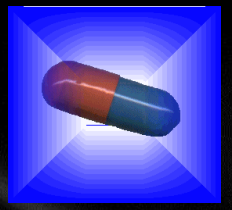

General Coronary Artery Disease and Stable Exertional Angina

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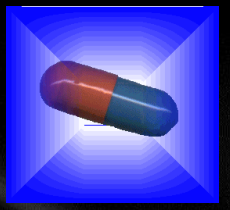


General Coronary Artery Disease and Stable Exertional Angina

Definition

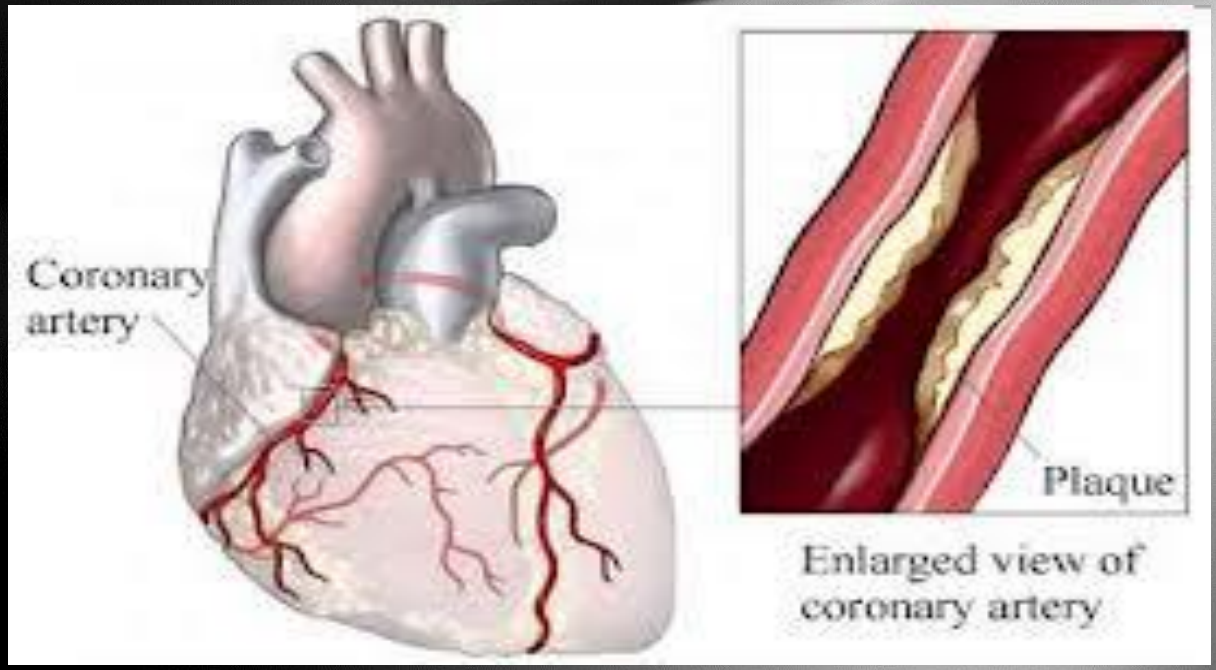
- Coronary artery disease (CAD) is most commonly defined as a >50% luminal stenosis of any epicardial coronary artery.
- Chronic stable angina is the typical manifestation of ischemic heart disease in nearly half of patients with CAD.

Epidemiology

- CAD is the leading cause of morbidity and mortality in Western Society.
- Prevalence of CAD in the United States was 7.6% as of 2006.
- CAD was responsible for 35.3% of all U.S. deaths in 2005.
- An estimated 785,000 Americans will have a first MI and 470,000 will have a recurrent MI in 2009. Another 195,000 will have a silent MI.

Etiology

- CAD most commonly results from luminal obstruction by **atheromatous** plaque.
- Other causes include congenital coronary abnormalities, myocardial bridging, vasculitis, prior radiation therapy, cocaine use, aortic stenosis, hypertrophic cardiomyopathy, coronary vasospasm, spontaneous coronary dissection, and syndrome X.



