I. **Introduction – The 2010 Top 200 Generic Drugs**
   a. More Rx’s are written for hypertension than any other condition (9 of the top 50 drugs are for HTN – combining 3 beta-blockers, 3 calcium-channel blockers, 2 ACE inhibitors, and 1 diuretic).
   b. Five of the top 50 drugs are for antibiosis.
   c. Five of the top 50 are for pain (all but one are opiates).
   d. Five of the top 50 drugs are for hyperlipidemia.
   e. Four of the top 50 drugs are for depression.
   f. Four of the top 50 are for asthma.
   g. Three of the top 50 are for hypothyroidism or anxiety.
   h. So, doctor, what do you make of these commonly prescribed drugs, and what do they imply about these conditions occurring in your patients? Should you be concerned about ocular manifestations? What about drug side effects?

II. **Depression**
   a. Very common – 2nd only to hypertension as the most commonly seen condition in primary care practice
   b. Lifetime prevalence of depression is 17%; 1 in 10 patients has a major depressive episode. Depression has a prevalence as high as 25% in nursing homes. Frequencies for men and women differ: 12% in men, versus 20% in women. The risk of suicide is 30-fold higher than in the community at large.
   c. Major depressive episode (“major depressive disorder” or MDD) = depressed mood or anhedonia for 2+ weeks, plus 3+ of the following: insomnia, feeling worthless or guilty, fatigue, diminished concentration, changes in appetite, psychomotor retardation, recurrent suicidal thoughts. The episode is characterized by a change in affect, behavior, and quality of life. Single depressive episodes raise risks of subsequent episodes: there is a 28% chance of a second episode in 1 year, with a 62% chance of a second episode in 5 years.
   d. Generally felt not to be related to a prior, predisposing stressful event. Somatic symptoms (anorexia, weight loss, constipation, poor sleep, lost libido, vague aches, or poor concentration) may be part of depression but can obscure the classic "low mood."
   e. Major depressive episodes need to be contrasted with dysthymia and bipolar disorder
      i. Dysthymia is depression for > 2 years; symptoms are less severe than in a major depressive episode
ii. Bipolar disorder is diagnosed by a single manic episode. Bipolar type I is alternation between fully manic and depressive episodes; bipolar type II is alternation between "hypomanic" and depressive episodes.

f. 50-70% of patients respond to initial therapy (either meds or psychotherapy). Therapy for a major depressive episode needs to be typically continued for months into the "maintenance period" as the initial episode improves. Therapy of MDD very often consists of trial-and-error with a variety of medications to find the right fit, buttressed by careful listening and analysis of symptoms and the patient’s progress, with modifications in the medication regimen.

g. Serotonin- and/or norepinephrine-reuptake inhibitors
   i. Tertiary amine tricyclics (Elavil, Sinequan, Tofranil) – older drugs, known as "tricyclics"
   ii. Secondary amine tricyclics (Norpramin, Pamelor) – also older drugs
   iii. Bicyclic = combined serotonin and norepinephrine reuptake inhibitors or SNRIs (venlafaxine/Effexor, desvenlafaxine/Pristiq, and duloxetine/Cymbalta) – newer drugs without as many adverse effects
   iv. Older tricyclic drugs were called "dirty drugs" due to their profound side effects that included sedation; orthostatic hypotension; cardiac side effects including ventricular arrhythmias and conduction defects; and anticholinergic problems including dry mouth, constipation, and urinary retention.

h. Selective serotonin reuptake inhibitors (SSRIs) are fluoxetine/Prozac, paroxetine/Paxil, sertraline/Zoloft, citalopram/Celexa, escitalopram/Lexapro, fluvoxamine/Luvox
   i. Minimal/variable sedation and few anticholinergic effects, also minimal/no cardiac effects
   ii. However, notorious for causing sexual dysfunction (delayed ejaculation and anorgasmia, with incidences up to 60% of patients) and GI upset (nausea, vomiting, diarrhea); also likely to cause anxiety and insomnia at start of therapy
   iii. Much preferred to the older tricyclic antidepressants due to side effect profiles

i. Mirtazapine/Remeron has a complex and unduplicated mechanism making it quite unique; effects are to enhance both norepinephrine and serotonin effects; no anticholinergic effects, less sexual dysfunction, but likely to cause somnolence and weight gain

