age 40.

- Also APOE4, the major genetic risk factor for AD, leads to excess amyloid buildup in the brain before AD symptoms arise. Thus, beta amyloid protein deposition precedes clinical AD.

- Further evidence comes from the finding that transgenic mice that express a mutant form of the human APP gene develop fibrillar amyloid plaques and Alzheimer's-like brain pathology with spatial learning deficits.

- However, deposition of amyloid plaques does not correlate well with neuron loss.

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More Details

- Beta-amyloid is a fragment from a larger protein called amyloid precursor protein (APP), a transmembrane protein that normally penetrates through the neuron's membrane.

- APP is critical to neuron growth, survival and post-injury repair.

- In AD, APP gets divided into smaller fragments by proteolyitc enzymes, producing beta-amyloid fibril, which forms clumps that deposit outside the neurons as senile plaques.

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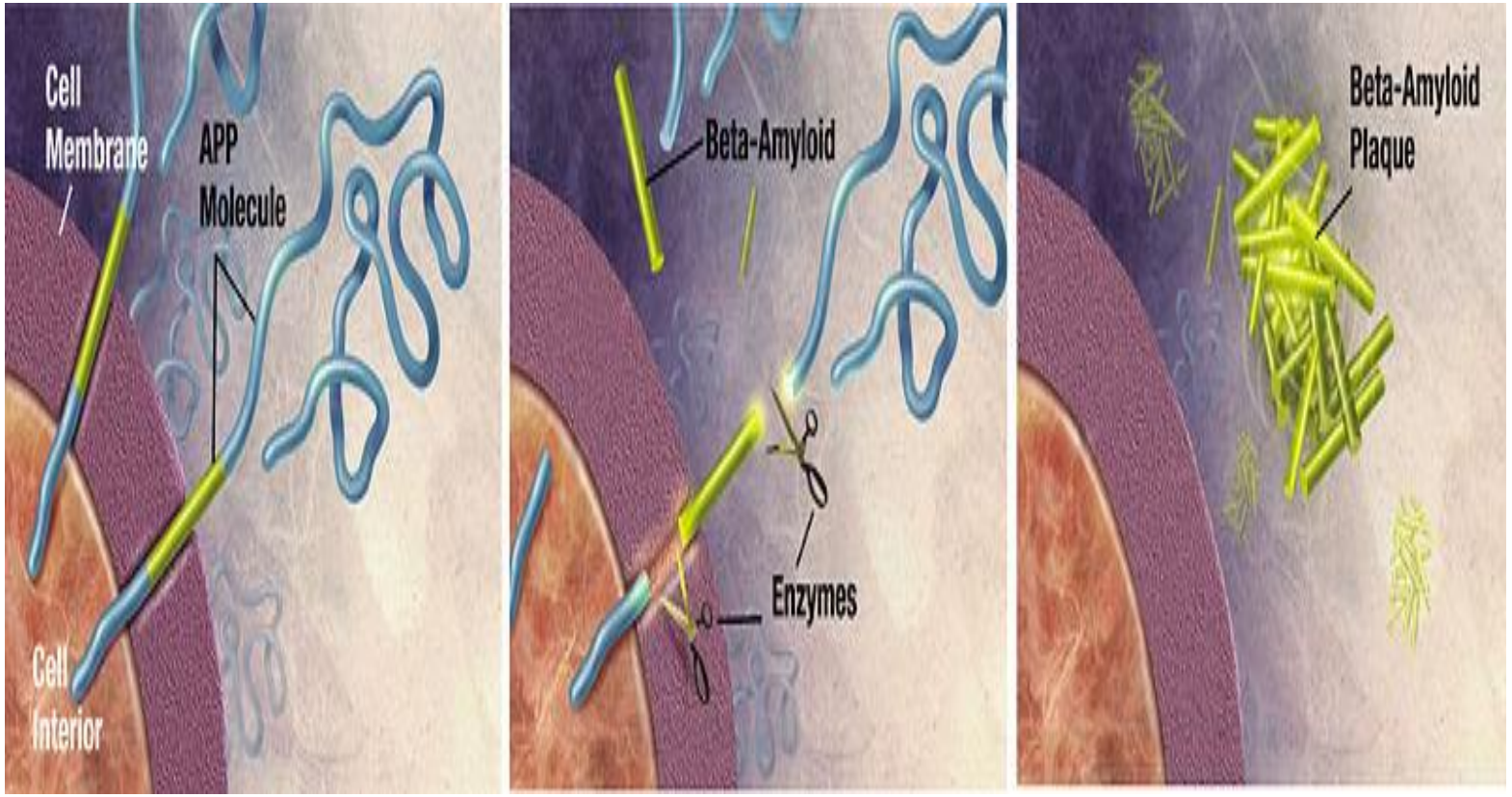
Enzymes act on the APP (amyloid precursor protein) and cut it into fragments forming Beta-amyloid plaque