Pathophysiology

- CAD manifestations include stable angina, ACS, CHF, sudden cardiac death, and silent ischemia.
- ACS represents a continuum of clinical presentations ranging from UA to ST-segment elevation MI (STEMI). ACS most often results from acute thrombosis of a coronary artery at the site of atheromatous plaque rupture or ulceration.
- Stable angina most often results from fixed coronary lesions that produce a mismatch between myocardial oxygen supply and demand. This mismatch is accentuated by increasing cardiac workload.
- Anginal symptoms usually develop when a fixed stenosis reaches 70% or greater. In the setting of increased myocardial demand or diminished oxygen supply, the fixed stenosis does not permit adequate distal perfusion and ischemia results, manifesting itself as angina.

Risk Factors

- **Hypertension**
- **Diabetes mellitus**: 2-4 times. Insulin resistance (such as metabolic syndrome).
- **Obesity** associated with additional cardiac risk factors, including *hypertension, diabetes, and lipid abnormalities*. A BMI of >25 kg/m^2 (overweight) & >30 kg/m^2 (obese).
- **Dyslipidemia**: ↑LDL, ↓ HDL, and ↑ triglycerides.
- **Family history of premature CAD**: 1ST degree male relative with CAD before age 55 or female relative before age 65.
- **Tobacco use** is associated with a marked increase in risk of CAD. The risk is reversible and smoking cessation restores the risk of CAD to that of a nonsmoker within approximately 15 years (Arch Intern Med 1994 Jan 24;154(2):169–175).

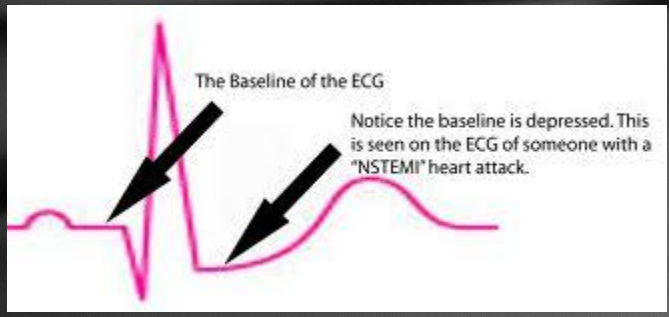
Prevention

- **Aspirin** (75 to 162 mg/d) should be considered in patients at higher risk of cardiovascular events (>10% risk of stroke or MI over 10 years). Aspirin has recommended to use for men aged **45 to 79** and women aged **55 to 79**
- **Regular cardiovascular risk assessment** commencing at age 20 and recurring every 5 years. The Framingham Risk Score is a commonly used algorithm for estimating risk of CAD.

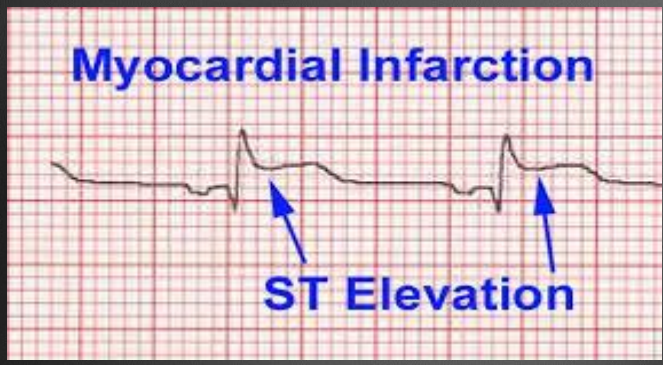
- **Risk factor modification** including *tobacco cessation*, *treatment of hypertension, diabetes, obesity, and lipid control*.
- **Initiation of statin therapy** may limit the risk of developing CAD in addition to subsequent MI and cardiac mortality in select patients who have an elevated CRP.
- **Current exercise guidelines** recommend a minimum of 30 minutes of moderate-intensity aerobic physical activity 5 days per week in addition to activities of daily living (Circulation 2007;116:1081–1093).
- **Hormone replacement therapy** is **not** indicated for either primary or secondary CAD prevention in postmenopausal women.