j. Norepinephrine- and dopamine-reuptake inhibitor is bupropion/Wellbutrin; considered to be the least likely to cause adverse drug events (ADEs) - less nausea, diarrhea, somnolence or sexual dysfunction vs. SSRIs

k. Clinical trials have indicated that some drugs work better for certain types of depression if there are comorbid features or other characteristics. Although the SSRIs revolutionized the treatment of depression in the 90’s, the older SSRI drugs are often used more for anxiety and the even-newer antidepressants are increasingly popular for depression treatment. A recent meta-analysis (JAMA 2010, see below) suggested that antidepressants work best for severe depression, while their benefits are lukewarm at best for mild
depression – however, just 2 drugs were evaluated (imipramine and paroxetine), and this remains unresolved as an issue.

l. There is significant controversy about treatment of depression, complicated by (A) proponents of drug therapy vs. "talk therapy"; (B) variable and contradictory results of drug trials; (C) appropriateness of drug therapy for mild depression (is it really depression or just ‘sadness’?); (D) lack of congruence between drug trials and 'real life' management strategies. The STAR*D Study attempted to provide practical guidelines for treatment (see references below).

m. References


III. Hypertension
a. Present in 1 in 4 adults in the US; current definition of hypertension is systolic > 140 or diastolic > 90. Source is the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).

b. 65 million Americans have BP > 140/90, are on HTN medications, or have been told twice that they have hypertension. Highest prevalence of hypertension is in African-Americans and the elderly, particularly women. Lifetime risk of HTN is about 90% for patients who live to an age of 80-85.

c. Hypertension is a risk factor for stroke (CVA), myocardial infarction (MI), renal failure, heart failure, progressive atherosclerosis, and dementia.
   i. Target organ disease related to HTN can be cardiac, cerebrovascular, peripheral vascular, renal, and/or ocular.
   ii. Each 20 mm systolic or 10 mm diastolic doubles the risk of cardiovascular disease. Death rates due to cardiovascular disease increase linearly from blood pressure as low as 115/75 (implying that there is really no "safe" blood pressure higher than that.)

d. Diastolic HTN is important for < 50 year-olds, but systolic HTN is much more important in older patients, harder to control, and a larger predictor of cardiovascular disease. Isolated systolic HTN (defined as > 160 and < 90) is very common in patients over 75 years of age.

e. The JNC 7 Report from 2003 is the current source for recommendations about management of hypertension. It differs somewhat from European guidelines, which are more complex, with more detailed sub-groupings, but which significantly do not include "pre-hypertension" in the groupings (see below).

f. NEW standard from JNC 7 – normal is systolic < 120 and diastolic < 80.

g. New standard from JNC 7 – pre-hypertension is systolic 120-139 or 80-89. This classification derived from Framingham study that noted a doubling of risk from BP in this range compared to less than 120/80.

h. NEW standard from JNC 7 – Stage I HTN is systolic 140-159 or diastolic 90-99.

i. NEW standard from JNC 7 – Stage II HTN is systolic ≥ 160 or diastolic ≥ 100.

j. Compelling conditions are additional risk factors to place an individual with HTN into a higher risk group; compelling conditions are coronary heart disease (CHD, which is angina or past MI), heart failure, diabetes mellitus, chronic renal disease, or stroke (past TIA or CVA).

k. Lifestyle modification = dietary changes to lose weight (goal is achieving BMI of 24.9 or less), reduced sodium intake, increased fruit/vegetables in diet, reduced fat, 30 minutes/day aerobic exercise, ≤ 2 drinks/day, stop smoking. Advised for any stage of HTN (pre-hypertension, stage I, or stage II).

l. Pre-HTN treatment: lifestyle modification

m. Stage I HTN treatment
   i. Diuretic (still most preferred drug – reduces sodium and fluid volume, with adjusted peripheral resistance later)
      1. Thiazides: hydrochlorothiazide (HCTZ), indapamide (Lozol)
      2. Potassium-sparing: triamterene (HCTZ/triamterene = Maxzide)
   ii. Angiotensin converting enzyme inhibitor (ACEI – blockades formation of angiotensin II, a vasoconstrictor)
      1. captopril (Capoten), enalapril (Vasotec), lisinopril (Prinivil), fosinopril (Monopril), quinapril (Accupril), benazepril
(Lotensin), ramipril (Altace), moexipril (Univasc),
trandolopril (Mavik)