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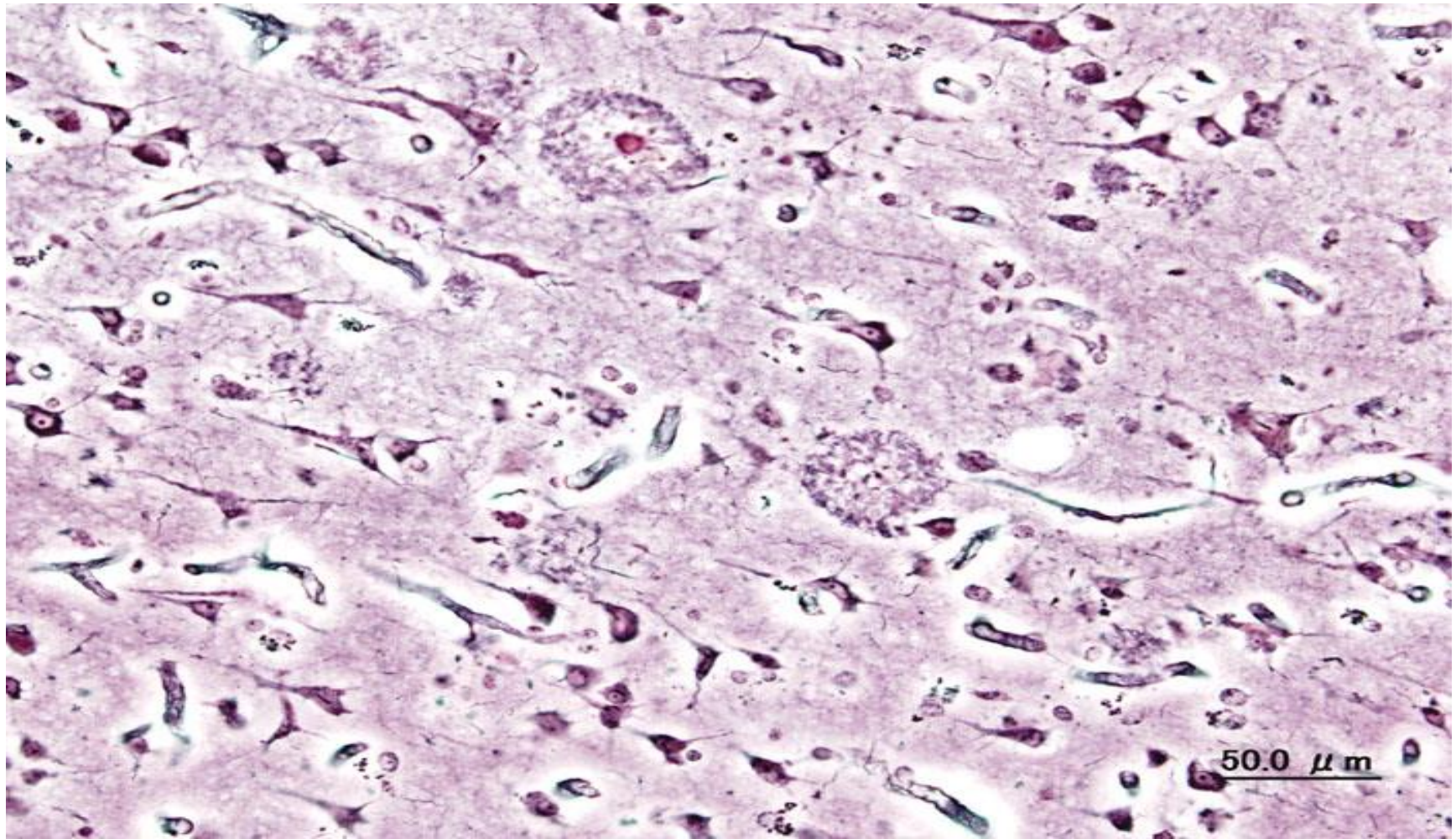
Senile plaques in cerebral cortex of person with Alzheimer's disease. (Silver impregnation)



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3. Tau Hypothesis - tau protein abnormalities initiate AD, whereby hyperphosphorylated tau pairs with other threads of tau forming neurofibrillary tangles inside nerve cell bodies.

- When this occurs, the microtubules disintegrate, collapsing the neuron's transport system, resulting in malfunctions in communication between neurons and later in cell death.

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- **More Details** - Every neuron has an interior cytoskeleton, partly comprised of microtubules that act like tracks, guiding nutrients and molecules from the body of the cell to the ends of the axon and back.

- The tau protein stabilizes the microtubules. In AD, tau undergoes chemical changes, pairing abnormality with other tau protein threads, creating neurofibrillary tangles, which disintegrate the neuron's transport system.

- This eventually leads to cell death.

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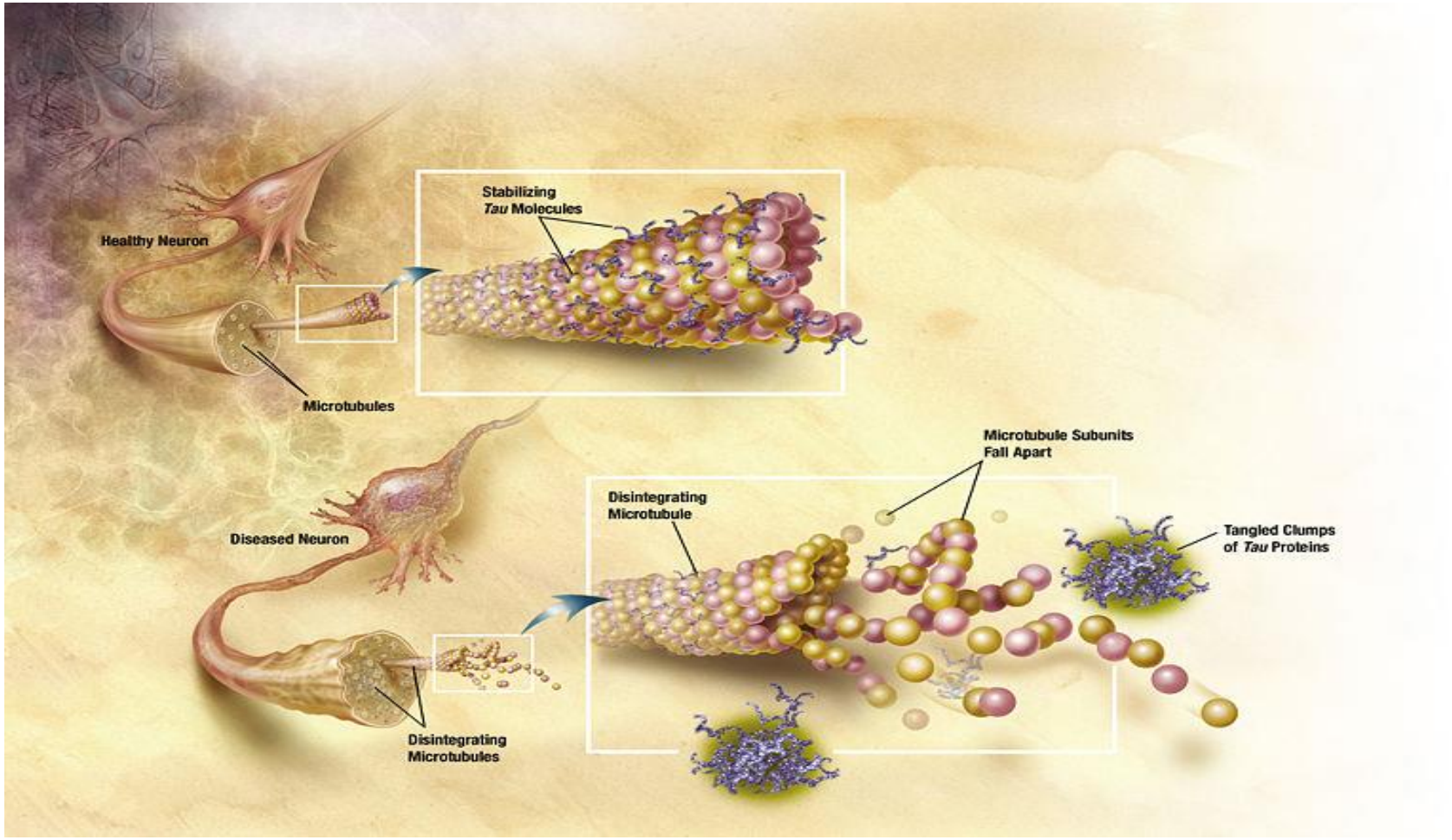
Changes in tau protein lead to neurofibrillary tangles in neurons and cell death



