Cardiovascular

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Acute Coronary Syndromes

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ACS

- STEMI
  - S-T Elevation
  - Biomarkers
- Non-STEMI
  - No S-T Elevation
  - Biomarkers
- Unstable Angina
  - Chest pain at rest
  - New onset, limits activity
  - Increase or worsening in symptoms
  - No Biomarkers

Symptoms of MI

- Chest pain
- Pressure
- SOB
- N/V
- Fainting
- Women can present with atypical symptoms

Risk Factors

- Age
  - Men > 45, women > 55
- Smoking
- Diabetes
- Hypertension
- Dyslipidemia
- Family history
- Obesity/lack of physical activity
- Use of stimulants like cocaine, amphetamines

Immediate Care

- Remember "MONAB"
- Morphine
  - Use only if significant pain
  - There is evidence that it may reduce the efficacy of P2Y12 inhibitors
- Oxygen
- Nitroglycerin
  - Helps relieve ischemia and chest pain
  - Hasn't been proven to improve outcomes
  - Monitor for hypotension risk
- Antiplatelet therapy
  - Aspirin 325mg – chew and swallow
  - P2Y12 Inhibitors
- Beta blocker
  - In the absence of contraindications (i.e. BP<90, bradycardia, heart block, uncompensated CHF)

Percutaneous Coronary Intervention (PCI)

- STEMI – PCI is treatment of choice
  - Within 12-24 hours
- If cannot do PCI, fibrinolytic therapy is alternative option
  - More likely in non-US locations/extremely remote locations
- Heparin based products given in conjunction
  - Bivalirudin is an alternative option in those who can't use heparin/enoxaparin

Fibrinolytics

- Tenecteplase, alteplase, streptokinase
  - Tenecteplase – best safety profile, similar efficacy to alteplase
  - Streptokinase – cheap, less effective, less intracranial bleeding
- Considered if PCI not an option, or don't have access in 120 minutes or less
- Contraindications
  - Any significant internal bleeding
    - Intracranial hemorrhage
    - Active GI bleeding
    - Uncontrolled, unresponsive hypertension (>180/110)

NSTEMI/Unstable Angina

- Higher score, more likely to do early invasive strategies (i.e. PCI)
- Thrombosis in Myocardial Infarction (TIMI) risk score
  - Age >65
  - CAD or CAD risk factors like smoking, hypertension, hypercholesterolemia, diabetes, tobacco
  - Recent aspirin use (last 7 days)
  - Severe angina
  - Elevated cardiac marker
  - ST change >0.5

Aspirin

- Always a drug of choice for prevention
- Also used in acute treatment/emergency situation
- Low dose is ok in majority of situations
- Higher dose (325 mg daily) may be used in clinical judgement scenarios where patients have had events despite low dose and GI/bleed risk remains low

Percutaneous Coronary Intervention (PCI)

- Expands/opens clogged vessel
- Placement of a stent will aid in keeping vessel open and facilitating blood flow
- Quicker revascularization, the better
- Prasugrel or ticagrelor typically preferred over clopidogrel in acute setting

Clopidogrel

- Used in combination with aspirin or alternative for those who can't tolerate aspirin
- Typically for at least 12 months following stenting
  - May be shorter for high risk bleeding complications
  - May be longer if multiple MI's or MI that happened while patient was on aspirin alone, based upon clinical judgement
- Prodrug
  - CYP2C19 converts to active form
  - Rapid metabolizers may be at higher risk of bleed
  - Poor metabolizers may have risk of non-response or increased risk of clot formation/MI (boxed warning) – recommend another P2Y12 inhibitor
  - Omeprazole can inhibit CYP2C19 – clinical impact still debated/controversial

Prasugrel

- Main side effect is bleed risk; higher risk in very elderly and low weight patients
- Boxed warning in patients 75 or older
- Avoid in patients with active bleeding or a history of TIA/stroke
- More potent P2Y12 blocking effects versus clopidogrel
- Possibly reduce dose in patients 60kg or less (5 mg)
- Normal maintenance is 10 mg
- Thrombotic thrombocytopenic purpura (rare)
- Avoids 2C19 pathway (different from clopidogrel)
- More expensive than clopidogrel

Ticagrelor

- Bleed risk
- Can increase uric acid
- Boxed warning for reduced effectiveness when patients are using aspirin doses greater than 100 mg
- 3A4 major pathway for metabolism – drug interaction risk
- Twice daily dosing is a downside compared to clopidogrel/prasugrel
- False negative results may occur when trying to diagnose heparin induced thrombocytopenia

Statin Therapy

- High intensity statin (atorvastatin, rosuvastatin) for most unless intolerant
- Consideration of ezetimibe or PCSK-9 inhibitor in those intolerant to statins
- Ezetimibe may be added to statin therapy
- Target LDL <70 mg/dL for highest risk patients
- See hyperlipidemia

Classic Medications on Hospital Discharge

- Aspirin
- P2Y12 inhibitors (i.e. clopidogrel)
- ACE or ARB
- Beta-blocker
- Statin

Atrial Fibrillation

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Symptoms of Atrial Fibrillation

- General fatigue
- Rapid and irregular heartbeat
- Fluttering or “thumping” in the chest
- Dizziness
- Shortness of breath and anxiety
- Weakness
- Faintness or confusion
- Fatigue when exercising

Classification of AFib

- Paroxysmal (<7 days)
- Persistent (>7 days and won't go back to normal on its own)
- Permanent (continuous Afib)

Controlling Rate

- Beta-blockers
- Calcium Channel Blockers
- Digoxin

Clinical Medication Pearls

- Beta-blockers
  - Usually first line
  - Generally avoid non-selective unless compelling indication
- Calcium Channel Blockers
  - Non-dihydropyridines
  - Heart failure risk
- Digoxin toxicity
  - GI symptoms, CNS, weight loss, bradycardia
  - Renal elimination
  - Target concentration <1ng/mL vs. CHF (0.5-0.8)

Rhythm Control

- Potassium Channel Blockers
  - Amiodarone
- Sodium Channel Blockers
  - Flecainide (Tambocor®)
  - Propafenone (Rythmol®)

Amiodarone Pearls

- Extremely long half life
- Liver toxicity
- Pulmonary toxicity
- Thyroid impact
- Drug interactions
- QTc prolongation

Anticoagulation

- Clot formation is one of the major risks with atrial fibrillation
- To be discussed further – see NOACs/Warfarin section
- CHADS2Vasc
  - CHF
  - Hypertension
  - Age (65-74 +1; 75 or greater +2)
  - Diabetes
  - Stroke (+2)
  - Vascular Disease history
- Score of 2 or greater; anticoagulation indicated

Valvular Heart Disease

- Anticoagulation – Mechanical Heart Valve(s) Replacement
  - Warfarin = Drug of Choice
  - Target higher INR – 2.5-3.5
- Direct oral anticoagulants
  - Not indicated for use in valvular replacement

2019 Atrial Fibrillation Guideline Update

- AHA/ACC/HRS
- NOACs Preferred in Afib
  - Dabigatran, rivaroxaban, apixaban, edoxaban
  - Class 1 recommendation
- Note: Betrixaban is only indicated for VTE prophylaxis

2019 Atrial Fibrillation Guideline Update

- End Stage Renal Disease/Dialysis anticoagulation selection
  - Warfarin OR apixaban
  - Class 2b recommendation
- Clinical considerations are important (diet, risk for interactions, age, past history of bleed, previous agents used, etc.)

2019 Atrial Fibrillation Guideline Update - ACS

- Triple therapy post-stent placement - clopidogrel is preferred over prasugrel (2a)
- Double therapy with a P2Y12 inhibitor and dose warfarin is reasonable post-stenting (2a)
- Double therapy with clopidogrel and low-dose rivaroxaban (15 mg daily) may be reasonable post-stenting (2a)
- Double therapy with a P2Y12 inhibitor and dabigatran 150 mg twice daily is reasonable post-stenting. (2a)
- If triple therapy is prescribed for patients with AF who are at increased risk of stroke and who have undergone PCI with stenting for ACS, a transition to double therapy at 4-6 weeks may be considered (2b)

Reversal Agents

- Idarucizumab – dabigatran
  - Use in the setting of life threatening or urgent, necessary procedure
  - Class 1 recommendation
- Andexanet Alfa
  - Reversal of apixaban and rivaroxaban
  - 2a recommendation
  - Boxed warning: Thromboembolic risks, ischemic risks, cardiac arrest, and sudden deaths:

Cardioversion in Atrial Fibrillation

- Cardioversion in new onset atrial fibrillation/atrial flutter can increase risk of thrombus
  - Electrical cardioversion is generally preferred in new onset atrial fibrillation
  - Especially if atrial fibrillation/flutter has been going on for a while (i.e. greater than 48 hours) or if duration is unknown
  - Initiate anticoagulation if planning to do cardioversion (continue for at least 3 weeks before and 4 weeks after cardioversion)
  - If cardioversion needs to be done urgently, need to use heparin infusion or LMWH – i.e. enoxaparin (warfarin would not be appropriate as it takes a while to get the INR therapeutic)
    - May also see NOACs used by some providers versus heparin products (used off label)
  - Medication cardioversion is generally considered second line (less effective)

Cardioversion Medication Options

- All have the risk of causing arrhythmias
  - Risk increased by electrolyte abnormalities, QT drug interactions (i.e. antipsychotic, quinolones, etc.), or preexisting QT prolongation
- Flecainide (Tambocor) – Class 1c antiarrhythmic
  - 1c mechanism – inhibition of sodium channels, which slows action potential
  - Risk of toxicity increases as renal function declines (CNS toxicity, arrhythmias)
  - 2D6 inhibitors may increase concentrations (i.e. bupropion, paroxetine, fluoxetine)
- Propafenone (Rythmol) – Class 1c antiarrhythmic
  - SE's – Taste disturbances, dizziness, CNS changes, visual changes
- Dofetilide (Tikosyn) – Class 3 antiarrhythmic
  - Dose adjustment in renal impairment
- Ibutilide (Corvert) – Class 3 antiarrhythmic
  - Boxed warning on avoiding use in patients with atrial fibrillation (benefits must outweigh risks)
- Dronedarone (Multaq)
  - Contraindicated in patients with heart failure exacerbation history or those in NYHA class 4
  - Avoid use with strong CYP3A4 inhibitors (many azole antifungals, clarithromycin, HIV boosting agents, etc.)
  - Liver risks

CHF

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CHF Characteristics

- Inability to effectively pump blood
- Elevated BNP (or pro-BNP)
- SOB, cough
- Fatigue, weakness
- Edema
- HFrEF

Staging

- New York Heart Association Classification – Patient Symptoms
  - Class – 1 Asymptomatic
  - Class – 2 Become winded with exertion
  - Class – 3 Trouble with regular activities
  - Class – 4 Most severe, symptoms even at rest
- ACC/AHA Classification
  - Class – A – At risk for heart failure but no evidence of heart disease or symptoms of heart failure
  - Class – B – Evidence of structural disease, but no signs and symptoms of heart failure
  - Class – C – Structural heart disease with symptoms of heart failure
  - Class – D – Refractory heart failure not responsive to treatments

Medications Frequently Used in CHF

- Diuretics
  - Loops
  - K+ sparing (MRAs)
  - Thiazide Like
- Quadruple Therapy
  - ARNI (or ACEI/ARB)
  - Beta-blockers
  - SGLT2 Inhibitors
  - MRAs

Loops

- Furosemide, torsemide, bumetanide, ethacrynic acid
- Can dramatically reduce electrolytes
  - Potassium, magnesium, calcium, sodium
- Risk of dehydration
  - Monitor kidney function
- Ethacrynic acid (no sulfa group)
- Frequent urination can be a big problem in our elderly patients who may already have frequency and/or incontinence
- Lowers blood pressure, orthostasis concern
- Ototoxicity risk (rare)
- IV to oral dosing ratio is approximately 1:2

Aldosterone Antagonists

- Spironolactone, Eplerenone
  - Heart failure compelling indication with mortality benefit
  - Should be used in NYHA Class II-IV with ejection fraction of 35% or less
- Hyperkalemia
- Gynecomastia
- Avoid eGFR <30 ml/min, K+ >5
- 100mg spironolactone/40 mg furosemide

Thiazide Like

- Metolazone
  - One hour before furosemide
  - Used to augment furosemide
  - Significant hyperkalemia risk when used with furosemide
  - Sometimes only need to use once or twice/week
- True thiazides (i.e. HCTZ)
  - Generally not used for CHF/fluid loss
  - Likely not as beneficial with CrCl <30

Beta-blockers/ACE Inhibitors

- See Hypertension for more clinical breakdown
- Generally try to push the dose
  - Not that easy in the elderly
  - Falls
  - Weakness
  - Kidney function
- Carvedilol, metoprolol succinate, and bisoprolol are most commonly used in CHF (proven mortality benefit)

ARNI

- ARNI – Angiotensin receptor – Neprilysin inhibitors (sacubitril/valsartan)
  - Avoid with hx of angioedema
  - 36 hour washout period when switching from ACEI
  - Morbidity/mortality reduction
  - Indicated in NYHA class 2-4
  - More hypotension than ACE/ARB (<100 mm Hg SBP avoid)
  - Evidence of greater benefit in specific subsets, but cost is a downside to use
  - Enalapril 10 mg or valsartan 160 mg or higher – may start higher dose (49/51 mg)
    - 24/26 mg BID naïve titrate to target of 97/103 mg of sacubitril/valsartan

SGLT-2 inhibitors

- Benefit in HFrEF even in patients without diabetes – dapagliflozin is first to get FDA approval
- In diabetes patients who need blood sugar lowering, it makes sense to start an SGLT-2 inhibitor in patients who have heart failure
- See diabetes for more monitoring/adverse effects information

Latest Guidelines – Important Updates

- SGLT2i – officially added to list of guideline-directed medical therapy (GDMT)
- HFpEF – SGLT2i (2a recommendation) with MRAs, ARBs and ARNI (2b)
  - LVEF 50% or greater

Other Chronic Management Options

- Ivabradine – Reduction in hospitalization
  - Indicated - LVEF <35%, HR >70 and taking beta-blocker
  - Visual disturbances, bradycardia
  - Low BP/low HR contraindications (BP<90/50, HR<60 prior to treatment)
  - Likely going to reserve for more refractory patients with paying close attention to vital signs as above
- Hydralazine/ISDN
  - Consideration in blacks or those intolerant of angiotensin blocking agents
  - Frequent dosing, higher incidence of dizziness, headache