iii. Angiotensin receptor blockers (ARB – block receptor for angiotensin II)
1. losartan (Cozaar), valsartan ( Diovan), irbesartan (Avapro),
candesartan (Atacand), telmisartan (Micardis), eprosartan
(Teveten), olmesartan (Benicar)

iv. Calcium channel blocker (CCB – blockades calcium channels, acting
as a vasodilator)
1. verapamil (Calan), diltiazem (Cardizem), nifedipine
(Adalat), nicardipine (Cardene), felodipine (Plendil),
amldipine (Norvasc), isradipine (DynaCirc)

v. Beta blockers (BB – reduce heart rate and cardiac output, plus
reduce rennin secretion in kidney); less in favor for HTN treatment
in Europe
1. atenolol (Tenormin), metoprolol ( Lopressor), timolol
(Blocadren), nebivolol (Bystolic), etc.

vi. Coformulations
1. ACEI/HCTZ – lisinopril/HCTZ (Prinzide), benazepril/HCTZ
(Lotensin HCT), moexipril/HCTZ (Uniretic)
2. ARB/HCTZ – losartan/HCTZ (Hyzaar), irbesartan/HCTZ
(Avalide), candesartan/HCTZ (Atacand HCT),
olmesartan/HCTZ (Benicar HCT), valsartan/HCTZ (Diovan
HCT)
3. ACEI/CCB – amlodipine/benazepril (Lotrel),
verapamil/trandolopril (Tarka)
4. ARB/CCB – valsartan/amlodipine (Exforge)
5. BB/HCTZ – metoprolol/HCTZ (Lopressor HCT)

n. Stage II HTN Treatment
i. 2 drugs in combination or coformulation
ii. Specific drugs as recommended for specific conditions (angina –
CCB; DM – ACEI)

o. References
i. ALLHAT Officers and Coordinators for the ALLHAT Collaborative
Research Group. Major outcomes in high-risk hypertensive
patients randomized to angiotensin-converting enzyme inhibitor or
calcium channel blocker vs. diuretic. The Antihypertensive and
Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT).

ii. Bibbins-Domingo K, Chertow GM, Coxson PG et al. Projected effect
of dietary salt reductions on future cardiovascular disease. N Engl

iii. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects
of ACE inhibitors, calcium antagonists, and other blood-pressure-
lowering drugs: results of prospectively designed overview of

iv. Chobanian AV, Bakris GL, Black HR et al. JNC 7 – Complete
Version. Seventh report of the Joint National Committee on
Prevention, Detection, Evaluation, and Treatment of High blood

pressure in African Americans. Consensus statement of the
Hypertension in African Americans Working Group of the


IV. Pain Control

a. Drugs for pain relief include NSAIDs, opioid combinations, and various medications for neuropathy.

b. Neuropathic pain is quite common; related to diabetes, infection (herpes zoster with post-herpetic neuralgia, HIV), nerve trauma (trigeminal neuralgia), stroke, or occurring idiopathically. Diabetes is the most prevalent cause and hyperglycemia is the primary risk for diabetic neuropathy.

c. Neuropathy: both "negative" (unable to sense pain) and "positive" symptoms (pain, paresthesias, burning, tingling, stabbing, "allodynia").
d. Diabetic neuropathy is implicated in up to 75% of amputations. Neuropathy (insensitivity) plus muscle atrophy leads to hammertoes, then to calluses, then to ulceration. Diabetic ulcers are estimated to occur in up to 25% of patients. Risk of an ulcer on a callus is 11-fold higher than in non-diabetics.

e. Pain control is both local (local analgesia) and within the CNS.

f. Blockade of stimulatory channels potentiates GABA (gamma amino butyric acid) by calcium blockade (gabapentin) or sodium channel blockade (amitriptyline), the end result being suppression of abnormal hyperexcitability. Gabapentin (Neurontin) does not bind to GASBA receptors but increases synthesis of GABA within the CNS.

g. Both gabapentin and amitriptyline have many side effects: somnolence for both; anticholinergic for amitriptyline, dizziness (gabapentin), or cardiac (orthostasis or arrhythmias from amitriptyline.)

h. Other drugs: anticonvulsants (Tegretol, Topamax, Lamictal, Zonegran) which potential GABA levels; antidepressant (Cymbalta), with FDA approval for neuropathy, acting to increase serotonin and norepinephrine in the CNS; tramadol (Ultram); and pregabalin (Lyrica), acting similarly to gabapentin. Opioids and SSRIs are ineffectual.