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Drugs For Alzheimer's Disease

Primarily acetylcholinesterase inhibitors, which reduce rate of acetylcholine breakdown:

1. Donepezil (*Aricept)*
2. Galantamine (*Razadyne*)
3. Rivastigmine (*Exelon* and *Exelon Patch)*

- Some what effective in mild to moderate AD, but are less likely to work as disease progresses

Common Side Effects

* Nausea and vomiting (10-20% of users) - linked to cholinergic excess (cholinergic syndrome)

Less Common Side Effects

- Muscle cramps
- Bradycardia
- Decreased appetite and weight
- Increased gastric acid production
- Tearing
- Increased Salivation

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Preserving Memory and Cognitive Function After Age 55

Brain and Memory – after age 55 there is a decline in brain synthesis of memory chemical and nerve transmission capacity.

Example of Memory Support Supplement:

CDP–choline – increases acetylcholine levels and maintains phospholipid structure of nerve cell membrane, enhancing nerve conduction

1. **Phosphatidylserine**- same role as CDP- choline
2. **Bacopa Monneiri** – brain antioxidant and maintains nerve conduction
3. **Huperzine A** – inhibits breakdown of acetylcholine (more specific than drugs and largely without side effects)

- Can't recommend these agents if patient taking Alzheimer's drugs due to risk of cholinergic syndrome (especially bradycardia)

Complete presentation on Nutritional Medicine in Alzheimer's disease is found in the Nutritional Medicine in Neurology Part 1 Section on the Global Integrative Medicine Academy Platform

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Part 20. Gout

Gout - a disease created by a buildup of uric acid in bloodstream

Crystals of monosodium urate or uric acid deposited on the articular cartilage of joints, tendons and surrounding tissues, causing inflammation and pain ((big toe, knee, elbow, ankle, hip, instep, wrist fingers, spine)

If untreated, the crystals form tophi, which can cause significant tissue damage.

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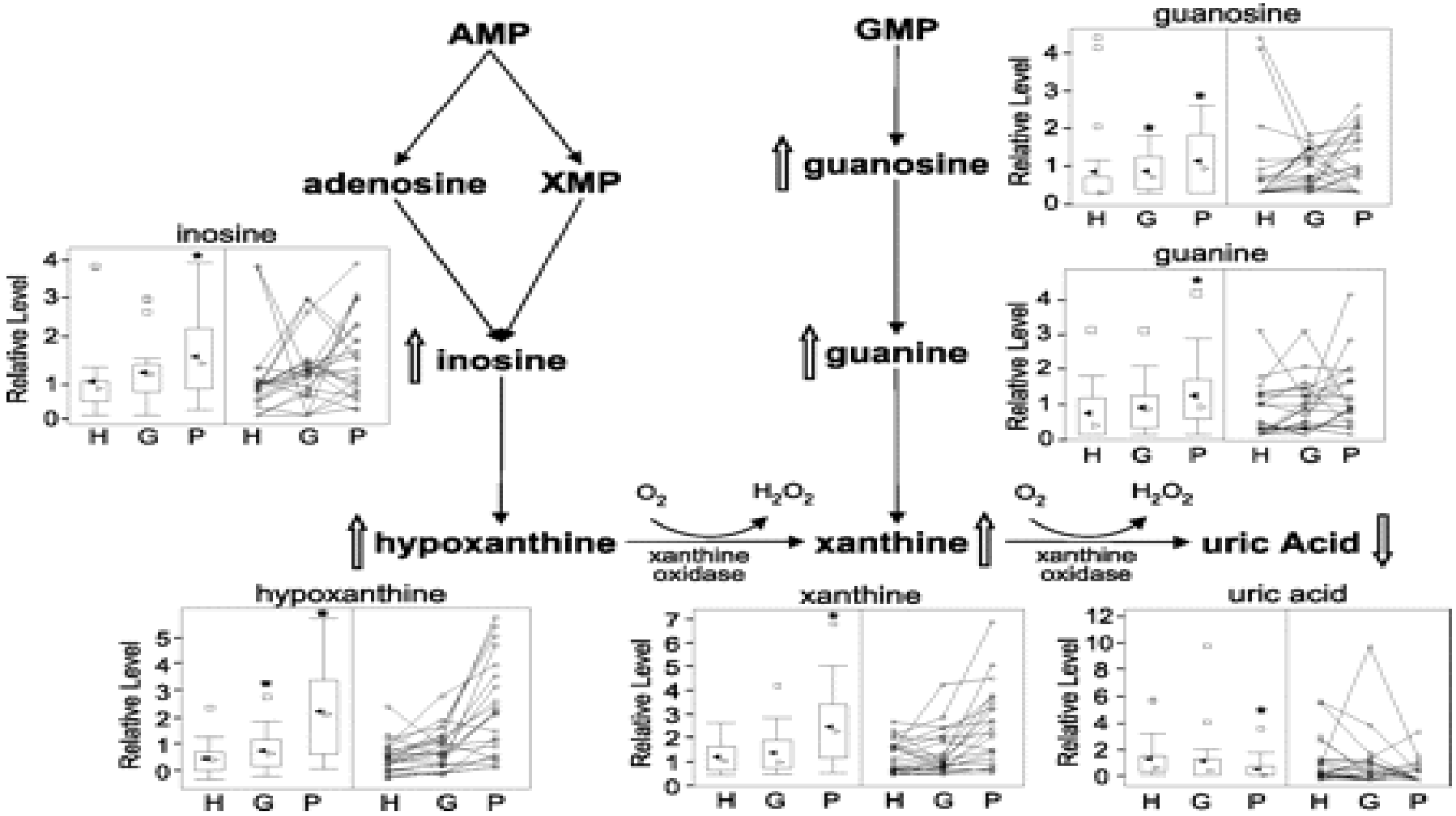
Purine Degradation Increases Uric Acid Production