Digoxin in CHF

- Increased mortality at higher levels
- Target 0.5-0.8
- Monitor closely
  - Changing renal function
  - Symptoms of toxicity

Classic Drugs that Exacerbate CHF

- NSAIDs
  - Sodium retention
  - Also risk of Kidney damage with ACE/Diuretics on board
- CCB's
  - Increase edema
- TZD's
  - Pioglitazone
- Pregabalin
- Cilostazol

Coronary Heart Disease and Cardiovascular Risk

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Coronary Heart Disease

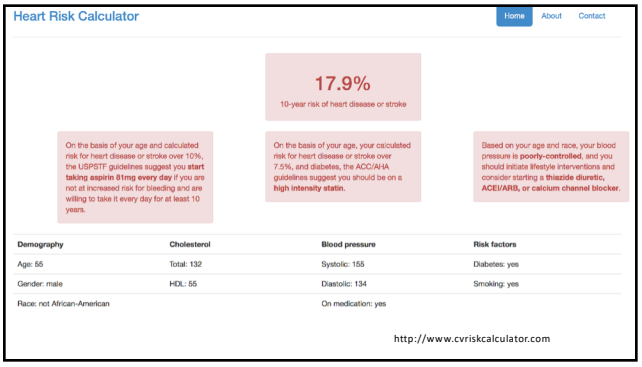
- Atherosclerosis, Coronary Artery Disease (CAD), Ischemic Heart Disease (IHD)
  - Plaque formation
  - Hardening of the arteries
- Can lead to;
  - Angina
  - Myocardial Infarction

Cardiovascular Risk Stratification Considerations

- Age
- Sex
- Family history
- Smoking
- Obesity
- Alcohol
- Hypertension
- Diabetes
- Metabolic Syndrome
- Physical activity
- Lipid levels
- Diet

ACC/AHA Risk Calculator – Primary Prevention

- Age
- Gender
- Race
- Cholesterol/HDL (doesn't use LDL in calculator, but if >190 recommend likely starting statin)
- Blood Pressure (level plus if on medication)
- Diabetes
- Smoking
- ***Provides 10 year risk as well as if aspirin is recommended



Link to Calculator

- http://www.cvriskcalculator.com

Aspirin – Primary Prevention

- ACC/AHA – recommended to be considered in patients at higher risk of CVD (age 40-70)
  - Weighed with risk of bleed
- US Preventive Services Task Force
  - 50-59 likely to have most benefit from the evidence
  - 60-69 less convincing evidence
- 70+ likely avoid (Beers criteria)
- Weigh risks of benefits versus risk of bleed for patients
- Major risk factors include; HTN, DM, smoker, elevated lipids

Goal – Reduce Risk of MI/Stroke

- Platelet inhibitors
- Statins
- Smoking Cessation
- Weight loss
- Anti-angina medications
- Antihypertensives

Antiplatelet medications

- Aspirin
- ADP inhibitors commonly used with aspirin in stenting, ACS
  - Clopidogrel, prasugrel
  - Possible alternative in primary prevention

Statin Consideration

- Adherence is critical
- Past history
- Some recommended to be dosed at night and some aren't
- Cost
- Life expectancy

Anti-Angina Medications

- Beta-blockers – avoid in vasospastic or Prinzmetal
- Nitrates: Isosorbide mononitrate, isosorbide dinitrate, nitroglycerin
  - Mechanism of Action: Direct acting vasodilation by nitric oxide which causes smooth muscle relaxation and reduction in blood pressure
  - Primarily used in the management of angina versus hypertension
  - Nitro sublingual for acute angina attack
    - Dose every 5 minutes and dial 911 if chest pain is not improving; maximum of 3 doses
  - Long acting nitrates (Imdur) used in the prevention of angina
  - Nitrate tolerance can begin to develop in 8-12 hours, so nitrate free period is ideal
  - Patch formulation (Nitro-Dur) – on for 12 hours, off for 12 hours
  - Avoid combination with PDE-5 inhibitors for erectile dysfunction (I.e. sildenafil)
- CCB's

Antihypertensive Therapy – Post-MI

- ACE/ARB
- Beta-blocker
- CCB

DVT/PE

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Deep Vein Thrombosis

- Deep Vein Thrombosis (DVT) symptoms
  - Redness, swelling, pain in leg
  - One sided
  - Warmth at site
  - Detected by ultrasound
- D-Dimer elevation may be helpful in guiding diagnosis

Pulmonary Embolism

- Pulmonary embolism (PE) symptoms
  - Shortness of breath
  - Chest pain
  - Light headed
  - Cough potentially with blood

Risk Factors for DVT/PE

- Patient history
- Hypercoagulable Disorders (i.e. Factor 5 Leiden)
- Immobility
- Atrial Fibrillation
- Medications
- Smoking
- Cancer

Medications – Increased Risk of DVT/PE

- Estrogen therapy/oral contraceptives
- SERMs
- Megestrol
- Testosterone
- Tranexamic acid

Important Considerations DVT/PE Treatment

- Drug Selection
  - DOACs preferred for most
  - Warfarin
  - LMWH
  - Heparin

Considerations in Selection

- Low-molecular weight heparin
  - Immediate action (unlike warfarin)
    - Often used for bridging
  - Drug of choice in pregnancy
  - Needle phobia
  - 1mg/kg BID or 1.5 mg/kg daily
  - Obesity – higher doses
  - Derived from pork products
- Contraindications
  - Heparin induced thrombocytopenia
  - Derived from pork products
  - Avoid in dialysis
- Warfarin/DOACs – See separate presentations

Length of Anticoagulation

- Known cause
  - Shorter duration
- Risk Factors
  - Longer term likely necessary
- First Episode (usually 3-6 months)
  - 3 months if provoked (i.e. surgery)
  - 3 months if high risk of bleed and unprovoked first episode
    - Continue longer with lower risk of bleed

Fibrinolytic Therapy

- Use typically limited to extensive, severe cases
- tPA (alteplase), Tenecteplase
- Streptokinase
  - Potentially more likely to cause allergic type reactions
- Bleeding risk (be aware of patients who may have or have recently had internal bleeding, also use with caution in patients who may have had recent head trauma) with all fibrinolytics
- Avoid use in active internal bleeding, recent head trauma, intracranial or spinal surgery, severe uncontrolled hypertension

Direct Oral Anticoagulants (DOACs)

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DOACs

- Gaining popularity
  - Atrial Fibrillation Guidelines (ACC) preferred
- Drug interactions
- Less monitoring
  - Is that good or bad?
- When might you not choose them
  - Patient stability
  - Prosthetic valves
  - Adherence issues (t ½ longer for warfarin)
  - CKD (apixaban may be the exception)
  - Cost/insurance coverage
  - Provider comfort/preference

Apixaban

- Apixaban
  - Twice daily
  - Possible dose adjustments based upon age, creatinine, weight
  - DVT Treatment 10 mg BID for 7 days then 5 mg BID
  - Afib – 5 mg BID
  - 2 of 3; age ≥ 80, body weight <60, or creatinine ≥ 1.5; reduce dose to 2.5 BID
  - Post op prophylaxis – 2.5 BID
  - Specific dose adjustments for 3A4 and P-glycoprotein inhibitors like clarithromycin, ketoconazole, itraconazole, ritonavir
  - Reversal - coagulation factor Xa [recombinant], inactivated-zhzo
  - Preferred DOAC in severe renal impairment (warfarin alternative) - ACC

Rivaroxaban

- Rivaroxaban
  - Once daily
  - 3A4/P-glycoprotein interactions possible
  - <30mls/min avoid use
  - DVT – 15 mg BID for 21 days followed by 20 mg daily
  - DVT prophylaxis – 10 mg daily; up to 35 days
  - Afib – 20 mg daily
  - May have to reduce dose in elderly with CrCl between 30-50 mls/min
  - Reversal - coagulation factor Xa [recombinant], inactivated-zhzo

Edoxaban

- Edoxaban
  - >95 mls/min boxed warning (stroke)
  - Once daily
  - Creatinine clearance 15-50 mls/min – dose reduction (30 mg daily)
  - Usual dosing = 60 mg daily
  - Reduced dose with 3A4/P-glycoprotein inhibitors
  - Avoid in very obese/low weight extremes

Dabigatran

- Direct Thrombin Inhibitor
- GI bleed risk >75 y/o
- Reversal agent available
- Dose adjustment in CKD
- Twice daily

Betrixaban

- Only indicated in VTE prophylaxis in hospitalized patients
  - Limits its widespread use
- Daily dosing
- Similar risks (bleed) to other agent
- P-glycoprotein inhibitors can increase concentrations (amiodarone, clarithromycin, verapamil, ketoconazole, azithromycin)
  - Reduce dose in half

Warfarin

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Warfarin Common Indications

- Atrial Fibrillation (2-3)
- DVT/PE (2-3)
- Prosthetic Mechanical Mitral Valve
  - 2.5-3.5
- Lower goals
  - High bleed risk
  - High fall risk

Warfarin - Pharmacokinetics

- Metabolized by
  - S-warfarin: CYP 2C9 (potent)
    - Metronidazole, fluconazole, Bactrim
  - R-warfarin: CYP 1A2, 2C19, 3A4
- Inducers can cause treatment failure
  - Carbamazepine, St. John's Wort
- Bound to albumin
- Half-life = 36-42 hours

Warfarin – Adverse Effects

- Bleeding
- Purple Toe Syndrome
  - Don't load warfarin
  - Painful purple lesions on toes and sides of feet

Warfarin – How long does it take to work?

- Half-life of clotting factors
  - II - 60 hrs (prothrombin)
  - VII - 6 hrs
  - IX - 24 hrs
  - X - 40 hrs (reduction of II and X = prolongation of PT)
- Half-life of anticoagulants
  - Protein C 6 hrs
  - Protein S 72-96 hrs

Causes of INR Variation

- Adherence
- Diet
- Drug Interaction
- Changes in Disease States
  - Liver
  - CHF
  - Fever

Dose Adjustments

- Goal INR 2-3
- 10-15% adjustments (based on total weekly dose)
- Aggressiveness based upon INR
- Hold doses for INR greater than 4 in most circumstances
- INR of 5+, may want to recheck

Vitamin K

- Elevated INR and bleeding
- INR greater than 9
- Not going to work instantly
- Transfusion for acute, severe blood loss
- INR 5-9, no bleeding
  - May give vitamin K, don't have to

Hyperlipidemia

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Cholesterol Basics

- High levels of cholesterol, particularly LDL is associated with heart disease
- Cholesterol deposits form in vessels
- Deposits can break loose and clog in vessels – heart attack/stroke happens
- Asymptomatic

Hyperlipidemia Basics

- LDL is primary focus for statin medications
  - Shift back toward target goals
- Triglycerides – primary target >500
  - Fibrates
  - Niacin

Cardiovascular Risk Stratification Considerations

- Age
- Sex
- Family history
- Smoking
- Obesity
- Alcohol
- Hypertension
- Diabetes
- Metabolic Syndrome
- Physical activity
- Lipid levels
- Diet

ACC/AHA Risk Calculator – Primary Prevention

- Provides 10 year risk as well as if aspirin is recommended
- Factors
  - Age
  - Gender
  - Race
  - Cholesterol/HDL (doesn't use LDL in calculator, but if >190 recommend likely starting statin)
  - Blood Pressure (level plus if on medication)
  - Diabetes
  - Smoking
- Primary prevention 5-10% risk – clinical gray area

Risk Stratification – Coronary Calcium

- Age 40-75, no diabetes, LDL between 70-190, ASCVD risk between 5-7.5% - clinical discussion, judgement, might consider coronary calcium testing in rare cases
- Age 40-75, no diabetes, LDL between 70-190, ASCVD risk between 7.5-20% - consider coronary artery calcium testing and moderate intensity if indicative of calcium buildup

Coronary Artery Calcium (CAC)

- Coronary artery calcium (CAC) – scored by points
  - <100 – lower risk, less likely to be aggressive with pharmacotherapy for LDL reduction
  - >100-300 – significant cardiovascular risk – likely to be more aggressive with LDL lowering agents
  - >300 – very high risk, LDL lowering therapy recommended
- CAC – scored by percentile
  - >75% percentile – more likely to add LDL lowering pharmacotherapy
  - <75% percentile – less likely to start LDL lowering pharmacotherapy and more likely to work on diet/lifestyle changes

Target Goal of LDL <70 is Back

- Very high risk cardiovascular patients
  - Previous MI, ischemic stroke, etc.
- High intensity statin
- Ezetimibe like to be first step after that to get patients to goal
  - Does have some cardiovascular outcomes data
- PCSK-9 inhibitors

High Intensity Examples

- Atherosclerotic CVD
- LDL >190
- Diabetes and CVD 10 year >7.5%
  - Age 40-75
- Age 75 – magic number to assess risk/benefits and aggressiveness of therapy

Table 1. Statin Therapy

Intensity	Definition	Dosage
Low	Daily dose lowers LDL-C by <30%, on average	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg
Moderate	Daily dose lowers LDL-C by approximately 30% to <50%, on average	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2-4 mg
High	Daily dose lowers LDL-C by approximately ≥50%, on average	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg

C: cholesterol; XL: extended-release.
Source: Reference 1.