i. References


V. Anxiety

a. Generalized anxiety disorder (GAD) is a common psychiatric condition, probably second only to depression. Described as 6 months of symptom duration (prominent worrying and impairment) plus 3 or more of the following features occurring on most days: fatigue, restlessness, poor concentration, irritability, muscle tension, and unsatisfying sleep (but not anhedonia, which is seen in depression). GAD is characterized by unrealistic or excessive worry and is disproportionate to the severity of the stress. It is often described as uncontrollable and is diffused over many life events and activities ("generalized" as opposed to more focused worry with other anxiety disorders). Physical (somatic) symptoms include tachycardia, dyspnea, urinary frequency, tremor, or excessive sweating. In
contrast to GAD, mild anxiety sharpens the senses and probably improves performance.

b. Other anxiety disorders are panic disorder, obsessive compulsive disorder, social anxiety disorder, and PTSD. Generalized anxiety disorder is more common with the aging process (increasing exponentially with age) and more common in women (about twice as frequent as in men). GAD has frequent co-morbidities and major depression may co-exist in up to 2/3’s of patients.

c. Symptoms are physical (tachycardia, chest pain), cognitive (confusion, poor concentration, difficulty making decisions), behavioral (restlessness, agitation), affective (crying, hostility), and uncontrollable worry (apprehension, dread). Symptoms are long-lasting, with a much greater duration than a panic attack.

d. Benzodiazepines (BZDs) are the cornerstone of therapy for anxiety. They act quickly, are dependable, and have a long history of trusted performance. They act by binding to the GABA receptor, thus potentiating its affinity for GABA, which is the predominant inhibitor neurotransmitter of the brain. Leading BZDs are alprazolam/Xanax, clonazepam/Klonopin, diazepam/Valium, and lorazepam/Ativan.

e. Physical dependence and withdrawal symptoms can occur with long-term BZD therapy but these drugs provide rapid relief. Other BZD side effects include sedation, incoordination, confusion, and anterograde amnesia.

f. Buspirone (BuSpar) is a non-BZD anxiety drug, taking about 2 weeks to have its effects noted, but has no sedating or muscle relaxant effects. It cannot be used on an as-needed basis.

g. Antidepressants (not all) are as effective as BZDs for anxiety and lack problems with dependence/abuse and adverse effects on memory and coordination.

h. SSRI antidepressants (specifically paroxetine/Paxil and escitalopram/Lexapro) are now considered to be as effective as BZDs, but take longer to have their benefits felt; they are safer since there is no interaction with alcohol and no dependence. Venlafaxine/Effexor is an SNRI and is as effective as the SSRIs listed above. Tricyclics are as beneficial but anticholinergic side effects are often intolerable.

i. References


VI. **Post-traumatic stress disorder (PTSD)**

a. PTSD demographics: following sexual assault, witnessing mass casualties in war or natural disasters, physical assault, motor vehicle accident, disease epidemics. PTSD diagnostic criteria were established in 1980 in the Diagnostic and Statistical Manual of Mental Disorders (DSM III), resulting from increased awareness due to the Viet Nam conflict. PTSD following armed combat has been known by a variety of names, including “soldier’s heart” (Civil War), “shell shock” (WW1), “battle fatigue” (WW2), and “Vietnam stress syndrome.”

b. Exposed to a traumatic event
   i. Witnessed/involved with events of actual or threatened death or serious injury to self/others
   ii. Response of intense fear, helplessness, horror

c. Characterized by three "symptom clusters"
   i. Re-experiencing
   ii. Avoidance/numbing
   iii. Hyperarousal

d. Cluster 1 = re-experiencing, characterized by:
   i. Recurrent recollections (thoughts, images) of the event
   ii. Event is repeated (reliving it, flashbacks, "dissociative flashbacks" occurring upon awakening)
   iii. Recurrent distressing dreams (nightmares)
   iv. Psychological distress or "physiological reactivity" at events/entities that symbolize or resemble the trauma

e. Cluster 2 = avoidance/numbing, characterized by:
   i. Avoiding thoughts, feelings, activities, places, people relating to or connected with the traumatic event(s)
   ii. Diminished interest/participation, reduced range of affect, detached or estranged from family and society

f. Cluster 3 = hyperarousal, characterized by;
   i. Persistent symptoms of increased arousal
   ii. Difficulty falling or staying asleep
   iii. Difficulty concentrating
   iv. Hypervigilance, exaggerated startle response

g. Duration of above symptoms is longer than 1 month

h. Symptoms cause marked distress and poor functioning in social and occupational situations. PTSD is a chronic disease, with frequent psychiatric and medical co-morbidities, marked functional impairment, and economic costs.