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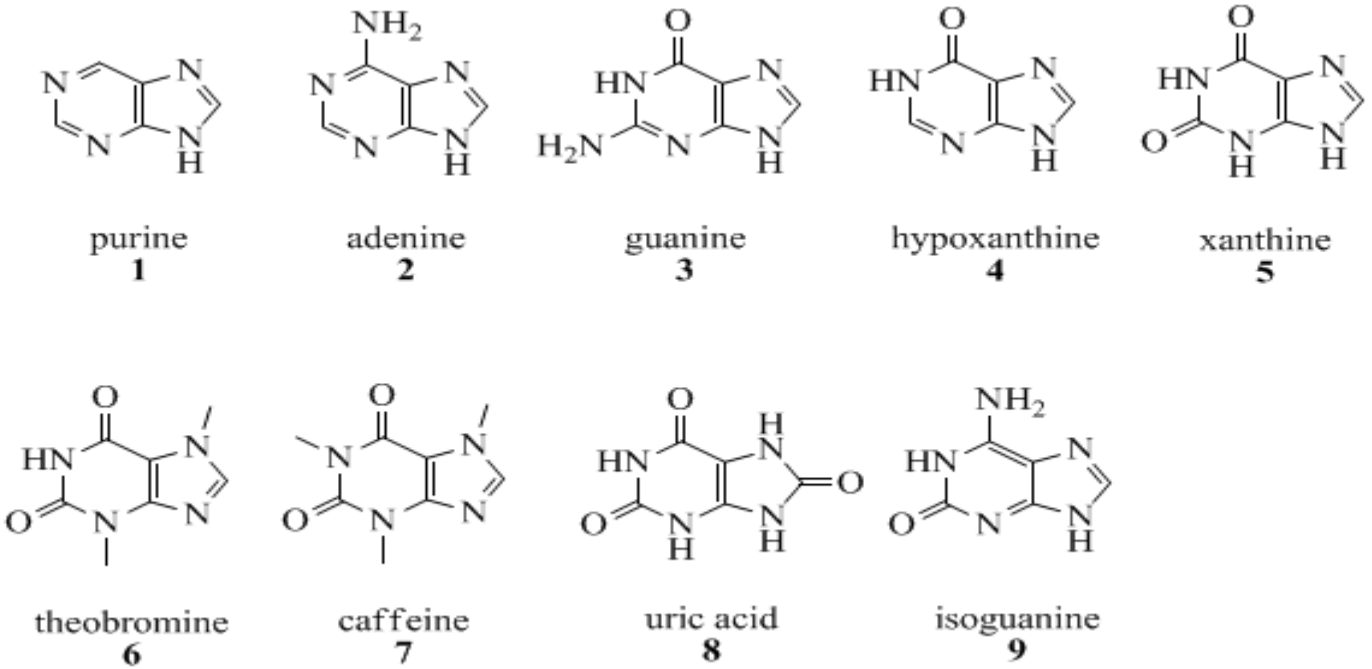
Common Purines: Note that caffeine is a purine that can interfere with excretion of uric acid



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Drugs To Treat Or Prevent Gout

1. Allopurinol - a xanthine-oxidase inhibitor, widely used to prevent attacks - blocks the conversion of xanthine to uric acid in purine metabolism

2. Uricosuric drugs (Probenecid and Losartin) - promote the renal excretion of uric acid.

In many cases, people are predisposed to gout because of insufficient renal excretion of uric acid.