LPharmacist.com

Clinical Pearls

- Rosuvastatin/Atorvastatin for high intensity
- Generally avoid simvastatin if not on/hasn't tried others
  - CYP3A4 interactions (amlodipine, amiodarone, diltiazem, etc.)
- Rosuvastatin
  - Most potent LDL lowering, less strict on interaction with gemfibrozil
- Atorvastatin
  - Covers moderate/high intensity nicely
  - Does have some 3A4 interaction potential
- Lovastatin
  - 3A4 potential

Clinical Pearls

- If myopathy on CYP3A4 agent, try an alternative that doesn't use that pathway
  - If tried atorvastatin, avoid lovastatin, simvastatin if alternatives have not been tried
  - Look for drug interactions that might be contributing
  - Co-Q10?
- Hydrophilic may help reduce myopathy
  - Pravastatin
  - Rosuvastatin
  - Fluvastatin
- Lipid checks – recommended to assess adherence

Alternative Options – High Risk Patients

- Rechallenge with statin is recommended
- Ezetimibe
- PCSK9 inhibitors
- Target LDL <70

Triglycerides

- Fenofibrate
  - Maybe less risk with statin interaction/myopathy
  - Not at high ASCVD risk and TG's greater than 500
- Gemfibrozil
  - Interaction with statins (rhabdomyolysis, CPK etc.)
- Niacin
  - Better at increasing HDL
  - Flushing/Uric acid
- Omega-3 Fatty Acids
  - Icosapent ethyl
  - Efficacy in CV risk reduction (patients who are already on a statin and need TG lowering)
  - TG 150-1,000

PCSK9 Inhibitors

- Alirocumab, evolocumab
- Humanized monoclonal antibodies
- $$$
- LDL reduction up to 60-70%
- Local injection reactions (pain, swelling)
- Hypersensitivity reactions (itching, rash)
- Low to no muscle toxicity

Hypertension Pearls

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Complications/Risks

- MI
- Stroke
- Kidney
- Vision
- Heart Failure
- Aneurysm

Setting Goals

- American Heart Association and American College of Cardiology
- Elevated systolic – 120-129 (do not begin pharmacotherapy, lifestyle interventions; exercise, DASH diet, etc.)
- JNC-8 cutoffs were 140/90 and 150/90 for elderly without higher risk disease states
- New updates lower threshold for pharmacotherapy in higher risk populations

Stage 1 Hypertension 130-139 or 80-89

- Lifestyle modification for low risk patients
- Medication therapy for high risk patients (Goal <130/80)
  - CV event
  - Diabetes
  - CKD
  - Risk stratification
    - If greater than 10% ASCVD 10 year risk
    - http://www.cvriskcalculator.com/

ISH

- Essential
  - Target BP reduction by at least 20/10 mmHg, ideally to < 140/90 mmHg
  - Aim for BP control within 3 months
- Optimal
  - < 65 years: BP target < 130/80 mmHg if tolerated
  - > 65 years: BP target < 140/90 mmHg if tolerated, but consider and individualized BP target depending on frailty, independence, and tolerability of medication

Clinical Factors

- Age/life expectancy
- Falls
- Hypotension history
- Drug induced hypertension
- Medical causes of hypertension

Drug Induced Hypertension

- NSAIDs
- Stimulants
- Corticosteroids
- Estrogen
- SNRI's
- ESA's

Medical Induced Hypertension

- Sleep apnea
- Thyroid
- Adrenal gland problems
- Illicit drug use/addiction
  - Opioid withdrawal

Hypertension Medications

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ACE Inhibitors

- Common Side Effects
  - Cough
  - Kidney impairment
    - Worry about 30% changes or more
    - Diuretics/NSAIDs
  - Hypotension
  - Hyperkalemia

Clinical Pearls

- ACE inhibitors can exacerbate CKD, but can also help be renal protective
- Lisinopril most commonly used
- Classic medication cause of angioedema (extremely rare)
- In some cases, African Americans may not respond to ACE Inhibitors as well as other ethnicities
- Avoid ACE/ARB combo

Compelling Indications

- Diabetes
- Stroke
- CAD
- CKD
- CHF

Angiotensin Receptor Blockers

- Losartan
- Valsartan
- Irbesartan

ARB Clinical Pearls

- Think ACE minus the cough
  - Hyperkalemia
  - Kidney function
  - Angioedema
  - Similar compelling indications

Thiazide Diuretics

- Memorable Side Effects
  - Increase urine output
  - Frequent urination
  - Electrolyte depletion
  - Low blood pressure
  - Hyperuricemia
  - Hypercalcemia
  - Increased risk of kidney failure
- Chlorthalidone has best outcomes data

Use Caution

- Gout
- Poor kidney function (CrCl <30)
- Timing near night
- Hyperglycemia

Calcium Channel Blockers

- Dihydropyridines – amlodipine, nifedipine, felodipine
- Non-dihydropyridines – verapamil, diltiazem
- Dose dependent edema
- Constipation
- Simvastatin interaction

Calcium Channel Blockers

- Compelling Indications
  - Angina
  - Atrial Fibrillation (diltiazem, verapamil)
  - CVD risk
- Caution
  - Heart failure

Beta-Blockers

- Cardioselective
  - Metoprolol
- Non-selective
  - Propranolol
- Alpha and Beta blockade
  - Carvedilol, labetalol

Beta-blockers

- Compelling Indications
  - CHF
  - MI
  - Angina
  - Afib

Beta-blocker Pearls

- Asthma/Airway disease
- Pulse
- Hypoglycemia masking
- Risk of rebound hypertension
- Non-selective uses
  - Tremor
  - Esophageal varices
  - Thyroid storm
  - Migraine

Alpha-Blockers (for hypertension)

- Doxazosin
- Prazosin
- Terazosin

Alpha-Blocker Pearls

- Orthostasis
- BPH compelling indication
- Typically dosed at night
- Prazosin off label for nightmares

Hydralazine

- Multiple doses
- Contraindicated in coronary artery disease
- Lupus type syndrome
- Vasodilator – hypotension risk may be a little greater than other antihypertensives

Clonidine

- Centrally acting side effects (depression, sedation, dizziness)
- Bradycardia
- Dry mouth
- Avoid in elderly
- Rebound hypertension
- Lots of unique uses
  - Opioid/nicotine withdrawal
  - ADHD
  - Clozapine excessive salivation

Aldosterone Antagonists

- Spironolactone, Eplerenone
  - Heart failure compelling indication with mortality benefit
  - Should be used in NYHA Class II-IV with ejection fraction of 35% or less
- Hyperkalemia
- Gynecomastia
- Avoid eGFR <30 ml/min, K+ >5
- 100mg spironolactone/40 mg furosemide

Peripheral Vascular Disease

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Factors That Can Contribute to PVD

- Smoking
- Diabetes
- Obesity
- High cholesterol
- High blood pressure
- Clot formation
- Viscosity of the blood

Peripheral Vascular Disease

- Lack of or inadequate blood flow to legs, extremities
- Causes claudication
  - Pain when walking as demand for blood flow/oxygen increases
- Symptoms will get worse the further the patient tries to walk
- Sharp, cramping, sometimes numbness type pain usually relieved by resting for a period of time
  - Calf muscle often affected
- Atherosclerosis, narrowing of the arteries is the usual cause
- May see wounds that won't heal (inadequate blood flow)
- Risk of amputation
- Pedal pulse absent or very weak

Medications

- Statins
- Treat hypertension
- Manage diabetes
- Antiplatelet therapy (aspirin or clopidogrel if aspirin is contraindication)
- Smoking cessation
- Weight loss

Cilostazol

- Trial for 3 months
  - If no improvement discontinue
- Administer on empty stomach
- Boxed warning – don't use in heart failure
- Possibility to alter bleed risk
- Possible 2C19 and 3A4 interactions

Pentoxifylline

- Possible antiplatelet activity
  - Reduces blood viscosity
  - Increase bleed risk potential
- GI side effects if anything
- Generally not that effective
  - Rarely see it used
- Bypass surgery if severe enough

Stroke and TIA's

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Types of Stroke

- Hemorrhagic
- TIA
- Ischemic
  - Local (Atherosclerotic)
  - Heart (Atrial Fibrillation)

Classic Signs

- Face drooping
- One sided arm weakness
- Slurred Speech
- Confusion
- Vision changes
- Fall

Classic Risk Factors

- Hypertension
- Smoking
- Atrial Fibrillation
- Diabetes
- Hyperlipidemia
- Age
- Genetics

Prevention of Stroke

- Manage modifiable risk factors
  - Hypertension
  - Smoking
  - Weight loss
  - Diabetes
  - Statins

Options for Long Term Management of Stroke

- Atherosclerotic
  - Aspirin
  - Aggrenox (Aspirin/Dipyridamole)
  - Clopidogrel
    - Ticlopidine – neutropenia
    - Avoid prasugrel – Boxed warning to avoid use in patients with stroke
  - Dual antiplatelet (i.e. clopidogrel and aspirin) therapy may be considered short term (3 weeks) in high risk patients
- Cardioembolic (Atrial Fibrillation)
  - DOACs
  - Warfarin
  - Aspirin

Pulmonology

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Asthma

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Asthma Versus COPD

- Reactive
- Younger onset
- Reversible
- Wheeze
- Inflammation

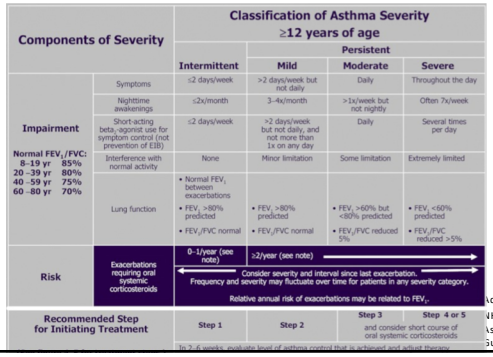
- Triggers
  - Exercise
  - Cold air
  - Infection
  - Environmental allergies
  - GERD
  - Medications (i.e. beta-blockers)

Factors in Classification

- Frequency of exacerbations requiring oral steroids
- SABA use
- Interference with activity
- Nighttime awakenings
- FEV (peak flow)
  - Target 80% of predicted or better

Rule of 2 in Asthma

- ≤ 2 times/week – use of albuterol
- ≤ 2 nighttime awakenings/mo
- > 2 refills per year on rescue
- ER visits/hospitalizations



Components of Severity		Classification of Asthma Severity ≥12 years of age			
		Intermittent	Persistent: Mild	Persistent: Moderate	Persistent: Severe
Impairment	Symptoms	≤2 days/week	>2 days/week but not daily	Daily	Throughout the day
	Nighttime awakenings	≤2x/month	3–4x/month	>1x/week but not nightly	Often 7x/week
	Short-acting beta$_2$-agonist use for symptom control (not prevention of EIB)	≤2 days/week	>2 days/week but not daily, and not more than 1x on any day	Daily	Several times per day
Normal FEV$_1$/FVC: 8–19 yr 85%; 20–39 yr 80%; 40–59 yr 75%; 60–80 yr 70%	Interference with normal activity	None	Minor limitation	Some limitation	Extremely limited
	Lung function	• Normal FEV$_1$ between exacerbations • FEV$_1$ >80% predicted • FEV$_1$/FVC normal	• FEV$_1$ >80% predicted • FEV$_1$/FVC normal	• FEV$_1$ >60% but <80% predicted • FEV$_1$/FVC reduced 5%	• FEV$_1$ <60% predicted • FEV$_1$/FVC reduced >5%
Risk	Exacerbations requiring oral systemic corticosteroids	0–1/year (see note)	≥2/year (see note)		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV$_1$.			
Recommended Step for Initiating Treatment		Step 1	Step 2	Step 3 and consider short course of oral systemic corticosteroids	Step 4 or 5
		In 2–6 weeks, evaluate level of asthma control that is achieved and adjust therapy.			

Adapted from NHLBI – Asthma Guidelines

Asthma Control Test - Questions

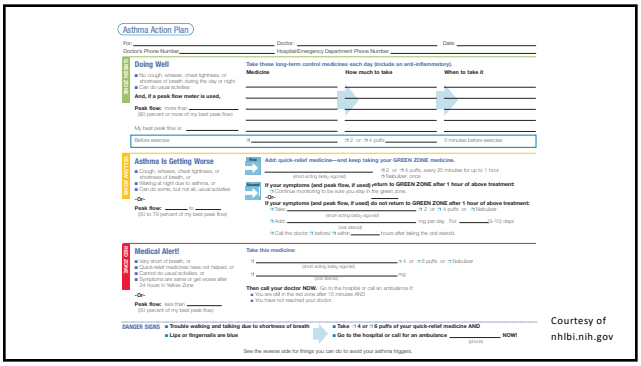
- In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?
- During the past 4 weeks, how often have you had shortness of breath?
- During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?
- During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?
- How would you rate your asthma control during the past 4 weeks?

ACT - Scoring

- 1-5, 5 = none of the time or not at all
- <15 – likely very poor control
- 15-19 – could likely use some improvement
- 20+ - decent control

Asthma Action Plan

- Delineates green, yellow and red zones for asthma care based upon peak flow readings
- Peak flow meter (kazoo looking device for home use) can aid in recognizing exacerbation in patients diagnosed with asthma
- The asthma action plan also designates specific actions to take when the patients peak flow reading is in each respective zone (i.e. call your doctor now, change medications, begin steroid therapy, etc.)



Courtesy of nhlbi.nih.gov

Global Initiative For Asthma (GINA)

- "GINA no longer recommends starting treatment of asthma with short-acting beta2-agonist reliever inhalers on their own. Instead, GINA recommends that all adults and adolescents with asthma should receive either symptom-driven (for mild asthma) or daily inhaled anti-inflammatory controller treatment, to reduce their risk of serious exacerbations and to control symptoms."

GINA Asthma Management

- Historically, SABA alone was used
  - Helpful for relieving symptoms
  - Did not touch inflammation
- Recommends symptom-driven (PRN) or daily inhaled inflammatory controller treatment
- Avoid SABA alone
  - "Helps patients not develop a pattern of reliance early in the disease"
  - Use SABA in combination with ICS

Using PRN LABA/Steroid

- Budesonide 80 mcg/formoterol 4.5 mcg **or** budesonide 160 mcg/formoterol 4.5 mcg: 1 inhalation as needed; may repeat if no relief
- Salmeterol (component of Advair) – Onset is approximately 30 minutes – DO NOT USE
- Formoterol (component of Symbicort) – Onset 3 minutes

Steps in Asthma Treatment

- Intermittent – SABA alone (GINA guidelines recommend PRN steroid/beta agonist)
- Mild Persistent – SABA + Low dose inhaled corticosteroid
- Moderate Persistent – SABA + Medium dose inhaled corticosteroid or LABA/low dose CS combination
- Severe Persistent – SABA + ICS + LABA and/or montelukast

Beta-Agonists And Inhaled Steroids

- Beta-agonists
  - Acute relief of respiratory distress (SABA + formoterol)
  - AE's – shakiness, tremor, tachycardia, anxiety
  - Potential impact of reducing serum potassium, but rarely clinically significant with inhaled medications
  - Monitoring use of SABA and frequency of exacerbation in asthma is very important in assessing severity/staging of asthma
- Inhaled corticosteroids
  - Reduce inflammation
  - Increased risk of thrush (rinsing mouth important)
  - Long term systemic concerns are not as big of a deal with inhaled corticosteroids compared to systemic corticosteroids (i.e. hyperglycemia, osteoporosis, HPA suppression, etc.)