i. PTSD is not a simple diagnosis to make, since the great majority of patients with lifetime PTSD have co-morbidities (typically major
depressive episodes, alcohol dependence, or drug dependence.) Up to 88% of men and 79% of women with PTSD have co-morbidities.

j. The criteria for PTSD diagnosis are complicated. (N Engl J Med 2002 reference below has the most detailed criteria listing.) A short questionnaire is able to suggest PTSD. Questions relate to a patient's reactions to a stressful event, those reactions happening 2 or more times in the past week:
   i. Upsetting thoughts of memories about the event that enter your mind against your will
   ii. Upsetting dreams about the event
   iii. Acting or feeling if the event is happening again
   iv. Feeling upset by reminders of the event
   v. Bodily reactions (racing heart beat, upset stomach, sweating, dizziness) when reminded of the event
   vi. Difficulty falling or staying asleep
   vii. Irritability or outbursts of anger
   viii. Difficulty concentrating
   ix. Heightened awareness of danger to yourself or others
   x. Being jumpy or being startled at something unexpected

k. First line treatment = SSRIs
   i. Able to ameliorate the 3 core symptom complexes
   ii. Able to ameliorate depression or other anxiety disorders that may accompany PTSD, such as panic, social phobia, or obsessive compulsive disorder
   iii. Primary drugs are sertraline/Zoloft, paroxetine/Paxil

l. Other antidepressants: venlafaxine/Effexor (SNRI) is second line; third line drugs are tricyclics (amitriptyline, imipramine), and some MAO inhibitors (but little data on these groups, and their side effect profiles are more severe than the SSRIs).

m. Benzodiazepines: good for anxiety and sleep issues, but unable to ameliorate the 3 core symptom complexes; significant concerns for dependence/abuse with comorbid substance abuse so their use is typically avoided.

n. Atypical antipsychotics – for comorbid psychoses accompanying PTSD; not first or second line drugs, but used as needed (quetiapine/Seroquel, risperidone/Risperdal, etc.).

o. Anticonvulsants – help with reexperiencing symptoms, but uncertain benefits for numbing or hyperarousal symptoms.

p. Alpha-1 antagonist (prazosin) – benefit for relief of nightmares. Proposed mechanism is increased CNS adrenergic activity at night, with overstimulation of alpha-1 receptors in hippocampus and amygdala.

q. Beta blockers – specifically propranolol. Proposed mechanism of consolidation of short-term, labile memories into long-term memories occurs in the amygdala; propranolol is proposed to interfere with neurotransmitters participating in the consolidation of memories.

r. References


VII. Hyperlipidemia

a. 38% of deaths in US are due to cardiovascular disease (CVD). Atherosclerosis is a major cause of CVD (along with HTN and congenital heart disease). Many risk factors contribute to CVD: gender, age, family history, smoking, diabetes, HTN, and dyslipidemia (low HDL plus elevated atherogenic lipoproteins which are total cholesterol, LDL, and triglycerides.)

b. Modifiable risk factors are smoking, diabetes, hypertension, and dyslipidemia.

c. National Cholesterol Education Program (NCEP) released Adult Treatment panels, the latest (ATP III) being released in 2001-2002. The primary goal is reducing LDL; secondary objectives are lowering non-HDL cholesterol, by reducing triglycerides, increasing HDL, or both. Earlier NCEP reports date from 1988 and 1993. LDL standards have become even more stringent (LDL of 160 used to be acceptable for a low-risk patient!). A risk stratification is done using the Framingham criteria, which calculate coronary heart disease (CHD) risk for patients in 5-yr age groupings, using total cholesterol, smoker status, HDL level, and level of systolic BP (either treated or untreated.)
d. Optimal levels of LDL are now < 100 mg/dL, triglycerides < 150 mg/dL. LDL is exceptionally critical: 60-70% of circulating cholesterol is LDL and excessive LDL cholesterol enters arterial walls, undergoing oxidation which makes it atherogenic.