Overproduction of uric acid is less common and often a result of another disease where rapid cellular replication occurs (e.g. hemolytic anemias, myeloproliferative and lymphoproliferative diseases, psoriasis)

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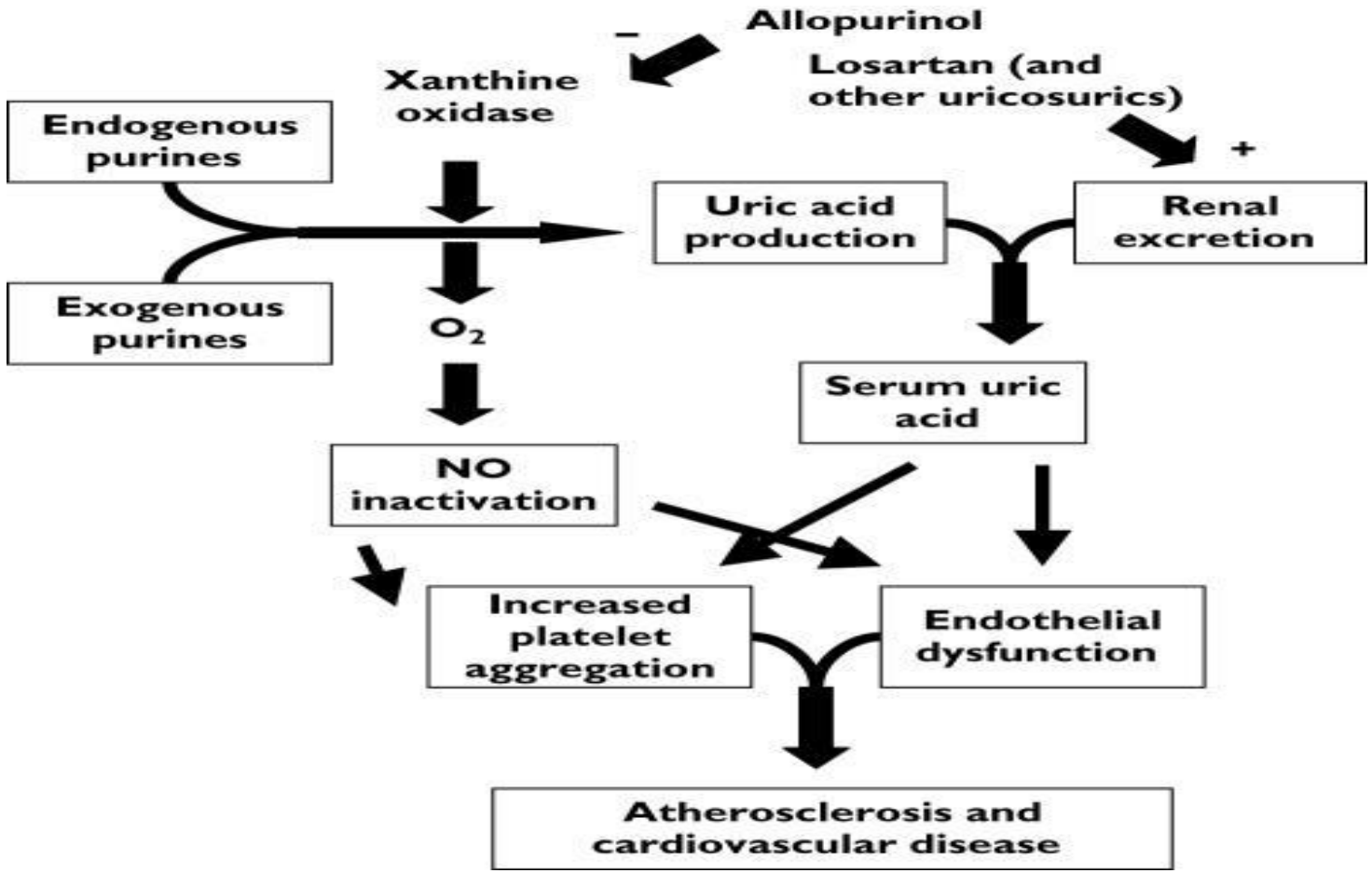
CVD Effects of Uric Acid

Br J Clin Pharmacol. 2006 December; 62(6): 633–644



3. Colchicine – inhibits inflammation induced by WBCs (anti-mitotic) and inhibits uric acid crystal deposition in tissues

4. NSAID's (other than aspirin) - indomethacin, naproxen, and sulindac (NSAID) are drugs of choice during an acute gouty attack. They have fewer side effects than the once popular colchicine

Note: Salicylic acid and high dose niacin compete with uric acid for renal excretion (ASA and white willow extract are contra-indicated). Vitamin C may increase excretion of uric acid

Nutritional Medicine in Gout management if found in the Nutritional Medicine in Arthritis, Autoimmune and Gout Section on the Global Integrative Medicine Academy Platform

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Part 21. Oral Contraceptives (Birth Control Pills)

Two Types:

1. Combined oral contraceptive pill contains estrogen and a progestogen (bind to progesterone receptors)
2. Progestagen only pill

Mechanisms Of Action:

- Estrogen (ethinyl estradiol) suppresses release of FSH, thereby inhibiting maturation of egg follicles in the ovaries

- Progestagen (norethindrone, levonorgestrel) suppresses release of LH, thereby inhibiting ovulation

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Some Common Oral Contraceptives:

Apri (same as Desogen and Ortho-Cept 28)
Aviane (same as Alesse-28)
Lessina (same as Levlite 28)
Necon (same as Ortho-Novum 1/35)
Ogestrel (same as Ovral)
Sprintec (same as Ortho-Cyclen-28)

Microgestin Fe (same as Loestrin Fe)
Kariva (same as Mircette)
Enpresse (same as Triphasil-28)

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Can be monophasic or biphasic:

Monophasic - same dose of estrogen and progestegan in all 21 active pills

Biphasic - provide varying doses of estrogen and progestagen during different stages of the menstrual cycle in an attempt to mimic the menstrual cycle or minimize side effects.