Associated Conditions

- **Stable angina**
- **Unstable angina**
- **Non–ST-segment elevation MI (NSTEMI)**



- **ST-segment elevation MI**



- **Congestive heart failure**

Diagnosis

Clinical Presentation

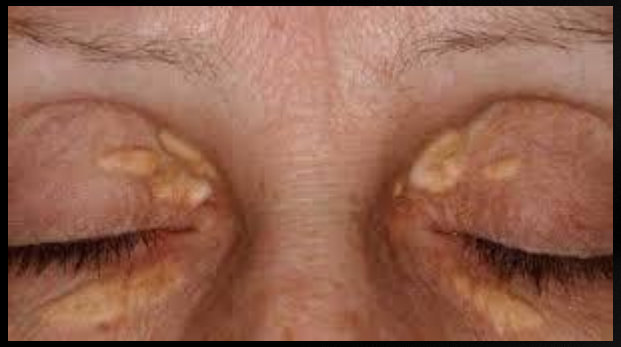
- **Typical Angina:** has three features: **(i)** substernal chest discomfort or heaviness with a characteristic quality and duration that is **(ii)** precipitated by stress and **(iii)** relieved by rest or nitroglycerin(NTG).
- **Atypical angina** has two of these three features.
- **Noncardiac chest pain** meets one or none of these characteristics.
- **The severity of angina** may be quantified using the Canadian Cardiovascular Society (CCS) classification.
- **Associated symptoms** may include *dyspnea, diaphoresis, nausea, vomiting, and dizziness.*
- **Female patients** and those with **diabetes** or **chronic kidney disease** may have minimal or atypical symptoms that serve as anginal equivalents. Such symptoms include *dyspnea, epigastric pain, and nausea*.

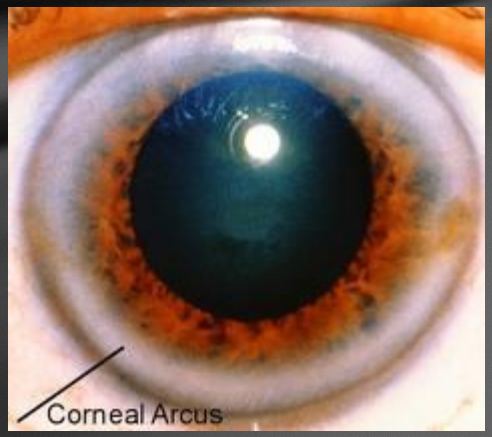
A careful history usually provides sufficient information to establish an appropriate pre-test probability of CAD.

In men and older women, the presence of typical angina in association with other cardiac risk factors is strongly predictive of CAD

Physical Examination

- **Clinical exam** should include *measurement of BP*, *heart rate*, & *arterial pulses*.
- **Cardiac exam** findings including *murmurs* & *gallops* are of high importance.
- **Clinical stigmata** of *hyperlipidemia* such as corneal arcus and xanthelasmas should be noted.





- **Signs of heart failure** including an S3 gallop, rales on lung exam, elevated jugular venous pulsation, and peripheral edema may also be present.

Differential Diagnosis

- A wide range of disorders may manifest with chest discomfort and may include both cardiovascular and noncardiovascular etiologies
- A careful history focused on cardiac risk factors, physical exam, and initial laboratory evaluation usually narrows the differential diagnosis.
- Despite these efforts, further diagnostic testing is often required to determine the likelihood of CAD.

Diagnostic Testing

1. Exercise stress testing (ETT)
2. Stress testing with imaging
3. Myocardial perfusion imaging.
4. Echocardiographic imaging.
5. Magnetic resonance perfusion imaging.
6. Pharmacologic stress testing

Treatment

The major goal of treatment

- to prevent MI,
- cardiac death,
- to reduce symptoms.

The recommended strategy for management of stable angina

- A combination of lifestyle modification,
- medical therapy,
- coronary revascularization

Aims of Medical treatment

- improving myocardial oxygen supply,
- reducing myocardial oxygen demand,
- controlling exacerbating factors (anemia, valvular disease),
- limiting the development of further atherosclerotic disease.

›

Medical Treatment

- **Aspirin** (75 to 162 mg/d) reduces cardiovascular events including repeat revascularization, MI, and cardiac death by approximately 33%.
  - *Aspirin desensitization* may be performed in selected patients with aspirin allergy.
  - *Clopidogrel* (75 mg/d) can be used in patients who are allergic or intolerant of aspirin.
  - *Dual therapy with aspirin and clopidogrel* may reduce the incidence of adverse cardiac outcomes in high-risk patients such as those with a prior MI.
- **β -Adrenergic antagonists** to control anginal symptoms by *decreasing heart rate* and *myocardial work leading to reduced myocardial oxygen demand.*

– The dosage in a resting heart rate of 50 to 60 bpm.