e. Patients are stratified into 3 groups for different levels of risk for CVD, with varying goals for desirable LDL levels. Diabetes is newly established as a major risk factor: LDL particles more readily penetrate vascular endothelium in diabetics or those with the metabolic syndrome (abdominal obesity, hypertension, insulin resistance or impaired fasting glucose, dyslipidemia, and elevated C-RP and fibrinogen). Successful control of diabetes does not eliminate it as a risk factor.

f. HIGHEST RISK PATIENT has: coronary artery disease (CAD) or other atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, symptomatic carotid disease) or diabetes or a greater than 20% risk of coronary heart disease (CHD) within 10 years (per Framingham risk projection system). Desired level of LDL < 100. INTERVENTION: if LDL is ≥ 100, introduce lifestyle changes; if LDL is ≥ 130, institute therapy.

g. MIDDLE RISK PATIENT does not have CHD/CAD or atherosclerotic disease, but has ≥ 2 risk factors from among the following: cigarette smoking; HTN (> 140/90) or on therapy for HTN (successfully treated HTN does not eliminate it as a risk factor!); low HDL (< 40 mg/dL); family history of premature CHD (men < 55, women < 65); age (men over 45 years of age, women over 55 years of age). Desired level of LDL < 130. INTERVENTION: if LDL is ≥ 130, introduce lifestyle changes; if LDL is ≥ 130 and there is a 10-yr risk of CHD between 10-20%, start therapy; if the 10-yr risk of CHD is < 10%, then introduce therapy if LDL is ≥ 160.

h. LOW RISK PATIENT has 0 or 1 risk factors from the list above. Desired level of LDL < 160. With few exceptions, persons in the low risk category have a 10-year overall risk for CHD that is < 10%. INTERVENTION: if LDL is ≥ 160, introduce lifestyle changes; if LDL is ≥ 190, start therapy.

i. Lifestyle changes
   i. Weight reduction (which will lower LDL and raise HDL) and increased physical activity (which will raise HDL)
   ii. Stop smoking (which will raise HDLs 10-20% within several weeks)
   iii. Reduced dietary intake of saturated fats and cholesterol
   iv. Use of viscous fiber (psyllium)
   v. Increased dietary intake of fiber (bran, vegetables, etc.)
   vi. Treat hypertension

j. Drug therapy for hyperlipidemia
   i. Statins inhibit HMG-CoA reductase, the rate-limiting step in cholesterol biosynthesis. Most potent to least potent: rosuvastatin/Crestor, atorvastatin/Lipitor, simvastatin/Zocor, pravastatin/Pravachol = lovastatin/Mevacor, and fluvastatin/Lescol. Myalgias and liver toxicity are not uncommon side effects
   ii. Bile acid resins enhance LDL clearance from plasma in bile: colestipol/Colestid, colestyramine/Questran, colesevelam/Welchol. Side effects (constipation, bloating, or gas) make them difficult to tolerate long-term.
   iii. Ezetimibe (Zetia) blocks receptor responsible for cholesterol uptake in the small intestine. Weak on its own but is coformulated with simvastatin in Vytorin.
iv. Niacin inhibits production of VLDL in the liver, which results in decreased triglycerides and LDL, and possibly an increase in HDL (although modest. Side effects include flushing, tingling, itching, rash, and headache. Extended-release has the lowest potential for flushing and liver toxicity. Must have baseline liver function tests measured before initiating therapy.

v. Fibrates reduce triglycerides, somewhat reduce VLDL levels; they are first line drugs for hypertriglyceridemia. Gemfibrozil/Lopid and fenofibrate/TriCor are the drugs.

vi. Fish oil. Marine-derived omega-3 fatty acids, eicosapentaenoic and docosahexaenoic acid, derive from green plants ingested by fish (salmon, herring, etc.). Plant-derived alpha-linolenic acid also provides omega-3 FA's (in vegetable oils and nuts). A therapeutic lowering of triglycerides requires up to 4 grams/day of EPA/DHA.

vii. Future drug family (CEPT inhibitors) for increasing HDL levels: dalcetrapib and anacetrapib, both in phase 3 clinical trials, with good safety profiles (thus far).