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Side Effects Acronym (ACHES)

A – Severe **Abdominal** Pain (this may related to liver, gallbladder disease or **thromboembolism in** hepatic vein or inferior vena cava)

C – Severe **Chest** Pain and/or short of breath (pulmonary embolism or heart attack)

H – Severe **Headache** (exacerbation of migraines)

E – **Eye** Problems (vision loss or blurring, speech problems – retinal or cerebrothrombosis)

S – **Severe** Leg Pain (deep vein thrombosis)

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Blood Clots - estrogen increases synthesis and release of fibrinogen from the liver to the bloodstream, thereby increasing clotting behavior and risk of thrombosis and thromboembolic disease.

Newer birth control pills, which have 35 ug of ethinyl estradiol are less risky in this regard compared to earlier versions that contained at least 50 ug of ethinyl estradiol per pill.

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Vitamin C and Birth Control Pills – 1000 mg of vitamin C supplementation can raise ethinyl estradiol levels by inhibiting liver detoxification enzymes that degrade this synthetic estrogen.

Thus, vitamin C should not be taken 4 hours prior or 4 hours after ingestion of oral contraceptives containing ethinyl estradiol

St. John's wort – can increase birth control detoxification, and thus increase risk of pregnancy while on the pill

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Part 22. Anti-Convulsant Drugs (Anti-Seizure, Anti-Epileptic)

General Remarks - The goal of anticonvulsant is to suppress rapid and excessive firing of neurons that start a seizure.

Failing this, a good anticonvulsant prevents spread of seizure within brain and offers protection against possible brain damage.

Clinical Application:

Epilepsy and Seizures

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Different Classes Of Anti-Convulsant Drugs:

1. Hydantoins – **increase seizure threshold** triggered by environmental changes or excessive stimulation

Examples:

- *Phenytoin (Dilantin)
- Mephenytoin
- Fosphenytoin

2. GABA Analogs – increase brain levels of GABA, which are inhibitory neurotransmitters

Example:

Valproic acid – also used as a mood stabilizer in bipolar depression

3. Carbamazepine – act in a similar fashion as hydantoins

Examples:

- Carbamazepine
- Oxcarbazepine

4. Barbiturates- decrease nerve transmission

Examples:

Phenobarbital

5. High CBD Medicinal Marijuana Products also show promise in seizure control

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Adverse Side Effects – many minor symptoms depending on drug-type used.

Note: Dilantin and related anti-convulsant drugs reduce Vitamin D status (decrease conversion of cholecalciferol to 25 hydroxycholecalciferol in the liver), and thus, vitamin D and calcium supplementation should be administered in these cases, with monitoring of vitamin D blood levels.

These patients require bone density testing periodically (often overlooked)

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Part 23 - Drug-Nutrient Interactions

Drug-Nutrient Interactions And Important Contra-Indications and Precautionary Measures Regarding Supplement Recommendations

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Six Biggest Concerns with Drug-Nutrient Interactions:

1. Bleeding Disorders
2. Brain Chemistry Imbalances (serotonin and cholinergic syndromes)
3. Adverse Cardiovascular Effects: Heart muscle (myocardial) dysfunction and Hypertension
4. Internal Organ Damage and/or toxicity (Liver and Kidneys) and Related Effects
5. Adverse Immune Effects
6. Glucose Intolerance

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1. Bleeding Disorders

A number of herbal and vitamin supplements, when ingested at or above specific dosages, are known to have anti-coagulant effects.

In certain instances, these products taken alone, or in combination with other anti-coagulant drugs have resulted in bleeding disorders

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A. Ginkgo Biloba Extract

Ginkgo biloba extract contains active ingredients known to decrease platelet aggregation.

Case 1: ASA plus Gingko (40 mg twice per day resulted in bleeding into the iris after one week)

Case 2: Warfarin plus Ginkgo (no dosage reported)

Case 3: Ginkgo alone (Bilateral subdural hematoma) – 60 mg twice daily

Case 4: Ginkgo alone – (subdural hematoma) – 50 mg, three times daily

- These bleeding episodes stopped in all cases reported above after Ginkgo was discontinued.

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B. Garlic

Garlic contains disulfide compounds (e.g. ajoene) that:

1. Decrease platelet aggregation
2. Increase fibrinolytic activity

Case 1 - Elderly man ingesting 2,000 mg of garlic (4 cloves) daily for an undetermined period of time, developed a spontaneous epidural hematoma (the patient denied use of any anti-clotting medication or anti-inflammatory).

Case 2 - A patient taking garlic prior to cosmetic surgery experienced bleeding complications and had a clotting time of 12.5 minutes. After cessation of garlic consumption, her clotting time dropped to 6 minutes and there were no complications during a second procedure.

As such, S. Mills and K Bone suggest that garlic intake and garlic supplementation should be discontinued 10 days prior to surgery. This also applies to Vitamin E (or any vitamin E containing supplements, as well as other anti-coagulant natural substances)

- N.B. Equivalent of one clove of garlic reduces platelet aggregation to the same degree as one aspirin (Ajoene content appears to be most responsible for anti-coagulant properties of garlic.

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Don’t recommend Garlic if patient taking:

1. NSAIDs
2. Plavix
3. Coumadin
4. Warfarin
5. Any other anti-coagulant medication

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C. Ginseng

- One case report of ginseng altering prothrombin time (INR).

- Ginseng antagonizes the effects of warfarin, **decreasing prothrombin time,** which returns to normal with discontinued use of ginseng.

D. Angelica Species (Dong Quai, e.g.,)

Case - A 46-year-old woman taking warfarin experienced increased strength of the anticoagulant properties of the drug after starting to use dong quai for menopause. Her bleeding tendency returned to normal after discontinuing the dong quai.