Severe Asthma

- Anticholinergics (tiotropium)
- Anti-IgE therapy (omalizumab)
- Anti-IL5 therapy (mepolizumab, reslizumab, benralizumab) – eosinophilic type asthma
- Oral corticosteroids (chronic)
- Theophylline
- Cromolyn

LAMA

- Long Acting Muscarinic Antagonists (LAMA) AKA Long Acting Anticholinergics
  - Alternative to those intolerant of LABA therapy
  - Add on in refractory patients
  - See COPD for more information

Biologics

- Biologic Agents
  - Omalizumab (Xolair)
  - Omalizumab – targeted for elevated IgE and asthma related to allergies
    - Boxed warning for anaphylaxis – administer in healthcare setting
  - Eosinophilic asthma – mepolizumab (Nucala), benralizumab (Fasenra), dupilumab (Dupixent), reslizumab (Cinqair) **tezepelumab (Tezspire) -also indicated for non-eosinophilic
  - Very costly
  - Used in severe, refractory cases

Theophilline

- Theophylline (Uniphyl)
  - Mechanism of Action: Inhibits airway smooth muscle phosphodiesterase's which can help relax the airway and allow for improved respiratory status
  - Last line therapy
  - Monitoring of drug levels (target usually 5-15)
  - Lots of drug interactions through CYP1A2
  - Lots of systemic effects
    - Similar effects to caffeine: GI, tachycardia, tremor, insomnia, anxiety

Acute Exacerbation

- Systemic Steroids for exacerbation
  - Usual adult dose range 40-60 mg/day (prednisone)
  - Prednisolone 0.5-1mg/kg/day for pediatrics
  - Usually no more than 10-14 days is necessary for acute exacerbation resolution (ideal to minimize length of steroid if possible to prevent risk of systemic effects)

Nebulizers

- Pediatrics/elderly
- Albuterol, levalbuterol
- LABA (formoterol, aformoterol)
- Budesonide
- Ipratropium
  - Ipratropium - combination with albuterol (Duoneb)
  - Revefenacin (LAMA)

COPD

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GOLD Staging

- 1 – mild (FEV1 >80% of predicted)
- 2 – moderate (FEV1 50-80)
- 3 – severe (FEV1 30-50)
- 4 – very severe (FEV1 <30)

ABCD - Classification

- Based upon symptoms and risk of exacerbations/hospitalization
- A – Less symptoms and low risk
- B – More symptoms but low risk
- C – Less symptoms but high risk
- D – More symptoms, high risk
- 2 or more exacerbations or 1 or more leading to hospitalization will put you in higher risk category per year (C or D)
- 0-1 exacerbations per year and no hospitalization (A or B)
- mMRC and CAT are assessments used to assess symptoms and the impact on the patients QOL

CAT and mMRC

- CAT (COPD Assessment Test)
  - Symptom assessment test that incorporates cough, phlegm, energy, sleep, and other factors
  - Scored from 0-40 with 40 being the worst
    - <10 less symptoms
    - 10 or greater more symptoms (places patient in B if low exacerbation risk)
- Modified Medical Research Council Questionnaire (mMRC)
  - 0-4 scoring based upon dyspnea symptoms with 4 being severe dyspnea that prevents leaving the house or when doing simple activities such as getting dressed
    - 0-1 – Less symptoms
    - 2-4 – More symptoms (places patient in B if low exacerbation risk)

Drug Therapy by ABCD Classification

- A – PRN SABA/SAMA (may be necessary in all classes)
- B – LAMA or LABA monotherapy
- C – LAMA (if additional therapy is necessary, you'd like add LABA)
- D – LABA, LAMA, +/- ICS +/- roflumilast +/- azithromycin

General Medication Flow

- SABA/Short Acting Anticholinergic
  - Or Combo
- Long Acting Anticholinergic (LAMA)
- Long Acting Beta Agonist (LABA)
- Inhaled corticosteroids (ICS)
- Roflumilast
- Azithromycin
- Theophylline

Adverse Effects Beta Agonists, Anticholinergics

- Beta Agonists (i.e. albuterol, salmeterol)
  - Tachycardia
  - Tremor
- Anticholinergic (i.e. ipratropium, tiotropium)
  - Dry mouth

Inhaled Corticosteroids

- Reduces Exacerbations
- Not used as monotherapy in COPD
- Systemic Corticosteroids
  - Avoid long term if possible
  - OP, GERD, HPA suppression, Diabetes

Roflumilast

- Reduces exacerbations
- $$
- SE risks
  - Weight loss, GI
  - Psychiatric concerns
- 3A4 Interactions
  - Inducers – treatment failure (rifampin, St. John's wort, carbamazepine, etc.)

Other Alternatives

- Theophylline
  - Drug levels (10-20)
  - Drug interactions (CYP1A2)
    - Quinolones, macrolides
    - Sympathomimetics
  - Systemic effects – Ramps you up; insomnia, tremor, tachycardia, GI upset
- Azithromycin
  - Frequent exacerbations – prophylaxis
  - Watch QTc prolongation risk

Classic Medication Causes of Respiratory Issues

- Amiodarone
- Nitrofurantoin
- Beta-blockers
  - Can blunt response to medications (beta-agonists)

Other Considerations

- Oxygen
- Vaccination
- Smoking
- Alpha-1 antitrypsin deficiency (AATD) screening

Anticholinergics

- Aclidinium (Tudorza Pressair)
- Glycopyrronium (Seebri Neohaler)
- Ipratropium (Atrovent)
- Tiotropium (Spiriva)
- Umeclidinium (Incruse Ellipta)

Beta Agonists

- Arformoterol (Brovana)
- Formoterol (Foradil; Perforomist)
- Indacaterol (Arcapta Neohaler)
- Salmeterol (Serevent)
- Olodaterol (Striverdi Respimat)

Corticosteroids

- Beclomethasone (Qvar)
- Fluticasone (Flovent)
- Ciclesonide (Alvesco)
- Mometasone (Asmanex)
- Budesonide (Pulmicort)
- Flunisolide (Aerobid)

Combination Inhalers

- Albuterol and ipratropium (Combivent Respimat; Duoneb)
- Budesonide and formoterol (Symbicort)
- Fluticasone and salmeterol (Advair)
- Fluticasone and vilanterol (Breo Ellipta)
- Formoterol and mometasone (Dulera)
- Tiotropium and olodaterol (Stiolto Respimat)
- Umeclidinium and vilanterol (Anoro Ellipta)
- Glycopyrrolate and formoterol (Bevespi Aerosphere)
- Indacaterol and glycopyrrolate (Utibron Neohaler)
- Fluticasone and umeclidinium and vilanterol (Trelegy Ellipta)

Pulmonary Hypertension

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Pulmonary hypertension

- Elevated pressure in lung arteries
  - Narrowing, damage, blockage
- Can result in right side heart failure (HFpEF)
  - SOB
  - Fatigue
  - Edema
  - Poor perfusion
  - Tachycardia

Classification of Symptoms

- Class 1 – Patients without symptoms at rest or during exercise (diagnosis unlikely)
- Class 2 – No symptoms at rest, but SOB with daily tasks (i.e. walking, stairs, etc.)
- Class 3 – No symptoms at rest, but very short of breath, possibly feel faint, and feel limits with what they can do in normal activities
- Class 4 – Symptoms at rest (usually hospitalized), may have edema secondary to right sided heart failure

Management – Non-Vasoreactive Patients

- Endothelin Receptor Antagonists
  - Ambrisentan, bosentan
  - REMS program – pregnancy, fetal risks
  - Liver toxicity (Bosentan, REMS)
  - Edema, headache
- Sildenafil, tadalafil
  - Nitrate interaction
  - Flushing
  - Headache
  - Tadalafil has longer half-life
- Combination Therapy
  - Stage 2 or 3 PAH
- Monotherapy for Stage 1

Management

- CCB's
  - Vasoreactive Pulmonary Arterial Hypertension (10-20%)
  - Usually well tolerated
- Prostanoids (i.e. epoprostenol, iloprost)
  - Stage 4
  - IV administration for acute issues (epoprostenol)
  - Potential for tolerance and rebound if abruptly discontinue
  - Bleed risks – platelet inhibition
  - Diarrhea, flushing, muscle pain

Endocrinology

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Diabetes: Compelling Indications, Complications, and Goals

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Diabetes Monitoring

- A1C target of less than 7 in most nonpregnant patients (ADA)
- A1C target less than 6.5 can be considered so long as risks of hypoglycemia are minimal and adverse effects are minimized
- Age greater than 65 with few chronic conditions who have good cognitive function and functional status may have a goal of <7.5
- Risk of hypoglycemia, older age, cognitive impairment, limited life expectancy are all examples of situations where relaxed A1C goals may be appropriate (i.e. A1C less than 8 or even <8.5)
- Blood sugars
- Kidney, eye, feet

Glucose Monitoring

- 80-130 mg/dL – Premeal
- <180 mg/dL – Postmeal
- <70 mg/dL - Hypoglycemia

Complications

- Cardiovascular Disease
- Neuropathy
- Nephropathy
- Retinopathy
- Gastroparesis
- Amputation risk
- Infection risk

Preventative Medications

- Remember cardiovascular risk factors and use of statins, antihypertensives, and aspirin
  - Moderate to high intensity statin is indicated (age 40-75) for primary prevention in patients with diabetes
  - <7.5% 10 year ASCVD risk – moderate
  - >7.5% - high
- Majority of diabetics with latest guidelines based upon CV risk calculation will have a BP target goal of <130/80
  - ACE Inhibitor or ARB will be the first line antihypertensive with dihydropyridine calcium channel blocker (i.e. amlodipine) being the second best alternative

Preventative Medications (cont.)

- Aspirin
  - Most likely, but:
  - Consider risk with other medications (i.e. Warfarin, NSAIDs, etc.)
  - Past history
  - Bleeding
  - Risk calculators (See CHD lecture)
  - Dose of aspirin @ 81 mg is usually sufficient barring other rationale

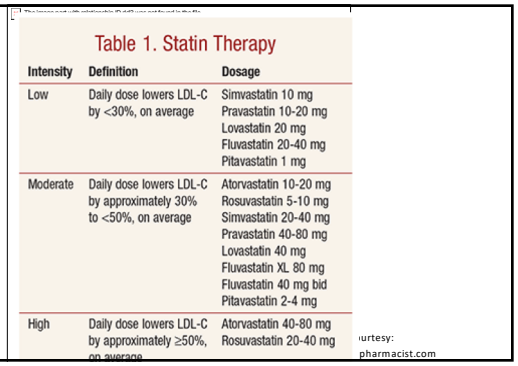

Table 1. Statin Therapy

Intensity	Definition	Dosage
Low	Daily dose lowers LDL-C by <30%, on average	Simvastatin 10 mg Pravastatin 10-20 mg Lovastatin 20 mg Fluvastatin 20-40 mg Pitavastatin 1 mg
Moderate	Daily dose lowers LDL-C by approximately 30% to <50%, on average	Atorvastatin 10-20 mg Rosuvastatin 5-10 mg Simvastatin 20-40 mg Pravastatin 40-80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2-4 mg
High	Daily dose lowers LDL-C by approximately ≥50%, on average	Atorvastatin 40-80 mg Rosuvastatin 20-40 mg

urtesy:
pharmacist.com

Hypertension

- ACE OR ARB
  - Renal protection
- CCB
- Thiazide

Diabetic Neuropathy

- Gabapentin/pregabalin
- SNRI's
- Topical Lidoderm
- TCA's

Gastroparesis

- Cause of GI nausea/upset in diabetes patients
- Metoclopramide
  - Parkinson's disease risk
- Erythromycin
  - Drug interaction risk
- Be careful with anticholinergics
  - Exacerbate gastroparesis

Changes That Can Impact Diabetes

- Steroids
- Beta-blockers
- Infections
- Dementia
- Medications that suppress or stimulate appetite

Treatment of Hypoglycemia

- Glucagon
  - Alertness compromised
  - <54
  - Nasal and injection available
  - Still need to give sugar (IV or oral)
- Sugar replacement
  - Aspiration
  - Choking

Diabetes: The Medications

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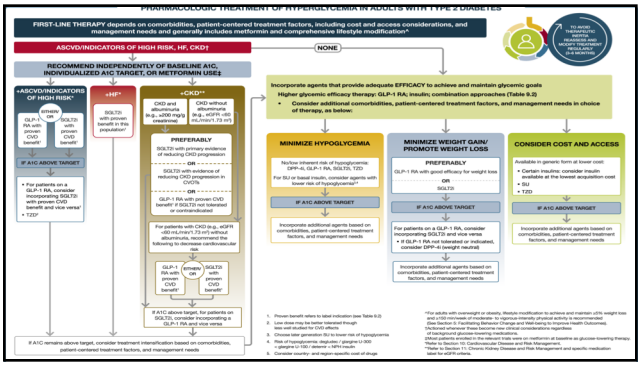
Metformin

- First line for most
- Kidney function
  - Target 45 mls/min
- GI side effects – give with food
  - Diarrhea
- Weight neutral to weight loss
- Low risk hypoglycemia
- B12
- Hold during contrast administration for 48 hours



SGLT-2 Inhibitors

- Empagliflozin, canagliflozin, dapagliflozin
- Caution in patient with urinary infection history (drugs increase sugar to the urine which can be food for bug)
- Mild diuretic type effect – watch BP, volume depletion, dehydration risk
  - Monitor K+; hyperkalemia risk especially in patients on ACE, ARB, etc.
- Caution on bone fracture risk, euglycemic ketoacidosis
- Contraindicated in eGFR <30
- Benefits
  - Cardioprotective effects (reduction in major CV events)
  - Some evidence of benefit in heart failure irrespective of diabetes diagnosis - dapagliflozin and empagliflozin
  - Renal benefit (dapagliflozin)
- Rare: Extremely rare association of necrotizing fasciitis of perineum, amputation
- A1C lowering effect is typically less than 1 point when used as monotherapy