– Use of β-blockers is **contraindicated** in patients with severe active bronchospasm, significant AV block, marked resting bradycardia, or poorly compensated HF.

– β -Blockers may worsen coronary vasospasm and should be avoided in such patients.

Calcium channel blockers

can be used either in conjunction with/or β-blockers in the presence of contraindications or adverse effects.

- often used in conjunction with -blockers if the latter are not fully effective at relieving anginal symptoms.
- Both long-acting dihydropyridines and nondihydropyridine agents can be used.
- effective agents for the treatment of coronary vasospasm.
- The use of short-acting dihydropyridines (nifedipine) should be avoided due to the potential to increase the risk of adverse cardiac events

Nitrates

- *long-acting* formulations for chronic use or sublingual preparations for acute anginal symptoms (adjunctive antianginal agents).
- Sublingual preparations should be used at the first indication of angina or prophylactically before engaging in activities that are known to precipitate angina. Patients should seek prompt medical attention if angina occurs at rest or fails to respond to the third sublingual dose.

Nitrate tolerance resulting in reduced therapeutic response may occur with all nitrate preparations.

The institution of a nitrate-free period of 10 to 12 hours (usually at night) can enhance treatment efficacy.

ACE inhibitors

- reduction of exercise-induced myocardial ischemia in patients with stable angina and normal LV function receiving optimal -blocker therapy.
- ACEI therapy in high-risk patients with vascular disease or diabetes and at least one other cardiovascular risk factor reduced the rate of death, MI, or stroke.

Ranolazine

is a novel antianginal agent that does not depend upon reductions in heart rate or BP. Its exact mechanism of action is unknown; however, it appears to have effect on cardiomyocyte metabolism and sodium ion channel function. It has shown benefit in the symptomatic relief of refractory angina.

Cholesterol-lowering agents

including *statins, fibrates, bile acid sequestrants, and niacin* reduce recurrent events and improve overall outcome in patients with established CAD.

- HMG-CoA reductase inhibitors (statins) are the best studied agents and have been shown to limit atherosclerotic burden and reduce cardiac outcomes in patients with CAD.
- Recent studies have demonstrated that more intensive statin therapy is superior in preventing cardiovascular outcomes.

Coronary revascularization

- In general, medical therapy with at least two, and preferably three, classes of anti-anginal agents should be attempted before this approach is considered a failure and coronary revascularization pursued.
- In patients with stable angina and preserved LV function, medical therapy results in similar cardiovascular outcomes when compared to percutaneous coronary intervention (PCI). Of the patients who receive medical therapy only, there is a higher need for revascularization to control anginal symptoms.
- PCI and/or coronary artery bypass graft (CABG) surgery is indicated in patients who present with the following:

–Angina refractory to medical therapy
–Angina and reduced LV function
–Severe activity limiting angina (CCS class III–IV)
–Angina in the presence of left main or severe three-vessel CAD
–The choice between PCI and CABG is dependent on the coronary anatomy, medical comorbidities, and patient preference. CABG is preferred in diabetics with multivessel disease and LV dysfunction

The Syntax trial compared PCI versus CABG in patients with previously untreated three-vessel CAD or left main CAD. The study demonstrated an increased risk of major adverse cardiac and vascular events in the PCI group attributable to repeat intervention (Syntax: N Engl J Med 2009 March 5;360:961).

CABG carries a 1% to 3% mortality rate, 5% to 10% incidence of perioperative MI, and a small risk of perioperative stroke. The use of internal mammary artery grafts is associated with 90% graft patency at 10 years, compared with 40% to 50% for saphenous vein grafts. The long-term patency of a radial artery graft is 80% at 5 years. After 10 years of follow-up, 50% of patients develop recurrent angina or other adverse cardiac events related to late vein graft failure or progression of native CAD.