- Dong quai contains at least six coumarin derivatives, which decrease platelet clotting function and increase risk of photosensitivity-induced dermatitis

Other Coumarin-containing herbs Used by Women:

1. Licorice – may also increase blood pressure due to presence of glycyheritinic acid

2. Red Clover – may also increase photosensitivity-induced dermatitis and bleeding disorders.

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E. Coenzyme Q10 Supplementation

Cases - 4 case reports where CQ10 supplementation has interfered (countered) with the ant-coagulant effects of warfarin on prothrombin time (increases clotting)

- Coenzyme Q10 molecule resembles vitamin K and thus, may have procoagulant tendencies as a result

- Taking CoQ10 with anticoagulant requires monitoring of INR

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F. Cranberry

Cases - at least five case reports suggesting that cranberry juice increases the activity of warfarin, possibly by inhibiting the breakdown of warfarin in the body.

Because of this potential interaction, people taking warfarin should avoid, or limit the intake of, cranberry juice.

Women taking cranberry extract supplements to prevent urinary tract infections require INR monitoring if taking an anticoagulant drug

G. Devil's Claw

Case - was associated with purpura (bleeding under the skin) in a patient treated with warfarin.

People taking warfarin should avoid taking devil's claw. The harpogoside content may potentiate the effect of warfarin

Devil's claw has also re-activated old peptic ulcers.

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H. St John's Wort (Hypericum perforatum) – may upregulate detoxification enzymes

- According to a preliminary report, volunteers taking 900 mg per day of St. John's wort were given a single dose of an anticoagulant similar in action to warfarin. There was a significant drop in the amount of the drug measured in the blood.

- Seven case studies reported to the Medical Products Agency in Sweden also found a decrease in the anticoagulant activity of warfarin when St. John's wort was taken at the same time. This may have occurred because constituents in St. John's wort activate liver enzymes that are involved in the elimination of some drugs.

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Other Popular Natural Health Products – potentially affecting prothrombin time (no human cases yet reported)

1. **Ginger** – gingerols exhibit anti-platelet clotting properties
2. **Feverfew** – parthenolide exhibits anti-clotting properties
3. White Willow Bark Extract – contains salicylic acid. At low concentration (15% std grade) studies do not demonstrate an anti-platelet clotting tendency
4. Turmeric – curcumin affects prostaglandin synthesis
5. Essential oils (Borage, Flaxseed, Fish oil) – Omega-3 fats decrease platelet clotting behavior via effects PG-3
6. Vitamin E - Safe up to 400 I.U. per day in conjunction with warfarin or aspirin. Testing at 800 I.U. and 1,200 I.U. per day yield equivocal results on safety with respect to altering the INR
7. Bromelain enzymes – may decrease platelet clotting tendency and increases fibrinolysis
8. Papain enzymes – these proteolytic enzymes may also potentiate the effect of warfarin]
9. Saw Palmetto

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2. Brain Chemistry Effects

A. **Ginseng** and MAOI Anti-depressants – reports of mania behavior (headache, euphoria, CNS stimulation and tremors)

B. **Valerian Root** – excessive sedation if taken concurrently with barbiturates or anti-histamines.

Valerian should be avoided by patients taking benzodiazepines, barbiturates, opiates, anti-histamines and alcohol, as their effects may be prolonged and/or amplified.

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C. Mild Serotonin Syndrome

St. John's Wort, and possibly 5-Hydroxytryptophan can increase brain levels of serotonin and thereby potentiate the effects of:

- Serotonin reuptake inhibitors (SRRI) (e.g. Prozac)
- Monoamine oxidase inhibitors (MA0)
- Tricyclic Antidepressants (TAD)

Although 5-HTP can be used if proper monitoring is in place. It may enhance drug effect and patient outcomes.

In this instance there is an increased risk of serotonin syndrome, which involves the following signs and symptoms:

1. Muscle rigidity
2. Hyperthermia
3. Autonomic instability
4. Mental confusion
5. Myoclonus
6. Delerium
7. Coma

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D. **Coma From Kava**

Kava plus alprazolam (benzodiazepine) has induced coma.

It is imperative not to recommend Kava or Valerian supplements in combination with any drugs that induce a sedative or anti-anxiolytic effect.

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E **Seizures and Ma Huang (ephedra)**

- Ma Huang (ephedra) can induce seizures in otherwise normal individuals

- It should not be used by epileptics.

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F. **California Poppy and Opioid Drugs**

As the alkaloids from California poppy also bind to opioid and serotonin receptors, this drug-nutrient combination may potentiate effects of opioids and cause coma or depressed respiration, with life-threatening consequences.

California poppy can be used as night-time medication in place of opioid dose to help with sleep in patients with night-time pain induced insomnia

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3. Heart Muscle Dysfunction

A. Digitalis/Digoxin Toxicity

- **Hawthorn and Ginseng** are known to potentiate the action of other cardioglycoside medications, such as digitalis/digoxin (elevates serum digoxin levels)- very dangerous situation.

- Ginseng slows drug detoxification in liver

- Hawthorn increases cyclic AMP, increasing force of contraction of the heart (as does digitalis via increased intracellular calcium)

B. Hypertension and Licorice

- Licorice root alone or in combination with tricyclic antidepressants can elevate blood pressure.

- Licorice root also affects renin-angiotensin-aldosterone system and has produced hypokalemia leading to heart arrhythmias and as well as hypertension. This effect is caused by glycyrrhizin or glycyhrrhitinic acid.

- DGL chewable tablets contain deglycyrrhizinated licorice, which does not affect heart or blood pressure, as it heal ulcers

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Side Note - Most of the Licorice candy available in North America is flavored with anise oil, not Licorice.

- Authentic Licorice candy contains between 0.26 mg/g and 7.9 mg/g of glycyrrhizin; while medicinal Licorice products range from 0.30 mg/g to 47.1 mg/g of glycyrrhizin.

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C. Heart Attack and Sudden Death From Ephedra:

- **Ma Huang** (ephedra) has caused sudden death from heart attack, tachycardia, stroke and myocardial arrhythmias when taken alone

N.B.: The most commonly reported herbal product to produce adverse reactions with more than 17% of all adverse reactions reported dealing with side effects from Ma Huang (over 800 reports)

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- As a result the FDA proposed limits on the use of ephedrine-containing products: a maximum of 8 mg/dose and 24 mg/day for no more than a week, and combined with no products that contain caffeine.