k. References


VIII. Anti-platelet and anticoagulant drugs in stroke prevention
a. Factors increasing risk of a stroke are (1) non-modifiable (age, male gender, non-white ethnicity, family history, and past CVA); and (2) modifiable (HTN, DM, atrial fibrillation, carotid artery disease, hyperlipidemia, cigarette smoking, obesity, and high alcohol use). Whenever possible, modifiable factors should be addressed, more aggressively depending on the overall risk analysis.

b. There are two broad types of stroke:
   i. Hemorrhagic strokes, caused by saccular aneurysms of large/medium intracranial arteries or hypertensive intracerebral hemorrhages.
   ii. Ischemic strokes, resulting from (a) large vessels, (b) small vessels, or (c) cardioembolic phenomena.
   iii. Both hemorrhagic stroke and ischemic stroke cause abrupt dysfunction of neurologic tissue, leading to neurologic deficits such as hemiparesis, hemisensory loss, aphasia, ophthalmoplegia, and visual field cuts.

c. Hemorrhagic stroke
   i. 10-20% of total of all strokes, with risk increasing with age
   ii. Results from either a saccular aneurysm of an intracranial artery or more likely a hypertensive intracerebral hemorrhage of a HTN-damaged vessel.
   iii. Occurs in daytime, during activity, presenting with focal neurologic deficits, headache, nausea & vomiting, reduced consciousness, and/or elevated blood pressure.
   iv. Both types of strokes cause neurologic deficits (hemi-losses) but since a cerebral hemorrhage causes leakage of blood, other things happen.
      1. Blood leakage displaces and compresses adjacent tissue, which raises ICP, and eventually spreads into ventricles and subarachnoid space.
      2. Hemorrhage can cause additional symptoms beyond the hemi neurologic deficits, such as severe headache (from increased ICP), progressive deterioration after the stroke onset (from continued bleeding), vomiting (from increased ICP), neck stiffness (from meningeal irritation), and coma (from bilateral cerebral dysfunction).

d. Ischemic strokes comprise three different types
   i. Atherothrombotic (large vessel) strokes are 50% of the ischemic stroke subtype. Atheroma develops with thrombosis of large vessels (carotids or aortic arch), lumen narrows with reduced blood flow, but the critical event is the rupture of the fibrotic cap of the atheroma.
   ii. Lacunar (small vessel) strokes are 25% of ischemic strokes. Vessels involved are middle cerebral artery, circle of Willis, or basilo-vertebral arteries.
iii. Cardioembolic strokes are 20% of the ischemic stroke subtype, resulting from atrial fibrillation or abnormal heart valves (mechanical or diseased).
e. Symptomatology of ischemic strokes: sudden onset of focal brain dysfunction, acute neurologic deficit (facial paralysis, limb drift, abnormal speech), severe headache, change in consciousness, or TIAs increasing in severity/frequency.
f. Prevention of strokes requires treating modifiable factors for atherosclerosis (HTN, isolated systolic HTN in the elderly, hyperlipidemia, smoking), since atherosclerosis of large vessels is the biggest cause of stroke.
g. Beyond treatment of modifiable risks, prevention of strokes also uses antiplatelet aggregation drugs (which reduce thrombus formation by reducing aggregation of platelets on diseased arteries); the strategy reduces risk by 20-30%. Drugs utilized are aspirin (typically 81 mg), clopidogrel/Plavix (if intolerant of aspirin), both for reducing stroke risk. An additional drug is coformulated dipyridamole/aspirin (Aggrenox) but only for patients with a history of stroke already.
h. Anticoagulation with warfarin reduces risk of cardioembolic phenomena in patients with atrial fibrillation or mechanical heart valves. ASA, Plavix or Aggrenox are never used.
i. Warfarin is also used for prevention of deep venous thrombosis (DVT) and pulmonary embolism (which is potentially fatal). A triad of risk factors contributes to DVT: venous stasis (due to immobilization, hospitalization, obesity) plus hypercoagulability (inherited or acquired, i.e. antiphospholipid antibody syndrome) plus endothelial damage (from trauma or surgery).
j. Warfarin interferes with synthesis of vitamin K-dependent clotting factors in the liver; it specifically interferes with transformation of vitamin K, thus resulting in inactivated clotting factors.
k. There are 2 non-warfarin drugs that are presently in use, neither with the repetitious need for prothrombin times every 2 weeks, nor with the food-drug interactions that plague warfarin users. However, neither is fully approved for all warfarin indications. Dabigatran (Pradaxa) is approved only for high-risk atrial fibrillation, and not yet approved for moderate/low-risk a-fib. Rivaroxaban (Xarelto) is only approved (at present) for prophylaxis of DVT following hip or knee replacement surgery (which is typically 3-4 weeks only)
l. References


xi. Runchey S, McGee S. Does this patient have a hemorrhagic stroke? Clinical findings distinguishing hemorrhagic stroke from ischemic stroke. JAMA 2010; 303:2280-6.