The risks of elective PCI include <1% mortality, a 2% to 5% rate of nonfatal MI, and <1% need for emergent CABG for an unsuccessful procedure. Patients undergoing PCI have shorter hospital stays and similar outcomes with respect to subsequent cardiac events and mortality compared to those undergoing CABG. PCI does have a higher rate of target lesion stenosis that can be minimized using drug-eluting stents (DES).

Alternative therapies

available for patients with chronic stable angina who are refractory to medical management and who are not candidates for further percutaneous or surgical revascularization.

Transmyocardial laser revascularization has been delivered by percutaneous and epicardial surgical techniques. Surgical transmyocardial laser revascularization has been shown to improve symptoms in patients with stable angina, although the mechanism that is responsible is controversial. No benefit has been demonstrated in terms of increasing myocardial perfusion or mortality.

Therapeutic angiogenesis is a novel approach that aims to facilitate the growth of collateral blood vessels by delivering proangiogenic growth factors (VEGF and FGF) to the myocardium. Small studies have suggested some benefit in exercise capacity and myocardial perfusion.

VI. NE System

Almost all NE pathways in the brain originate from the cell bodies of neuronal cells in the locus coereleus in the midbrain, which send their axons diffusely to the cortex, cerebellum and limbic areas (hippocampus, amygdala, hypothalamus, thalamus).

- **Mood: -- higher functions performed by the cortex.**
- **Cognitive function: -- function of cortex.**
- **Drive and motivation: -- function of brainstem**
- **Memory and emotion: -- function of the hippocampus and amygdala.**
- **Endocrine response: -- function of hypothalamus.**

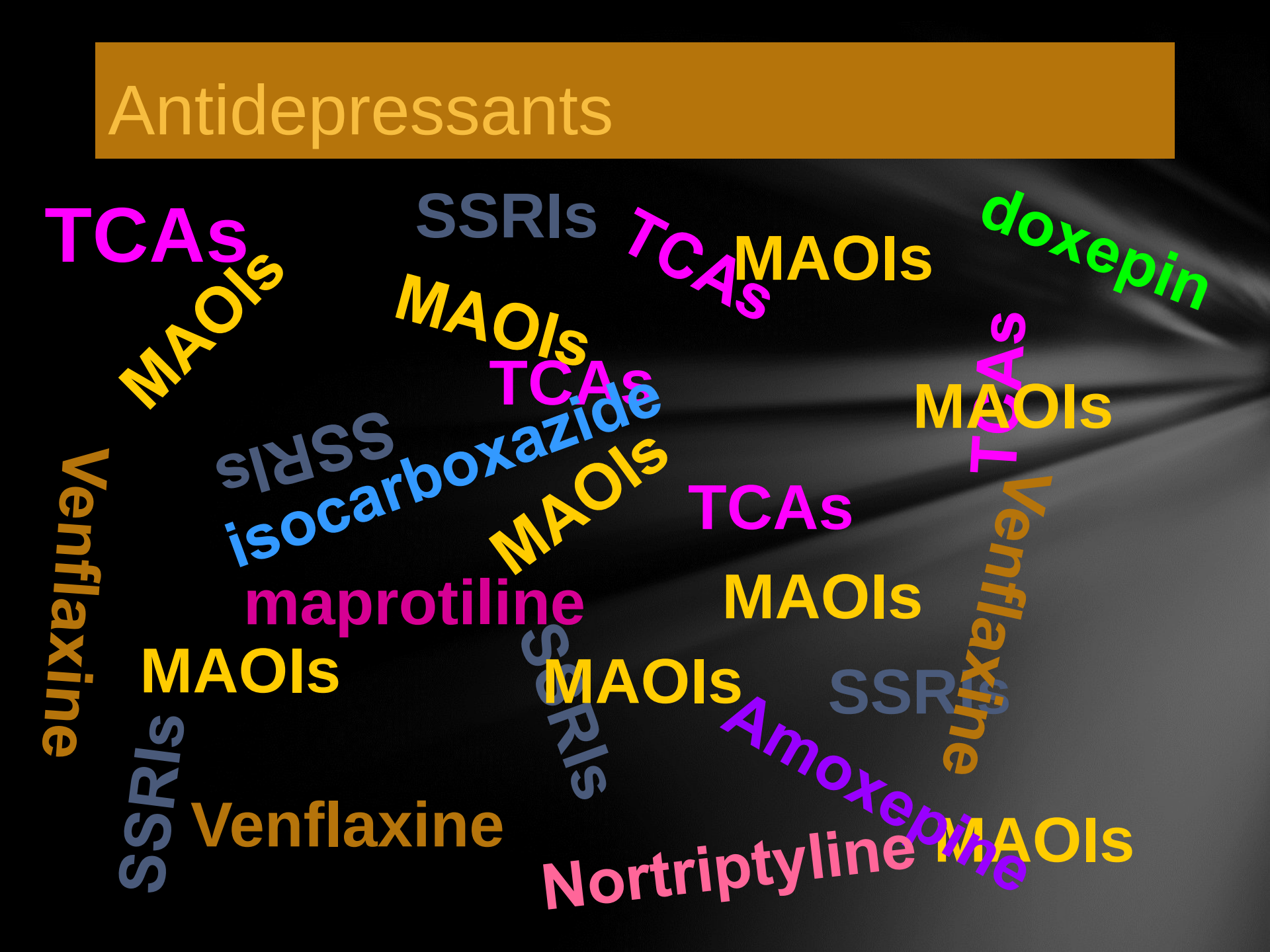
α and β receptors.