GLP-1 Agonists

- Incretin
  - Post-prandial
- N/V SE's
  - (slow GI tract - can alter absorption of some drugs)
- Injection (oral semaglutide)
  - Weekly, daily, twice daily
- $$$
- Thyroid tumor risk, pancreatitis
- Weight loss
- Cardiovascular risk reduction

Sulfonylureas

- Glipizide, glimepiride, glyburide
- Hypoglycemia
- Weight gain
- Chlorpropamide (rarely used) SIADH risk

DPP-4 Inhibitors

- Sitagliptin, linagliptin etc.
- Well tolerated
- Increases incretin
  - Post-prandial
  - Promotes fullness
- Weight neutral
- $$$
- Generally low hypoglycemia when used alone
- Avoid combo with GLP-1
- Less potent A1C reduction than other agents

TZD's

- Reduces insulin resistance in peripheral
- Weight Gain
- Edema
- CHF risk

Alpha-glucosidase inhibitors

- Acarbose, miglitol
- Prevent breakdown of complex sugars in the gut
- GI side effects
- GI SE's and frequent dosing make these medications seldom used
- If patient has hypoglycemic episode, you MUST use simple sugars (i.e. glucose tablets)
  - Complex sugars may not be broken down due to the drugs MOA
- Hypoglycemia risk typically not an issue if used alone

Glinides

- Repaglinide
- Stimulates insulin release
- Hypoglycemia
- Weight gain risk
- Needs to be dosed with meals
- Frequent dosing can be a downside

Max A1C Lowering

- Metformin 1-2
- GLP1 – 1.5-1.8
- SGLT2 – 1
- SU 1-2
- DPP4 - 0.8
- TZD – 0.8

Insulin

- Sliding Scale
  - Short term use
- Long Acting
  - Targets fasting
- Rapid Acting
  - Targets post-prandial
- Diet Changes

Long Acting

- Glargine, detemir, degludec
- Fasting blood sugars
  - Will bring down all blood sugars (lasts all day)
- Weight gain, hypoglycemia
- Degludec has a much longer duration of action than detemir/glargine; be careful with increasing dose to quickly as it will take longer to get to steady state ("ultra-long acting")
  - May have to wait longer before increasing (up to 5-7 days versus 2-3 days for glargine/detemir)
- Typically target about 10% increases in dose for patients not at goal

Intermediate Acting Insulin

- Intermediate Acting Insulin
  - NPH
  - Rarely used due to use of long acting
  - May seen in;
    - Cost concerns
    - Refractory patients
    - Been on it a long time
  - May be used in combination with rapid acting insulin and dosed twice daily for those who have difficulty with basal/bolus regimens

Short Acting

- Short acting
  - Regular insulin
  - Typically given before the meal, rapid acting easier to manage
  - Can be a challenge in cognitively impaired elderly patients who may not remember to eat or decide not to eat following dose of insulin
  - Available without a prescription
  - Cheaper

Rapid Acting

- Rapid acting
  - Insulin aspart, lispro, glulisine
  - Give with meals or just prior
  - Useful in preventing/bringing down post-prandial blood sugars (those big spikes following meals)
  - Can be used just once or twice daily in Type 2
  - Sliding scale is not ideal management

Blood Glucose Targets

- Postprandial
  - Rapid acting insulin
  - Sulfonylureas
  - DPP-4
  - GLP-1
  - Glinides
  - Alpha-glucosidase inhibitors
- Preprandial/fasting
  - Long acting insulins
  - Metformin
  - TZDs
- Both
  - SGLT-2

Type 1 Diabetes

- Insulin therapy
- Insulin pumps growing in popularity versus basal/rapid acting injections
  - Allows for potential tighter control and more flexibility with meals
- If basal/bolus method used, rapid acting injections necessary for meals
- Frequent blood sugar checking necessary
- Initial dose requirements can vary but 0.5-1 units/kg in divided doses (for those using basal/bolus method) may be appropriate starting place
- Insulin requirements are often less in Type 1 than Type 2 diabetes

500 Rule

- Estimation of insulin to carb ratio – 500 rule
  - Used to help a patient determine how much insulin to use based upon carbohydrate intake
  - Take 500 divided by the total daily dose of insulin
  - Resulting fraction is the approximate rapid acting insulin to carb ratio for that patient
  - I.e. – patient takes a total daily dose of insulin of 30 units: 500/30 = 17/1 (carbs/unit of insulin)
  - *Use rule of 450 for regular insulin

1800 Rule

- Insulin correction factor – 1800 rule
  - Estimates amount of blood sugar lowering effect per unit of insulin
  - Divide 1800 by the total daily dose of insulin
  - I.e. – patient takes a total daily dose of insulin of 60 units: 1800/60 = 30; 1 unit of rapid acting insulin would bring down the blood sugar by 30 mg/dL
  - This can be applied if the patient needs extra blood sugar lowering above and beyond the requirements for the anticipated meal/snack intake
  - *Use rule of 1500 for regular insulin

Sick Day – Type 1 Diabetes

- Illness can lead to hormone (epinephrine and cortisol) production and an increase blood sugar
  - Risk of diabetic ketoacidosis for type 1 patients
- Can be complicated by diet changes (i.e. nausea/vomiting) – decreased medications/insulin may be necessary if inadequate oral intake
  - Risk of hypoglycemia
- Increase blood sugar checking
- Check for ketones in the urine
- Consider small insulin boluses throughout the day as needed based upon blood sugar reading
  - 5-10% of total daily dose
- Persistent vomiting and hypoglycemia
  - May need to go to ED or hospital

Thyroid Disorders

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Hypothyroidism - Diagnosis

- Usually elevated TSH and low T4
- Symptoms
  - Lethargy
  - Cold
  - Weight Gain
  - Constipation
  - Hair loss/Skin Dryness
  - Lack of energy

Levothyroxine

- Usual starting dose 25-50 mcg/day
- Binding interactions
  - Consistency with administration
- Follow up – 6 weeks to 3 months

Drugs That Can Impact Thyroid Function

- Amiodarone
  - Hyperthyroid or Hypothyroid
- Lithium

Levothyroxine Interactions

- Enzyme Inducers
  - Phenobarbital
  - Carbamazepine
- Binding interactions
  - Calcium
  - Cholestyramine
  - Sucralfate
  - Iron

Hyperthyroidism

- Methimazole
- PTU
  - Liver toxicity
- Risk
  - Weight Loss
  - Tachycardia
  - Insomnia
  - Nervousness
  - Osteoporosis

Thyroid Storm

- Symptoms
  - Tachycardia
  - Anxiety
  - Agitation
  - Psychosis
  - Elevated temp
- Treatment
  - Beta-blocker
    - Helps with tachycardia/anxiety
  - Antithyroid medication
    - I.e. PTU/Methimazole

Menopause and Estrogen Use

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Menopause Symptoms

- Hot flashes
- Fatigue
- Mood/depression related concerns
- Vaginal atrophy/dryness
- Night sweats
- Insomnia
- Weight gain

Loss of Estrogen Risks

- Osteoporosis
- Cardiovascular disease
- Incontinence
- Sexual problems (decreased libido, vaginal dryness etc.)

Management of Symptoms

- Hormone replacement therapy
- Very effective, but comes with risks
- If patients need to use estrogen replacement
  - Minimize length of therapy if possible
  - Minimize dose if possible
  - Various dosage forms patch, tablet, ring
- For patients with intact uterus
  - Need to utilize progestin if estrogen is going to be used to reduce the risk of uterine cancer

Benefits and Risks of Estrogen

- Osteoporosis
- Colorectal Cancer
- Improve menopausal symptoms
- Clots
- CHD
- Breast Cancer
- Endometrial Cancer

Goals of Estrogen Therapy

- Treat symptoms
- Limit length of use
- Minimum Effective Dose
- Avoid use
- Discontinue
- Use local if possible (vaginal atrophy)

Alternatives to Estrogen

- Bazedoxifene/estrogen combination (Duavee)
  - Classification: Tissue Selective Estrogen Complexes – TSECs
  - SERM combined with estrogen
  - Potential option to avoid progestin risks/side effects
- Non hormonal medications may be helpful for menopausal symptoms like hot flashes, mood changes
  - SNRI's
    - Venlafaxine
  - SSRI's
    - Paroxetine, citalopram
  - Anticonvulsants
    - Gabapentin

Obesity

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Obesity

- BMI >30
- Complications
  - Diabetes
  - Cardiovascular risk
  - Pain/physical complications
  - Sleep Apnea
  - GERD
- Patients are often unrealistic about weight loss and may feel defeated
  - Target 5-10% weight reduction

Options for Treatment

- Diet changes/calorie reduction
- Exercise
- Medications
  - OTC/Herbals
- Surgery

AGA Clinical Practice Guidelines

- Moderate Evidence
  - Semaglutide 2.4 mg
  - Liraglutide 3 mg
  - Phentermine-topiramate ER
  - Naltrexone-bupropion ER
- Low Evidence
  - Phentermine
  - Diethylpropion
- Avoid - Orlistat

Phentermine

- Stimulant
  - Acts via norepinephrine effects
  - Warnings/precautions regarding patient with cardiac complications/risk
    - Hypertension
    - Atrial fibrillation
  - Insomnia
- Controlled substance
  - Caution/avoid if history of addiction/drug abuse

Topiramate

- Seizure medication/migraines
- Cognitive slowing
- Combination product with phentermine

Bupropion

- Stimulating type antidepressant
- Avoid in seizures
- Smoking cessation benefit
- Combination with naltrexone

Orlistat

- Blocks fat absorption in GI tract
- Relatively safe
- Problematic oily diarrhea if patient has significant fat intake in diet
- May decrease fat soluble vitamin absorption
  - ADEK
  - Supplement with multivitamin may be necessary

Avoiding Weight+ Medications

- Antidepressants
  - Mirtazapine
  - TCA's
  - Paroxetine
- Sulfonylureas
- Pioglitazone
- Depakote
- Antipsychotics

Malabsorption, Malnutrition and Nutritional Deficiencies

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Malabsorption Disorders

- Lack of absorption of essential nutrients
- Cause
  - GI damage, alteration to GI tract
  - Surgery, Celiac disease, Crohn's
- Symptoms
  - Diarrhea
  - Weight loss
  - Poor growth (kids)
  - Anemia
  - Fatigue
  - Failure to thrive

Contributors to Malnutrition

- Cancer
- Dental Issues
- Restricted diets
- Finances
- Depression
- Taste/smell alterations
- Socially eating
- Alcoholism

Weight Loss – Medication Causes

- Digoxin
- Stimulants
- Acetylcholinesterase Inhibitors
- Diuretics
- *Be aware of timing of medication changes

Malnutrition Concerns

- Weight Loss
- Vitamin Deficiency
  - I.e. B12, thiamine, folic acid, etc.
- Low Albumin
  - Phenytoin
- Frailty

Replacement of Essential Nutrients

- B12
- Vitamins A, D, E, K
- Iron
- Thiamine
- Folic acid
- Electrolyte replenishment
  - Magnesium
  - Potassium
  - Calcium

Vitamin B12

- Deficiency
  - Can cause cognitive impairment/dementia if severe enough
  - Metformin, PPI's – possible contributors
  - Pernicious Anemia
    - Lack of intrinsic factor
    - GI absorption compromised
    - B12 injections
- Folic acid, iron, B12
  - See anemia

Thiamine

- Supplementation common for alcoholics
- Deficiency
  - Wernicke's encephalopathy
  - Acute delirium
  - Amnesia

Vitamin D

- Treatment of deficiency
  - Vitamin D 50,000 units weekly X 8 weeks
- Maintenance
  - Vitamin D 50,000 units/month
  - Vitamin D 1,000-2,000 units/day
- Target levels >30 (some may argue a little higher)
- Medication contributors
  - Anticonvulsants (phenytoin, phenobarbital, carbamazepine)
  - Leuprolide

Parenteral Nutrition

- IV nutritional supplementation
- Use oral when possible due to risks
  - Infection risk
  - Electrolyte/fluid abnormalities
  - Hyperglycemia
  - Refeeding syndrome*
  - Liver damage

Refeeding Syndrome

- Body adaptation to replacement of nutrients after starvation period
- Lipids/protein are energy sources in fasting state
  - Shift to carbs with TPN
  - Cells shift to storing/synthesizing fat/protein
    - Requires use of electrolytes
  - Electrolyte deficiencies possible
    - Potassium
    - Phosphorus
    - Magnesium
- Close monitoring of electrolyte/fluid status when initiating TPN

Caloric Requirements

- Harris Benedict equation
  - Weight, height, age, gender
  - Don't memorize
- Stress level on patient
  - Mild – 20-25 kcal/kg/day
  - Moderate 25-30 kcal/kg/day
  - Severe 30-40 kcal/kg/day
    - Severe burn patient example

Kcal Per Nutrient

- Carbs
  - 3.4 kcal/gm
  - D10% 340 kcal/L
- Protein
  - 4 kcal/gm
- Lipids
  - 9 kcal/gm
  - 10% lipid solution – 1.1 kcal/ml

Targeted Replacement (TPN)

- Carbs
  - 5 grams/kg/day
- Protein
  - 1-2 gram/kg/day (higher stress, target higher replacement)
- Fat (20-40% of caloric intakes)
- Fluid replacement (30-40 mls/kg/day)
  - 70 kg = 2,100 - 2,800 mls

Addison's Disease and Cushing's

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Addison's Disease

- Defined by a deficiency in cortisol (from adrenal gland)
  - Corresponding aldosterone deficiency
- Results in; - possible adrenal crisis
  - Low blood pressure
  - Hyperkalemia
  - Hyponatremia
  - Hypoglycemia
  - Skin darkening

Management

- Exogenous steroids
  - Prednisone/hydrocortisone
  - Lifelong therapy likely unless identifiable/treatable reason for deficiency
- Mineralocorticoid replacement
  - Fludrocortisone
    - Helps with hyponatremia
    - Side note – often used in the management of severe hypotension due to dialysis

Adrenal Crisis

- Acute, severe, symptomatic adrenal gland failure
  - Hypotension
  - Loss of consciousness
  - Hyperkalemia, hyponatremia
  - N/V
- IV glucocorticoid (hydrocortisone)
- Fluid replacement
- Sodium monitoring
- Dextrose – to treat hypoglycemia