IX. Osteoporosis

a. Bone mass or mineral density (BMD) is reduced, causing "microarchitectural deterioration" and increased bone fragility with increased susceptibility to fractures. Defining osteoporosis is difficult; WHO states "compromised bone strength predisposing to increased risk of fractures."

b. Type I – post-menopausal, driven by reduced estrogen

c. Type II – "senile" – driven by reduced GI absorption of calcium, increased parathyroid hormone (PTH), and reduced vitamin D activation

d. Type III – related to medications (steroids, heparin, anticonvulsants) or immobilization.

e. Bone is constantly turned over. Vitamin D and PTH stimulate osteoclasts to mobilize trabecular (spongy) bone by resorption, and then osteoblasts replenish it.

f. Women at age 50+ have a lifetime risk of vertebral fracture of 1 in 3, and risk of hip fracture of 1 in 6. Hip fractures are associated with significant cost (in-patient and nursing home care), morbidity, and mortality (as high as 38% mortality in the first year following the hip fracture.)

g. Osteoporosis is clinically silent until a fracture occurs.

i. Vertebral (compression) fractures are related to bending and lifting and infrequently to actual falls; 2/3's are asymptomatic but symptoms are non-specific lower back pain. Vertebral fractures lead to kyphosis and "dowager's hump."

ii. Wrist fractures, from a fall (falling on the extended wrist)

iii. Hip fractures, mainly resulting from a fall (90% result from a fall from standing height)

h. Tested by DEXA (dual-energy X-ray absorptiometry), which measures central BMD (hip and spine, L1-L4). A "T-score" results, which is the number of standard deviations of BMD in the patient compared to young
(24-45 y.o.) females. A negative T score (BMD is low) of -2.5 or lower is diagnostic for osteoporosis, while a T score from -1.0 to -2.5 is diagnostic of osteopenia.

i. Risk factors for osteoporosis are environmental (cigarette smoking, alcoholism, inactivity, thin or low body weight, low calcium intake, heavy caffeine intake), drug therapy (steroids, antiepileptic drugs, anticoagulant drugs), rheumatologic disease (RA, ankylosing spondylitis), genetics (white race, a first-degree relative with a fracture), and infrequent weight-bearing exercise such as walking.

j. Drug therapy works to reduce bone resorption.

k. Biphosphonates inhibit the normal function of osteoclasts (which is absorption and removal of bone); the result is increased bone mineral density. Drugs used in the US are alendronate/Fosamax, risedronate/Actonel, and ibandronate/Boniva.

l. Biphosphonates are associated with ocular inflammation. The worst offender (pamidronate/Aredia) is used for tumor-induced hypercalcemia or Paget's disease, not osteoporosis; alendronate and risedronate are less toxic. Cases of scleritis, episcleritis, iritis, and conjunctivitis are reported with this drug class.

m. Other treatments
   i. Dietary: calcium and vitamin D supplements
   ii. Hormone replacement therapy increases BMD and provides a reduced risk of fractures (but HRT increases breast cancer risk and does not reduce risk of CVD, so harmful effects are likely to outweigh the benefits)
   iii. SERM – selective estrogen receptor modulator (raloxifene/Evista); inhibits bone resorption but not as effective as biphosphonates so is reserved for women who cannot tolerate biphosphonates.
   iv. Calcitonin (Miacalcin) – inhibits osteoclast activity; administered as a nasal spray
   v. Teriparatide (Forteo) – recombinant PTH administered daily (once-daily PTH dosing stimulates osteoblasts but continuous PTH exposure stimulates osteoclasts)

n. References

X. **Conclusions** – Some of these very commonly managed conditions have little impact on eye health or the visual system, and the drugs used for their treatment have similarly little ocular impact. Other conditions (hypertension, hyperlipidemia, stroke risk and prevention) have tremendous interrelationships with the visual system. Finally, other conditions may have little direct impact but the medications used in their management may have marked ocular toxicities associated with their regular utilization.