- The Drug Enforcement Agency proposed that products containing over 2% ephedrine be subject to the Controlled Substances Act. Individuals with cardiovascular or thyroid disease and diabetes should avoid these products altogether, as should those consuming caffeine, theophylline, cardiac glycosides, and monoamine oxidase (MAO) inhibitors

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D. **Glucosamine and Hypertension**

In rare instances glucosamine supplementation has increased blood pressure marginally. In patients with a blood pressure above 130/80 or those on anti-hypertensive drugs, blood pressure should be monitored during the first few week of glucosamine supplementation.

The mechanism of action has not be elucidated, but the presence of sulfate is not responsible in glucosamine sulfate. Glucosamine sulfate does not contain sodium contrary to myths promoted by certain supplement companies.

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4. Internal Organ Damage and Related Effects

A. St. John's Wort

- Can reduce action of concurrent medications because it accelerates liver detoxification centers (i.e., digoxin, theophylline, cyclosporine, phenprocouman (longer acting coumarin type drug)

- Increases risk of photosensitivity-induced dermatitis.

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B. Kava Kava

- Long-term use can produce abnormal liver function tests, yellow scaly rash and increased cholesterol.

- A total of 11 patients who used kava products had liver failure and underwent subsequent liver transplantation . On March 25, 2002, in response to five such case reports (four in Europe and one in the United States), the Food and Drug Administration (FDA) issued a consumer advisory and subsequently completed an investigation already underway of a similar U.S. case.

- This report presents the investigation of the two U.S. cases of liver failure associated with kava-containing dietary supplement products and summarizes the European cases.

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C. Radioactive Iodine Therapy and Kelp – human cases have shown that patients receiving radioactive iodine to treat thyroid cancer (or Grave's Disease) should not take Kelp or any form of iodine supplementation (and prescribed a low iodine diet).

- Iodine from supplements (like Kelp) can compete with radioactive iodine for uptake by thyroid cells (and thyroid cancer cells), decreasing the effectiveness of the treatment.

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D. **Vitamin A and Accutane**

Any supplement dosage of Vitamin A above 2500 IU per day should be discouraged in patient taking Accutane for acne treatment. Vitamin A can increase risk of side effects:

Liver Damage – rising liver enzymes

High Lipids

Headaches etc.

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5. Adverse Immune Effects

Echinacea

Can exacerbate autoimmune conditions through overstimulation of the immune system (possibly Ginseng and Astragalus as well)

6. Glucose Intolerance

Glucosamine Sulfate

- Experimental studies and a few human reports suggest that there is a potential for Glucosamine supplementation to increase insulin resistance in a diabetic or pre-diabetic patient.
- As such, diabetic (both type 1 and 2) and prediabetic patients should have their blood glucose monitored during the first month of glucosamine supplementation.

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Other Consideration:

1. Zinc Toxicity in Macular Degeneration Rx and Treatment of Colds and Sore Throat:

- Some supplements used therapeutically to help manage macular degeneration, contain high doses of zinc. You must be careful not to cause zinc toxicity by providing additional zinc from a multiple vitamin (or other vitamins or functional drinks or bars) that together result in total zinc supplementation at or above 60 mg/d, which is threshold level at which some people show signs of zinc toxicity. Many supplements used to treat macular degeneration contain 40 – 70 mg of zinc in the daily dosage.

- Zinc toxicity can occur in both acute and chronic forms. Acute adverse effects of high zinc intake include nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, and headaches. One case report cited severe nausea and vomiting within 30 minutes of ingesting 4 g of zinc gluconate (570 mg elemental zinc) e.g. treat sore throat.

- Intakes of 150–450 mg of zinc per day associated with such chronic effects as low copper status, altered iron function, reduced immune function, and reduced levels of high-density lipoproteins.

- Reductions in a copper-containing enzyme, a marker of copper status, have been reported with even moderately high zinc intakes of approximately 60 mg/day for up to 10 weeks.

- Zinc dosage used in the AREDS study (80 mg per day of zinc in the form of zinc oxide for 6.3 years, on average) has been associated with a significant increase in **hospitalizations for genitourinary causes**, raising the possibility that chronically high intakes of zinc adversely affect some aspects of urinary physiology.

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FDA (U.S.A.): Special Nutritionals Adverse Event Monitoring System

(searchable database of MedWatch: http://vm.cfsan.fda.gov/`dms/aems)

Of the limited number of dietary supplement adverse event reports to the FDA in 1998:

- 7% involved St. John's Wort
- 8% involved Ginkgo Biloba
- ≥17% involved ephedra-containing products; 800 reports of adverse effects:
  - Nervousness
  - Insomnia
  - Irritability
  - Psychosis
  - Headache
  - Dizziness
  - Seizures
  - Stroke
  - Premature ventricular contractions
  - Increased Blood Pressure
  - Myocardial Infarction (heart attack)
  - Death

Final Considerations: Herbal products should be discontinued 2 weeks before elective surgery, and their use reported to the anesthesiologist before any surgical procedure because of the potential for unexpected effects

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Final Note: We will explore the main actions of chemotherapy and cancer treatment drugs in the Adjunctive Nutritional Management of Cancer section on this platform:

- Anthracyclines
- Alkylating Agents
- Anti-Mitotics
- Biologics (Monoclonal Anti-bodies, Vaccines, Immunotherapies)
- Methotrexate
- Off-label Use of Certain Drugs
- Insulin-Potentiation Therapy

Exam Questions:

- Therapeutic Action of Drug Class
- Clinical Applications
- Major Side Effects
- Drug-Nutrient Interactions