Cushing's

- Opposite of Addison's
  - Excessive corticosteroid (cortisol)
  - Caused by oversupply of exogenous
- Weight gain
- Hyperglycemia
- Moon face/buffalo hump – fat distribution changes
- Acne
- HTN
- Osteoporosis

Treatment – Cushing's

- Remove exogenous steroids
  - SLOWLY!!!
- Abrupt discontinuation of long term steroids
  - Adrenal insufficiency
- Treat underlying cause if not due to excessive supplementation of steroid
  - I.e. cancer
  - Surgery, radiation
- Cabergoline – may help normalize production of cortisol
  - Low success rate
  - Dopamine agonist
    - May see used for elevated prolactin levels
    - Psych/GI adverse effects

Gastrointestinal Disorders

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GERD, PUD, and Dyspepsia

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GI Risk Considerations

- GI Diagnosis
  - PUD (Don't forget about H. Pylori)
  - GERD
  - Heartburn
  - Barrett's
- Length of medication use
- Reason for initiation

Proton Pump Inhibitors

- Incredibly common medication
- Often used for prophylaxis
- Often never reassessed
- Sometimes necessary long term

PPI Risks

- Fracture
- C. Diff
- Low Magnesium
- Pneumonia
- B12

PPI Drug Interactions

- Cefuroxime (concentrations reduced) – all PPI's
- Reduced iron absorption
- Rifampin/St. John's Wort – can reduce concentrations
- Omeprazole (2C19)
  - Clopidogrel (reduced concentrations)
  - Cilostazol (increased concentrations)
  - Citalopram/escitalopram

H2 blockers

- Kidney disease
  - Dose adjustments
- Confusion/CNS effects with accumulation
- Cimetidine – bad idea
  - Numerous 3A4 drug interactions

Antacids

- Calcium containing products
  - Constipation
  - Binding interactions
  - Work quickly
  - Don't last long
  - Rare accumulation of calcium if frequent use
    - Combination with HCTZ

Step Down Versus Step Up

- Step Down
  - Reducing PPI to less potent acid blocker
  - H2 Blocker
- Step Up
  - Start with antacid and/or H2 blocker
  - Step up to PPI if inadequate control

Classic Medication Causes of GI Issues

- Steroids
- Bisphosphonates
- Digoxin toxicity
- NSAIDs
- Metformin
- Acetylcholinesterase inhibitors
- GLP-1
- Antibiotics

H. Pylori

H. Pylori

- Major cause of GI ulcers
- Able to tolerate acid environment of stomach
- Breath test for diagnosis
- Symptoms
  - N/V
  - Abdominal pain
  - Weight loss
  - Burping

Treatment

- Typically 10-14 days
- Different regimens (see next slide for combo's)
  - Amoxicillin
  - Clarithromycin
  - Metronidazole
  - Bismuth
  - Tetracycline

Treatment

- Bismuth, metronidazole, tetracycline, PPI
- Amoxicillin, clarithromycin, PPI
- Clarithromycin, metronidazole, PPI
- Regimen considerations
  - Resistance
  - Previous treatments
  - Penicillin allergy

Clinical Pearls - Antibiotics

- Clarithromycin
  - Drug interactions via 3A4
  - QTc prolongation
- Metronidazole
  - Avoid alcohol
  - Neuropathy (more likely with long term use)
- Tetracycline
  - Binding interactions
  - Sun sensitivity

Crohn's Disease

Crohn's Versus Ulcerative Colitis

- Major Differences
  - Crohn's located "patches" throughout intestinal system
    - Can impact all the way through the intestine
  - Ulcerative colitis – continuous area in the colon and typically just the inner lining
  - Fistula's and strictures common in Crohn's

Treatment

- Dependent upon
  - Location
  - Severity
  - Maintenance or Remission
  - Past history

Severity Scale

- Crohn's Disease Activity Index
  - <150 remission
  - 150-220 mild
  - 220-450 moderate-severe
  - >450 severe (fulminant)

More Symptoms = Higher Score

- Fever
- Vomiting
- Obstruction
- Cachexia
- Abdominal pain
- Anemia/blood loss
- Tachycardia
- Frequency of loose stools
- Fistula or abscess

Goal of Therapy, Low Risk – Inducing Remission

- Induce remission
- First Line: Budesonide taper over 12 weeks – mild patients
- Why budesonide?
  - High-first pass metabolism
  - Limit systemic exposure

Drug Choice – High Risk, Remission Induction

- TNF-alpha inhibitor (infliximab, adalimumab, etc.)
- Combined with immunomodulator (i.e. MTX, azathioprine)
- Corticosteroids can be considered in addition
- For maintenance, these agents will likely be considered for long term use (except corticosteroids)

Maintenance (Preventing relapse)

- Options include
  - Anti-TNF therapy (moderate/high risk likely Rx to use)
  - Azathioprine, MTX, or 6-MP
    - Do thiopurine methyltransferase (TPMT) genetic testing (AZA, 6-MP)
  - Extend budesonide length of therapy (not ideal)
  - 5-ASA or sulfasalazine (colitis only)
    - Better for ulcerative colitis
    - Bacteria in the colon help breakdown sulfasalazine to 5-ASA component (most active)

Other Recommendations

- NSAIDs should be avoided – risk of exacerbating disease
- Cigarette smoking can worsen disease activity – avoid
- Symptom Management
  - Loperamide
  - Cholestyramine
  - Colestipol

Ulcerative Colitis

Symptoms

- ”Inflammatory” Bowel Disease
- Diarrhea, urgency
- Cramping
- Pain
- Possible blood
- Fatigue
- Fever

Crohn’s Versus Ulcerative Colitis

- Major Difference
  - Crohn’s located “patches” throughout intestinal system
    - Can impact all the way through the intestine
  - Ulcerative colitis – continuous area in the colon/large intestine and typically just the inner lining
  - Smoking may REDUCE symptoms in UC

Severity

- Ulcerative colitis disease activity index
  - Stool frequency
  - Bleeding
  - Mucosal appearance
  - Subjective rating of disease
- Up to 12 points (12 being the worst)

Medications

- Mesalamine
  - More appropriate in mild disease
  - Enema/suppository form can be helpful as typically only the colon is affected with Ulcerative Colitis versus Crohn’s disease
    - Enemas have deeper penetration into the colon than suppository
  - Patients may not like enema form
  - Combination topical and oral may be used in mild-moderate flare

Medications

- Biologics
  - Infliximab, adalimumab, vedolizumab, golimumab, tofacitinib, ustekinumab
  - Preferred for most in moderate to severe UC patients versus step up type treatment where 5-asa compounds are tried and failed first
  - Biologic naïve, infliximab or vedolizumab are preferred
  - Non-response to infliximab, choose ustekinumab or tofacitinib
  - Infection risk
    - Screen for active/latent TB prior to and during use

Infliximab

- Common AE's
  - Infusion reaction
  - GI
- Possible increased LFT's
- With mild to moderate infliximab infusion reaction, you may reduce the infusion rate; severe acute reaction, you may need to stop the drug
  - Typically doesn't involve IgE
- Infliximab infusion reaction prevention may include the use of an antihistamine and acetaminophen

Medications

- Sulfasalazine
  - See Rheumatoid Arthritis
- Corticosteroids
  - Moderate to severe flare of ulcerative colitis (or non-responders to 5-ASA therapy)
  - Topical and/or oral can be utilized depending upon extent and severity of flare
  - 5-ASA products and steroids can be used together in severe cases
  - IV steroids in hospitalized/fulminant patients

Medications

- Immunosuppressants
  - Cyclosporine/azathioprine – one of these may be utilized in refractory patients
- Symptom management
  - Psyllium – bulk up stool, try to reduce diarrhea
  - Loperamide – antidiarrheal
    - Be very cautious with antidiarrheal agents as they can potentially cause toxic megacolon
  - Acetaminophen – pain (remember to avoid NSAIDs)
  - Chronic bleeding (assess need for iron and B12 deficiency)
- Surgery is curative for ulcerative colitis, but patients will likely have to have an ostomy bag
  - Big differentiator with Crohn's disease

Mild-Moderate UC Flare Treatment

- Dual topical and oral 5-ASA may have highest efficacy rates
- Topical 5-ASA (i.e. mesalamine)
  - Rectal administration (suppositories/enemas)
  - Enema can have further penetration than suppositories
  - Benefit onset can be quick (few days), but healing may take a few weeks
- Unwilling to do topical therapy?
  - Oral is an option, but has lower efficacy rates
- Non-response
  - Add in topical steroid (i.e. beclomethasone)
  - Budesonide

Severe/Fulminant

- ≥6 per day bloody stools
- Systemic effects
  - Tachycardia
  - ESR elevation
  - Fever
- Severe pain
- Anemia
- Weight loss

Severe/Fulminant UC Flare

- Combination
  - Systemic steroids
  - Topical 5-ASA
  - Oral 5-ASA
- Hospitalized patient
  - IV steroids
  - Infliximab/cyclosporine/surgery
  - Watch lytes and fluid status
  - Cipro/metronidazole if infection suspected and needs to be treated

Use Caution

- Avoid drugs that slow the GI tract
  - Anticholinergics
  - Opioids
  - Loperamide
- GI bleed risk
  - NSAIDs
  - Antiplatelets, anticoagulants

Hepatitis

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Hepatitis/Hepatotoxicity

- Hepatitis
  - Inflammation of the liver
  - Elevation in ALT/AST
  - 3x ULN
- Common causes
  - Hepatitis A, B, C
  - Drugs
  - Alcoholics
    - See cirrhosis

Drug Induced Causes

- Amiodarone
- Isoniazid
- RA drugs
  - MTX, leflunomide, sulfasalazine, hydroxychloroquine
- Valproic acid
- Rifampin
- Statins

Hepatitis A

- Vaccine available
- Fecal/oral transmission
  - Unsafe water in more 3rd world countries
- Symptoms
  - Mild fever, N/V, muscle pain, anorexia
- Usually self limiting, but rare cases of hepatic failure
  - Supportive care is mainstay
  - Immunoglobulin therapy – may be administered with vaccine

Hepatitis B

- Blood, semen, vaginal transmission
- Symptoms
  - N/V, anorexia, mild fever, muscle aches
  - Many patients will be asymptomatic
  - Immune response causes issues and can cause liver injury
    - Can lead to HE, coagulopathy, confusion, ascites
- Risk of liver cancer
- Vaccination available

Drugs

- PEG interferon alfa 2a
  - Boxed warning on psych, autoimmune, infectious issues
  - Hair loss, GI, CNS changes are common adverse effects
- Entecavir (nucleoside), tenofovir (nucleotide)
  - Lactic acidosis and hepatomegaly boxed warning

Hepatitis C

- Blood transmission (IV drug abusers)
- Patients born from 1945-1965 are at highest risk due to previously poor infection control practices
- Some cases will clear on their own, some will become chronic
- Direct acting antivirals are drugs of choice
  - Ledipasvir/sofosbuvir (Harvoni)
- No vaccine

Needle Stick Injuries

- Hepatitis B vaccination!
- Post Exposure Management
  - Information gathering
  - Patient exposure/past medical history
    - Hep B/Hep C testing – source
  - If cannot find out patient's history, must assume they are positive for disease
- Antibody titer – use this to assess vaccination status and to identify if post exposure prophylaxis is necessary

Hepatitis B - Immune Globulin

- Give within 24 hours of exposure if possible
  - 7 days at latest
- Hepatitis C
  - Monitor
    - Early treatment if infected
  - IG not available at this time
  - Vaccination not available

Cirrhosis

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Cirrhosis – Major Complications

- Edema
- Ascites
- Esophageal Varices
- Hepatic encephalopathy

Common Medications

- Spironolactone
- Loop diuretics
- Propranolol
- Lactulose

Edema/Ascites

- Diuretic Combo
  - Furosemide 40mg
  - Spironolactone 100mg
- Close electrolyte monitoring
- Gynecomastia

Hepatic Encephalopathy

- Accumulation of toxins due to poor liver function
  - Toxins impact the brain
    - Cognitive symptoms (i.e. confusion, lethargy)
- Ammonia (NH3)
- Lactulose
- Neomycin, rifaximin

Portal Hypertension

- Increased pressure in portal venous system
- Veins can swell and increase due to this increased pressure
  - Leading to rupture and possible bleed
    - Esophageal varices
- Non-selective beta-blocker used to treat
  - Propranolol

Urology

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BPH

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BPH Characteristics

- Enlargement of the prostate
- Impairs urination
  - Frequency
  - Incomplete bladder emptying
  - Low flow
  - Incontinence

BPH Treatment

- Alpha Blockers
- 5-Alpha Reductase Inhibitors
- Surgery (TURP)

Alpha-Blockers

- Tamsulosin
  - Not used for hypertension
  - Works quickly
- Non-selective agents
  - Terazosin
  - Doxazosin
- Risks
  - Orthostasis

5-Alpha Reductase Inhibitors

- Finasteride, Dutasteride
- Takes weeks/months to begin to work
- Actually shrink prostate
- Decreased libido
- Pregnancy risk

Drugs That Exacerbate Frequency

- Diuretics
- Caffeine
- ETOH

Drugs That Exacerbate Retention

- Anticholinergics
- Alpha agonists (Midodrine)
- Pseudoephedrine

Urinary Incontinence

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Definitions

- Incontinence
  - Go when you don't want to (can't control)
  - Weakness or loss of voluntary control of urinary sphincter
- Frequency
  - Feeling of having to go all the time
- Retention
  - "retaining" – incomplete emptying of the bladder
    - Most common cause (males) - BPH

Types of urinary incontinence

- Stress
  - Physical exertion (i.e. sneeze, cough)
- Urge
  - Over Active Bladder (OAB)
  - Feel the need to go, but maybe don't make it in time
  - Immobility
  - MS, Parkinson's, Diabetes
- Overflow
  - Blockage (BPH)
  - May dribble urine
- Functional
  - Patient who has dementia

Anticholinergics

- Anticholinergics; AKA antimuscarinic
  - Tolterodine, oxybutynin, solifenacin, darafenacin, trospium
  - Antagonist at muscarinic receptors which prevents the action of acetylcholine; resulting in relaxation of bladder smooth muscle which can reduce urge, spasms, and frequency
  - Make sure these drugs are actually effective: if not, try another agent or discontinue to avoid possible adverse effects
    - Most efficacy in urge/over-active bladder type incontinence