VII. Serotonin System

As with the NE system, serotonin neurons located in the pons and midbrain (in groups known as raphe nuclei) send their projections diffusely to the cortex, hippocampus, amygdala, hypothalamus, thalamus, etc. --same areas implicated in depression. This system is also involve in:

- **Anxiety.**
- **Sleep.**
- **Sexual behavior.**
- **Rhythms (Suprachiasmatic nucleus).**
- **Temperature regulation.**
- **CSF production.**

Antidepressants



Antidepressants

1. Tricyclic anti-depressants (TCAs).

   Imipramine, desipramine, nortriptyline,
   protryptyline, amytriptiline, doxepin,
   clomipramine, trimipramine, amoxapine.

2. Monoamine oxidase inhibitors (MAOIs).

   Isocarboxazid, phenelzine, tranylcypromine.

3. Selective serotonin reuptake inhibitors (SSRIs)

   citalopram ,Fluoxetine, fluvoxamine, sertraline,
   paroxetine, trazodone.

4. Miscellaneous anti-depressants (Others)

   bupropion HCL, mirtazapine, nefazodone, trazodone, venlafaxine
   alprazolam, maprotiline, nomifensine,
   mianserin (TeCA).

Mechanism of Action

1. Inhibition of NE and 5-HT reuptake.
   (TCAs, SSRIs, Newer TCAs).

2. Inhibition of MAO enzymes.
   (MAOIs).

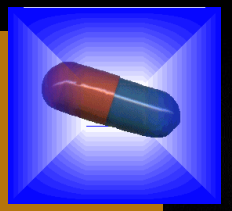
3. 5-HT_{2A} and 5-HT_{2C} antagonists.
   (Nefazodone, trazodone, mirtazapine)

4. Alteration of NE output .
   (Bupropion)

Tricyclic Antidepressants (TCAs)

- Characteristic three ring nucleus.
- Most are incompletely absorbed
- all are metabolized in liver(High first pass effect)
- High protein binding, high lipid solubility.
- **Imipramin & Amitryptaline** are the prototypical drugs
- Mixed NE & Serotonin inhibitors

Tricyclic Antidepressants (TCAs)



3°Amines: Imipramine, Amitriptyline

2°Amines: Desipramine, Nortriptyline

Selectivity 2° Amines -- NE ≥ 5-HT

3° Amines-- 5-HT ≥ NE

Tricyclic Antidepressants (TCAs)

Mechanism of Action:

- Inhibition of NT reuptake.
- Immediate action = >↑ NE and 5-HT in synapse.
- Takes up to 4 weeks for all TCA antidepressants to have an effect.

Tricyclic Antidepressants (TCAs)

Side Effects:

Atropine-like side effects: dry mouth, paradoxical excessive perspiration, constipation, blurred vision, mydriasis, metalic taste, urine retention => muscarinic blockade.

Orthostatic hypotension => α1-AR and possibly α2-AR blockade.

Drowsiness, sedation and weight gain => Histamine-Receptor blockade.