Anticholinergics

- Oxybutynin comes in a patch formulation (and oral)
  - Least selective, higher incidence on systemic anticholinergic effects
  - Cognitive impairment, constipation, urinary retention, dry eyes, dry mouth, increase fall risk
- Other, more bladder selective agents may be more expensive
- Trospium is least likely to cross blood brain barrier (potentially best in patient with preexisting dementia or other cognitive impairment)
- AE's
  - Confusion
  - Dry eyes, mouth
  - Constipation, slows GI motility
  - Retention

Beta-agonists

- Mirabegron, vibegron
  - Does have some selectivity for bladder receptors, but systemic side effects still possible
  - May increase pulse/blood pressure
  - Most efficacy shown in urge/OAB
  - Possible 2D6 interactions with mirabegron (vibegron avoids 2D6)

Drugs – Clinical Pearls

- 5-alpha reductase inhibitors
  - Sexual dysfunction
  - Fatigue
- Alpha blockers
  - Hypotension
- Diuretic timing/sleep (SGLT-2s as well?)
  - Urinary frequency

Stress Incontinence Treatment

- Kegel Exercises
- Alpha agonists
  - Midodrine
  - Pseudoephedrine
- Duloxetine – off label indication for stress incontinence
- Anticholinergics tried, but may not be that effective
  - Could be mixed incontinence if beneficial

Urge Incontinence

- Treatment
  - Anticholinergics
  - Beta agonist (mirabegron) – selective for Beta-3
- Topical estrogen – best utilized in females who are peri- or post-menopausal and have vaginal dryness with stress or urge incontinence
- Botox
  - Can help with spasms
  - Significant expense associated

Overflow

- Medication Treatment
  - Alpha-blockers
  - 5 alpha reductase inhibitors (BPH)

Sexual Dysfunction

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Psych

- SSRI's
- TCA's
- MAOI's
- Better options
  - Bupropion
  - Mirtazapine
- Antipsychotics (typicals maybe a little worse as well as risperidone)
- Lithium

Cardiac Medications

- Beta-blockers
- Thiazide Diuretics
  - Alternatives for HTN – ACE/ARB/CCB
- Clonidine, methyldopa

Other Medications

- Finasteride
- Dutasteride
- Antihistamines (drugs with anticholinergic effects)

Use of PDE-5 Inhibitors

- Sildenafil, tadalafil
- SE's
  - Dizzy, drop in blood pressure
  - Headache
  - Visual changes
  - Flushing
- Nitrate Interaction
- Strong 3A4 Inhibitors (i.e. azole antifungals) – may increase conc.
- Alpha-blockers

Drugs for Female Hypoactive Sexual Desire Disorder

- Flibanserin
  - 5-HT1A Agonist/5-HT2A Antagonist
  - Sedation/dizziness
  - Daily dosing
  - Contraindicated with alcohol (syncope risk)
  - 3A4 inhibitors increase risk of toxicity/AE's
- Bemelanotide
  - Melanocortin Receptor Agonist
  - PRN use at least 45 minutes before sexual activity
  - Max 8 doses/month
  - SubQ
  - Flushing, injection site reaction, alteration of skin pigmentation, small rise in BP, drop in HR, GI

Psychiatry

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Depression

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Depression – Kind of a Big Deal

- Suicide
- Circumstances
  - Finances
  - Job Loss
  - Living alone
  - Aging
  - Loss of Family/Friends

Common Diseases That Increase Risk of Depression or Depressive Symptoms

- MS
- Parkinson's
- Dementia
- Cancer
- Hypothyroid
- Nutritional factors
  - B12

Antidepressant Pearls

- Take time to work
- Selection
  - Adverse effects
  - Compelling indications
- Monitoring
  - PHQ-9
  - Higher number/worse depression
  - Not perfect

Common SSRI's

- Sertraline
- Escitalopram
- Citalopram
- Fluoxetine
- Paroxetine
- Fluvoxamine

SSRI Clinical Pearls

- Citalopram
  - QTc prolongation, limit dose in elderly to 20 mg daily; omeprazole interaction
- Fluvoxamine
  - Generally avoid, multiple 3A4 drug interactions
- Fluoxetine
  - A little more activating
- Sertraline
  - Loose stools/serotonergic
- Paroxetine
  - Generally avoid in elderly, mildly anticholinergic
  - 2D6 interactions
  - Tends to be more sedating/weight gain
- Controversial effect on platelets and bleeding

Common SNRI's

- Duloxetine
- Venlafaxine
  - Pain at higher doses
  - Challenging to taper down/off

Trazodone/Nefazodone

- Nefazodone – rare use, hepatotoxic
- Trazodone
  - Low doses insomnia
  - Orthostasis
  - Dry mouth
  - Sedation

Mirtazapine

- Weight gain
- Sedation
  - Lower doses

Bupropion

- Smoking cessation
- Activating
- Caution - Seizure disorder

TCA's – lots of them!

- Nortriptyline, Desipramine, Amitriptyline, Imipramine
- Anticholinergic
- Risk in overdose
- Nortriptyline – possibly better tolerated in elderly
- QTc prolongation
- Good for corresponding pain syndrome
  - Fibromyalgia
  - Neuropathy

Less Common Antidepressants

- Serotonin modulators and stimulators
  - i.e. vilazodone
- MAOI's
- Antipsychotic augmentation
- OTC's
  - St. John's Wort

Bipolar Disorder

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Bipolar Symptoms

- Very severe mood swings
- Mania
  - High self-esteem (grandiosity)
  - Way more talkative than normal
  - Constant changing of topics during conversation (racing thoughts)
  - Insomnia or just needing less sleep
  - Interrupts normal life (i.e. work, school, commitments), or others can identify that something is strange
  - Psychosis
- Hypomania
  - Patients experience a higher level of energy and/or and enhanced mood compared to normal, but it is generally not associated with impairment

Bipolar Disorder

- Very depressed stages
- Bipolar 1 – have had manic episode(s)
- Bipolar 2 – haven't had a manic episode (only hypomania)
- Risk of suicide
- Often huge social and financial problems
  - Relationships
  - Spending sprees with manic episodes
  - Legal problems
  - Work problems

Risk Factors

- Substance abuse
- Anxiety
- Post-traumatic stress disorder
- ADHD
- Family history

Lithium

- Target Concentration
  - Acute 0.8-1.2
  - Maintenance 0.6-1.0
- AE's
  - GI
  - Tremor
  - Slurred Speech
  - TSH
  - Kidney function
- Drug Interactions
  - NSAIDs
  - Thiazides
  - ACE Inhibitors

Valproic acid

- Indications - bipolar, seizures, migraines, sometimes used off label for aggressive type behaviors
- SE's – CNS sedation, GI upset, and lots of unique, rare side effects (reduced platelets, elevated ammonia, hair loss, LFT elevation)
- Typical target level 50-100
- Watch interaction with lamotrigine
- May cause weight gain
- Multiple dosage forms can have slightly different bioavailability
- Pregnancy risks

Lamotrigine

- Sedation, CNS side effects
- Hallmark RASH side effect – usually when started at too high of a dose or increased too quickly
- Takes a bit of time (weeks to months) to get to higher doses when titrating appropriately to minimize rash risk
  - If stopped for a significant period of time, need to start over at low dose and titrate slowly
- Drug interaction with valproic acid (likely need to reduce dose of lamotrigine)
- Enzyme inducers (i.e. phenytoin, carbamazepine) can reduce concentrations of lamotrigine in the body
- Usually best for bipolar patients with predominant depression symptoms

Carbamazepine

- Not a preferred first line agent in bipolar disorder
- CNS side effects, GI upset, elevated LFTs, alterations in WBC count, hyponatremia
- Monitor CBC, LFTs, and sodium (SIADH)
- Induces multiple CYP enzymes – be on the lookout for reduced concentrations of meds that are metabolized via this pathway (lots of common 3A4 interactions)
- Considered an auto-inducer – can reduce its own levels
- Levels aren't as important in treating trigeminal neuralgia (unless signs of toxicity)
- Steven Johnson's syndrome (SJS) – severe, rare rash is possible
  - HLA-B*1502 Allele at higher risk for SJS (higher incidence in patients of Asian descent)
- Usual target levels are 4-12 mcg/mL
  - Not necessary for trigeminal neuralgia

Antipsychotics

- Quetiapine – second line option for maintenance
- Other antipsychotics are options as well for refractory patients
  - Risperidone
  - Aripiprazole
  - Olanzapine
  - Long acting injectable agents

Bipolar Depression

- SSRI's
  - Can induce mania
    - Avoid monotherapy
  - Fluoxetine
  - Often used with mood stabilizer (i.e. Lithium, VPA, Carbamazepine)

Anxiety

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Association of Anxiety

- PTSD
- Substance Abuse
- OCD

Assessment

- GAD-7
  - 7 questions
  - Example: Feeling afraid something awful might happen
  - Scored from 0-3 for each question
    - Not at all
    - Several days
    - More than half the days
    - Nearly every day
  - Higher the score the worse
  - Obviously might not work in our dementia type patients

Acute Treatment

- Identify underlying cause
  - Pain
  - Infection
  - Hyperthyroid
  - Medications
    - Stimulants
    - Alpha/beta agonists

Medications

- SSRI's
- Benzo's
- Buspirone
- Other antidepressants
- Antipsychotics (usually with comorbidities)

SSRI's

- Won't work quickly
- Preferred for long term maintenance over benzo's
- Selection based upon adverse effects

Benzodiazepines

- Work quickly
- Controlled substance
- Avoid long acting if using as needed
- LOT in elderly
  - Less likely to accumulate
  - Inactive metabolites

Buspirone

- Usually well tolerated
- Takes time to work
  - Similar to SSRI's
- Not a controlled substance

Insomnia

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Insomnia Concerns

- Troubles
  - Getting to sleep
  - Staying asleep
- Quality of Life
  - Motivation
  - Ability to perform at work/school
- Short-term
  - A few weeks
- Chronic
  - Months

Non-Drug Interventions

- 1st Line Therapy
- Sleep Hygiene
  - Regular schedule
  - Snacks/warm milk
  - Avoiding Caffeine near bedtime
  - Minimize stimulation before bed
  - Exercise earlier in the day
  - Pain
  - Avoiding other stimulants

Pharmacotherapy

- Z-drugs
- Anticholinergics
- Melatonin
- Trazodone
- Benzo's
- Ramelteon
- Mirtazapine
- Suvorexant

Z-Drugs

- Fall risk
- Confusion
- Risk of dependence
- Abnormal sleep behaviors
- Helpful for onset and maintenance
- Zolpidem, eszopiclone
  - Dose restriction on zolpidem – limit to 5 mg, risk of next day impairment at 10 mg

Melatonin Receptor Agonist

- Ramelteon
  - Acts on MT1 and MT2 (melatonin) receptors to help induce sleep
  - Dizziness, GI side effects
  - Lower risk for falls and CNS effects in geriatric patients versus benzo's and Z-drugs
  - Most beneficial in sleep-onset

DORAs

- Suvorexant, lemborexant, daridorexant
  - Dual orexin receptor antagonists (DORA)
  - CYP3A4 inhibitors can raise concentrations and increase risk for toxicity
  - CNS SE's, dizziness, abnormal dreams
  - Controlled substance
  - Expensive
  - Helpful for onset and maintenance

Trazodone and Mirtazapine

- Trazodone
  - Lower doses typically used for insomnia (12.5-100 mg) especially in the elderly
  - Classically considered an antidepressant, but usually only at higher doses
  - Orthostasis, dry mouth, CNS changes, and priapism (rare) are possible adverse effects
  - Generally considered to be better tolerated in the elderly than "Z" drugs or anticholinergics
  - Onset and maintenance
- Mirtazapine
  - Often used at low doses for its sedative properties
    - May cause more activation as doses escalate
  - A potential option to help with insomnia, weight loss, and mental health disorder like depression or possibly anxiety
  - See depression section for more information

Melatonin

- Available OTC
- Considered "safe" by many patients due to it being a natural product
- Side effects of dizziness, GI, headache, lingering sedation throughout the day, possibly hyperprolactinemia with higher doses
- Not great clinical trial evidence of effectiveness, but some patients will swear by it
- Maybe not a terrible option versus anticholinergics and Z drugs
- For sedative effect, usual max dose around 10 mg/day
  - Most patients, target 1-5 mg range
- <1mg doses for altering circadian rhythm

Anticholinergics

- Diphenhydramine, doxylamine, doxepin, TCA's
- Retention
- Dry eyes
- Dry mouth
- Constipation
- Fall risk
- Confusion (interacts with dementia meds)
- Doxepin - evidence in sleep maintenance

Antipsychotics for Sleep

- Can be sedating
- Always avoid unless compelling indication
  - Hallucinations unresolved by other methods
  - Schizophrenia

Eating Disorders

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Common Eating Disorders

- Anorexia nervosa
- Bulimia nervosa
- Binge Eating

Anorexia Nervosa

- Abnormally low body weight
- Severe, consistent restriction of caloric intake that leads to weight loss or low weight
- Strong fear of weight gain or becoming overweight
- Altered perception of appearance, body shape

Anorexia Nervosa - Management

- Psychotherapy, nutrition rehabilitation
- Olanzapine
  - Severity of disorder will determine aggressiveness of using an antipsychotic
- Risperidone, other antipsychotics have not found benefit
- Antidepressants (SSRI) not proven effective in anorexia alone; option in patients with comorbidities (anxiety/depression)

Bulimia Nervosa

- Excessive (binge) eating
- Followed by vomiting (self-induced) or other method of weight loss
  - Use of drugs (laxatives, diuretics)
- Frequency – At least once per week for 3 months
- Psychological obsession/excessive concern about body image

Bulimia Nervosa

- Psychotherapy, nutrition rehab
- SSRI's
  - Fluoxetine, sertraline or other SSRI
  - Higher incidence of withdrawal syndrome with paroxetine, anticholinergic
    - Can be problematic in patients who may already be overweight
- Topiramate (tends to cause more weight loss)
- TCA if needs weight gain, watch cardiac and overdose risk
- Avoid MAOI's (DI's) and bupropion (seizures)

Binge Eating Disorder

- Feeling of lack of control over eating
- Eating an excessive amount (compared to most people)
- Rapid eating
- Becoming uncomfortably full
- Feeling disgusted, depressed, or guilty
- Can coexist/be confused with bulimia