Tricyclic Antidepressants (TCAs)

Side Effects:

Most serious side effect is cardiac toxicity => Palpitations, tachycardia, dizziness => excessive CNS stimulation => ↑NE in Heart.

Sexual dysfunction, including loss of libido, impaired erection and ejaculation and anorgasmia

Tricyclic Antidepressants (TCAs)

Other effects:

Metabolism is affected by: Smoking, Barbiturates, estrogens, neuroleptics and anticonvulsants.

Can lower seizure threshold.

All TCAs can cause: vagal block, postural hypotension, arrythmias, sinus tachycardia.

All potentiate CNS depressants (BZDs, Barbiturates, ETOH) => coma and death.

TCA administration in bipolar disorder may precipitate acute mania.

Fatal in overdose (a 2 wk supply can kill anyone).

X. MAO INHIBITORS

- Isocarboxazid
- Phenelzine
- Tranylcypromine.

X. MAO INHIBITORS

Developed for the treatment of tuberculosis (iproniazid derivatives) - 1951.

These drugs are not widely used today, although a small number of patients appear to do better in MAOIs than TCAs or the newer drugs.

Are readily absorbed from GI tract and widely distributed throughout the body.

May have active metabolites, inactivated by acetylation.

Effects persist even after these drugs are no longer detectable in plasma (1-3 weeks).

X. MAO INHIBITORS

Mechanism of action:

Inhibit MAO enzymes (non-selective):

1) Irreversible MAO inhibitors

Phenelzine and isocarboxazid => hydrazides.

2) Reversible MAO Inhibitors.

Tranylcypromine => non-hydrazide,

prolonged blockade, but reversible within 4hr.

X. MAO INHIBITORS

Mechanism of action:

- **Hit and Run**
- **Sympathomimetic effect (Hypertension)**
- **Sympathetic ganglionic effect (Hypotension)**

X. MAO INHIBITORS

Wine-and-Cheese Reaction

- Fatal interaction with tyramine-containing foods (fermented foods in particular, such as wine and cheese).
- ↓ MAO-A => ↑ Tyramine in the body =>↑NE in circulation => induces hypertensive crisis => can lead to intracranial bleeding and other organ damage.

FOOD INTERACTIONS WITH MAOIs: cheese, Sour cream, Yogurt, Beef or chicken livers, Fermented meats, Beer, Win, Coffee, Tea, Yeast extracts, Colas containing caffeine, Chocolate.

X. MAO INHIBITORS

Negative drug interactions with:

Any drug metabolized by MAOs* including SSRIs, TCAs and meperidine, alcohol, CNS depressants, sympathomimetics, phenylephrine (O/C nasal decongestants), amphetamines, and other indirect-acting adrenergic drugs.

* Interaction with drugs metabolized by MAOs (e.g. Meperidine (opioid analgesics) => hyperpyrexia or “hyperexcitation syndrome” involving high fever, delirium and hypertension).

X. MAO INHIBITORS

Other side effects:

Hypotension

Hepatotoxicity.

Sedation.

XI. SSRIs

- Fluoxetine
- Sertraline
- Paroxetine
- Fluvoxamine

(Labeled for obsessive-compulsive disorder)

XI. SSRIs

Most widely prescribed drugs for depression.

They have few side effects and seem to be rather safe. More rational prescribing and better patient compliance.

Adverse effects include: Headache, nausea,

decreased libido, decrease sexual function (citalopram, fluoxetine & fluvoxamine).

Low threat for overdose. Suicide may be considered in severe depression.

XI. SSRIs

Mechanism of action:

- Specific serotonin uptake inhibitors increase 5-HT by inhibiting reuptake.

Current theory holds that:

- Enhanced stimulation or responsiveness of postsynaptic 5-HT_{1A} receptors is particularly important in the action of antidepressants.

XI. SSRIs

Drug-drug interactions:

dangerous with other antidepressant drugs, MAOIs in particular.

”Serotonin Syndrome”:

- hyperthermia, muscle rigidity, myoclonus, rapid changes in mental status and vital signs.

Thus it is important to wait up to 6 weeks after medication is stopped, before starting with another drug.

XII. Heterocyclics

2nd Generation heterocyclics

- amoxapine
- maprotiline
- trazodone
- bupropion

Third Generation heterocyclics

- mirtazapine
- venlafaxine
- nefazodone

XII. Heterocyclics

The second and third generation antidepressants are by no means a homogeneous group.

As with the TCA's , they all have variable bioavailability.

High protein binding.

Some have active metabolites.

Trazodone and Venlafaxine have the shortest plasma half-lives, which mandates divided doses during the day.

Nefazodone and fluvoxamine cause inhibition of CYP3A4.

XII. Heterocyclics

Mechanism of Action:

1) NT reuptake inhibition.

maprotiline.

2) 5-HT receptor antagonism (for 5-HT_{2A} or $_{2C}$ receptors).

nefazodone, mirtazapine, and trazodone

3) Alteration of NE Output.

bupropion, amoxapine, and trazodone.

XII. Heterocyclics

Amoxapine. Metabolite of Loxapine (an anti-psychotic) -- retains some antipsychotic activity and has similar side effect of TCAs.

Maprotiline. A tetracyclic drug, resembles desipramine with less sedative and antimuscarinic side effects. Evokes seizures at high doses. Blocks NT reuptake.

XII. Heterocyclics

Trazodone. Antagonist of 5-HT receptors**. Unpredictable efficacy. Highly sedative (hypnotic), but minimal antimuscarinic action.**

Bupropion. Resembles amphetamine. Blocks DA reuptake (not important in depression). Causes CNS stimulation. Inhibits appetite. Aggravates psychosis.

XII. Heterocyclics Third Generation

Mirtazapine. A derivative of mianserin. Antagonist of 5-HT receptors.

Venlafaxine. Short plasma half-live, thus needs to be given in divided doses. Potent inhibitor of 5-HT uptake and weaker at NE reuptake

Nefazodone. Antagonist of 5-HT

XII. Atypical/Heterocyclic

2nd Generation heterocyclics

- Amoxapine
- Maprotiline
- Trazodone
- Bupropion

★ Similar to TCAs

★ ⇑NE output

★ α2-AR antagonist

★ 5-HT antagonists

★ SSRI-like

Third Generation heterocyclics

- Mirtazapine
- Venlafaxine
- Nefazodone

Table 30–5. Adverse effects of antidepressants.

Tricyclics	
Sedation	Sleepiness, additive effects with other sedative drugs
Sympathomimetic	Tremor, insomnia
Antimuscarinic	Blurred vision, constipation, urinary hesitancy, confusion
Cardiovascular	Orthostatic hypotension, conduction defects, arrhythmias
Psychiatric	Aggravation of psychosis, withdrawal syndrome
Neurologic	Seizures
Metabolic-endocrine	Weight gain, sexual disturbances
Monoamine oxidase inhibitors	Sleep disturbances, weight gain, postural hypotension, sexual disturbances (phenelzine)
Amoxapine	Similar to the tricyclics with the addition of some effects associated with the antipsychotics (Chapter 29)
Maprotiline	Similar to tricyclics; seizures are dose-related
Mirtazapine	Somnolence, increased appetite, weight gain, dizziness
Trazodone, nefazadone	Drowsiness, dizziness, insomnia, nausea, agitation
Venlafaxine	Nausea, somnolence, sweating, dizziness, sexual disturbances, hypertension, anxiety
Bupropion	Dizziness, dry mouth, sweating, tremor, aggravation of psychosis, potential for seizures at high doses
Fluoxetine and other serotonin reuptake inhibitors	Insomnia, tremor, gastrointestinal symptoms, rashes, decreased libido, sexual dysfunction, anxiety (acutely)

Clinical indication of AD drugs:

1. **Major depressive disorder (endogenous depression):**

   - TCA are thought to be useful in patients with poor appetite, psychomotor retardation, weight loss, decreased libido and poor sleeping.

   - SSRI cause decrease in appetite so ↓ weight.

   - MAOI is useful in patients with significant anxiety, phobic features and hypochondriasis.

2. **Panic disorder:** MAOI is used.

3. **Obsessive compulsive disorder:** SSRI is used.

4. **Enuresis:** TCA is used (Children with nocturnal enuresis).

Clinical indication of AD drugs:

5. Chronic pain; TCA especially when the pain is not particularly distinguished and commonly given with analgesia.

THANKS