Binge Eating Disorder

- SSRI's
  - Avoid paroxetine (weight gain trend)
  - Avoid fluvoxamine (DI's)
- Topiramate
- Stimulant

Coexisting Disorders Are Common

- Anxiety
- Depression
- Substance Use Disorder
- PTSD
- OCD

Notable Medication Issues

- Weight loss
  - Stimulants
  - Laxatives
  - Diuretics
  - Theophylline
  - Digoxin
  - Phentermine
  - Diabetes medications (GLP-1, SGLT-2, metformin)
  - Orlistat
  - Acetylcholinesterase inhibitors

Notable Medication Issues

- Weight Gain
  - Insulin and insulin secretagogues
  - Antipsychotics
  - Antidepressants
  - Pioglitazone
  - Seizure medications (VPA, carbamazepine, etc.)
  - Steroids
- Obsessive Behaviors
  - Dopamine Agonists (Pramipexole, ropinirole)

Schizophrenia

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Positive Symptoms

- Hallucinations
  - Visual
  - Auditory
- Delusions
  - Fixed, false belief
- Disorganized speech and thoughts

Negative Symptoms

- Flat affect
- Lack of interest in things previously enjoyable
- Trouble functioning in daily life
- Withdrawn, social isolation

Selection of Antipsychotic

- Based upon patient preference
- Adverse effect profile
- Previous trials
- Drug interactions
- Dosage forms
  - Adherence

Side Effect Profile, Clinical Considerations

- Sedation
- Weight Gain
- EPS
- Prolactin
- Anticholinergic
- Agranulocytosis
- QTC prolongation

Best efficacy

- Clozapine
  - Not used first line due to agranulocytosis and other risks
  - Reserved for refractory patients
- 5 boxed warnings
  - Neutropenia
  - Low BP, pulse, syncope
  - Seizure
  - Cardiomyopathy
  - Increased mortality when used in dementia-related psychosis (class warning)

Clinical Pearls

- Rarely are first generation antipsychotics (i.e. haloperidol) used due to very high rates of extra pyramidal side effects
- Extra pyramidal symptoms (EPS)
  - High risk: first generation agents like haloperidol, 2nd generation agents like risperidone, paliperidone and lurasidone
  - Low risk: quetiapine, clozapine, pimavanserin (only approved for Parkinson disease psychosis)

Clinical Pearls

- Metabolic syndrome
  - High risk: olanzapine, clozapine
  - Low risk: aripiprazole, lurasidone, ziprasidone
- Hyperprolactinemia
  - High risk: risperidone, paliperidone
  - Low risk: aripiprazole, lurasidone

Clinical Pearls

- QTc prolongation
  - High risk: ziprasidone, typicals
- Sedation
  - High risk: quetiapine, clozapine

Clinical Pearls

- Periodically monitor for metabolic syndrome in patients on any antipsychotic (lipids, A1C etc.)
- Long acting injectables are an option for many of the antipsychotics
  - Make sure oral test doses are done
- Aripiprazole often used for antidepressant augmentation
- To help with movement adverse effects (EPS) and also possibly with drooling, you may see anticholinergics used; i.e. benztropine, trihexyphenidyl or diphenhydramine

Neuroleptic Malignant Syndrome (NMS)

- Due to antipsychotic use
  - Usually happens when initiated or dose is increased
- Extremely rare
- Symptoms
  - High blood pressure
  - Tachycardia
  - Very high fever
  - CNS changes – agitation etc.
  - Muscle rigidity
  - Tremor

Neuroleptic Malignant Syndrome (NMS)

- DC medication
- Primarily supportive care
  - Cooling blankets
  - Cooled IV fluids
  - Antipyretics
- Dantrolene
  - Skeletal muscle relaxant
  - Can help bring down temperature
  - Possibly help with rigidity
  - Risk of liver toxicity
- Bromocriptine
- Benzodiazepines

Schizophrenia - Elderly

- Elderly Adults
  - Likely tried numerous agents
  - May be able to or have to decrease doses
- More concerned
  - Orthostasis
  - Movement disorders
  - QTc prolongation
- Less concerned
  - Metabolic syndrome

Substance Abuse

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Most Common Substance Abuse

- Alcohol
- Tobacco
- Prescription Drugs
  - Opioids
  - Benzo's

Signs of Alcohol Abuse

- Higher tolerance
- Blackouts
- Concerns from friends/family
- Legal or financial issues
- Liver disease
- Signs of intoxication
  - Slurred speech, poor gait, confusion, vomiting, euphoria, disinhibition

Alcohol Addiction

- Loss of control
- Lack of other interests
- Withdrawal symptoms
  - Sweating, shaking, anxiety, DT's
- Guilt
- Worry
- Change in relationships

Nutritional Deficiency

- Alcoholics often will have nutritional deficiencies
  - B12 deficiency
  - Thiamine
  - Folic acid
- Wernicke's Encephalopathy
  - Neurological disorder that can cause delirium
  - Typically due to lack of dietary thiamine

Alcohol Withdrawal

- Withdrawal symptoms when abstaining
  - Withdrawal symptoms include sweating, shakiness, GI upset, tremor
  - Severe withdrawal may include seizures, hallucinations and delirium tremens
- Delirium tremens
  - Most severe problem with withdrawal
  - Confusion, hallucinations, hypertension, sweating, tachycardia, agitation
  - Can be life threatening
  - DT typically begins 48-96 hours after last drink

Acute Withdrawal

- Severity of withdrawal scale
  - Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) – scored up to 67; higher score, the more likely patients need medication for withdrawal
  - >20 severe withdrawal
  - >8 consider pharmacotherapy
- Withdrawal seizures/DT's
  - Benzodiazepine – any can be used
  - Long-acting may provide more stable concentrations (i.e. diazepam, chlordiazepoxide)

Alcohol Treatment

- Craving/Pleasure reduction
  - Naltrexone
    - Careful in patients taking opioids; monitor LFTs, monthly injection or tablets
    - May give while still drinking
  - Acamprosate
    - Alternative to naltrexone
    - Frequent dosing
    - Diarrhea
- Negative feedback
  - Disulfiram
    - Cannot give while drinking
    - With ETOH – flushing, GI upset, headache, feel sick

Smoking Cessation

- First line Agents
  - Varenicline
    - Preferred by ATS
  - Nicotine replacement
  - Bupropion
- 2nd Line Agents
  - TCA's
  - Clonidine
- Counseling

Varenicline

- Partial nicotine agonist
- 12 week course which may be doubled to 24 weeks as necessary and tolerated for some patients
- Patients can still smoke while using this medication for the first week
  - Extended smoking duration added to labeling (can taper down over time, don't just have to quit after the first week)
- Notorious adverse effect of vivid dreams
- Possible risk of psych changes
- Insomnia
- Nausea/vomiting

Nicotine Replacement Products

- Patches
  - 3 doses; 21, 14, and 7 mg
  - Start with 21 mg for patients using 10 or more cigarettes per day
  - 14 mg patch for those using less than 10 cigarettes per day
  - Not intended for PRN use
  - Remove patch at night if patient experiences vivid dreams or sleep disturbances
- Gum
  - 4 mg and 2 mg dosages; use the 4 mg dose if the patient has their first cigarette within 30 minutes of awakening
  - Max 24 pieces per day
- Inhaler
  - 20 minutes of puffing recommended for best relief of cravings
  - Maximum of 16 cartridges per day

Nicotine Replacement Products

- Lozenge
  - Similar dosing to gum
  - Max 20 lozenges per day
- Nasal Spray
  - 2 sprays (1 in each nostril) considered one dose and is 1 mg of nicotine
  - Maximum of 40 doses per day (80 individual sprays)
- *Vaping is not considered a nicotine replacement product
- Smoking is generally discouraged while using NRT
  - Adjust dosing of NRT

Bupropion

- Activating
- Increases the risk of seizures (avoid use in patients with seizure history, alcohol abuse, and eating disorder history)
- Can be used for corresponding depression
- CYP2D6 inhibition
- May be used with NRT
- 150 mg BID target but once daily does have some proven efficacy

Alternatives

- Clonidine
  - Antihypertensive
  - Avoid in elderly
- Nortriptyline
  - Highly anticholinergic
  - Avoid in elderly

Signs of Opioid Overdose

- Respiratory depression
  - Snoring like noise
  - Benzodiazepines and other sedatives enhance risk
- Unconsciousness
- Pinpoint pupils
- No bowel sounds
- Response to naloxone

Opioid Overdose Management

- Naloxone
  - Opioid antagonist
  - Reverses effects of prescription narcotic medications such as hydrocodone, hydromorphone, oxycodone, etc. as well as heroin
  - Can be administered IV/IM/SC and intranasal
  - Several states have "Good Samaritan" laws providing immunity to those who assist someone having an opioid overdose

Signs of Opioid Withdrawal

- Withdrawal when stopping use
  - Nausea
  - Sweating
  - Anxiety
  - Insomnia
  - Chills
  - Irritability

Drugs to Manage Opioid Withdrawal Symptoms

- Withdrawal
  - Clonidine
  - Diphenhydramine
  - Trazodone
  - Simple analgesics
  - Loperamide

Opioid Use Disorder

- All combined with psychotherapy
- Buprenorphine/naloxone
  - Combination of a partial mu agonist and an opioid antagonist
  - Prevents reward, euphoria from other opioid agonists
  - May precipitate opioid withdrawal but can be started prior to complete withdrawal due to partial opioid agonist action
- Naltrexone
  - Mu antagonist
  - Needs to be taken regularly which many addicts may not be able to do
  - Long acting injectable available
  - Precipitates withdrawal so shouldn't be started for maintenance therapy until withdrawal is finished

Opioid Use Disorder

- Methadone
  - Very long half life
  - Prevents other opioids from binding to mu receptor so patients may not get as much euphoria from shorter acting opioids like heroin
  - Full agonist
    - Will cause sedation and other opioid like effects
  - Will prevent withdrawal as you are giving an opioid agonist
  - QTc drug interactions
  - Requires special dispensing from an opioid treatment program

Opioid Tapering in Chronic Pain

- ***Not Opioid Use Disorder
- 10% qweek as initial target (per CDC)
- Higher dosages, longer durations more difficult
- Withdrawal symptom management

Benzodiazepine

- Withdrawal
  - Anxiety
  - Irritability
  - Tremor
  - Confusion
  - Nausea
  - *Seizures
  - Psychosis
- Reversal agent
  - Flumazenil

Benzodiazepine Taper

- 25-50% reduction every 1-2 weeks
- Extended length of use may require longer, slower taper
  - More likely to experience withdrawal symptoms
- Total of 2-3 months is reasonable for most
- Consider transition to long acting agent (i.e. diazepam) if taking a short acting benzodiazepine

Bone, Joint, and Pain Disorders

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Gout

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Signs/Symptoms

- Classic symptom: severe pain in the big toe
- Redness, warmth, painful, swollen joint(s)
- Often at night
- Formation of urate crystals contributed by elevated uric acid

Target Levels and Hyperuricemia

- Ballpark normal uric acid levels (2.5-6 mg/dL)
  - Generally elevated in gout
- Urate crystals can form and cause kidney stones
- Tophi
  - Nodules at a joint or joint(s) because of crystallized urate deposits
  - Usually develop over longer periods of time
  - Can impact joint function
  - Generally more painful during a gout attack
- Guidelines recommend treating to a target goal urate level of 6mg/dL or less

Classic Risk Factors

- Alcohol use
- Metabolic disease/obesity
- Seafood (foods high in purines)
- Family history
- Males more common than females

Classic Drugs That Increase Uric Acid

- Loop/thiazide diuretic use decreases uric acid excretion
- Niacin
- Cyclosporine
- Tacrolimus

Acute Treatment Options

- Initiation and Discontinuation: Sooner the better, and discontinue within a couple of days of resolution
- NSAIDs
  - GI, CHF, Kidney
  - Naproxen may be easier on the gut versus indomethacin
- Steroids
  - Hyperglycemia, GI, Insomnia, OP
- Colchicine
  - Diarrhea
  - 3A4 inhibitors may increase concentrations

Chronic Management

- Allopurinol
  - First line agent
  - Side effects – rash, GI
  - Dose adjust with worsening kidney function
  - Used for PREVENTION, reduction of uric acid, NOT for acute treatment of a gout attack
  - Reduces production of uric acid in the body
  - ACE inhibitors/thiazides/penicillins may increase risk for allergic reaction with allopurinol
  - Azathioprine concentrations may be increased by allopurinol
  - Test for HLA-B*5801 in African Americans and Southeast Asian descent prior to starting

Chronic Management

- Febuxostat
  - Similar mechanism as allopurinol
  - Meant for prophylaxis
  - More expensive than allopurinol, but alternative if allopurinol ineffective/intolerable
  - Can increase azathioprine concentrations like allopurinol
  - FDA safety warning for an increased risk of cardiovascular death compared to allopurinol (because of this, this drug is often avoided or considered more of a last line option)

Chronic Management

- Colchicine
  - Dose limiting side effect is most often diarrhea (high percentage of patients)
    - Low dose has similar efficacy to high dose in acute treatment of flares with reduced adverse effects
  - Dose adjustments in CKD
  - Can be used for both treatment and prevention
  - CYP3A4 inhibitors may increase concentrations of colchicine
    - Including grapefruit juice
  - May increase risk of myopathy/rhabdomyolysis in patients on statins

Chronic Management

- Probenecid
  - Removal of uric acid in the body by increasing kidney excretion
  - GI upset adverse effect
  - Probenecid can raise the serum concentrations of numerous other medications
    - Penicillin's, quinolones, cephalosporins, NSAIDs, Nitrofurantoin, methotrexate,
  - Need adequate kidney function for the medication to work

Osteoporosis

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WHO Classification

- Normal; T-score greater than or equal to -1.0
- Osteopenia; -1.0 to -2.5
- Osteoporosis; -2.5 or below

FRAX Scoring

- Only recommended in patients who are untreated
- Treat if 10 year risk:
  - 3% or greater risk for hip fracture
  - 20% or greater risk for any osteoporotic fracture

Risk Factors – FRAX Assessment

- Female
- Age
- Low BMI
- T-score
- Steroid use
- Smoking
- ETOH
- Hyperthyroidism (chronic)
- Prior Fracture
- RA

Treatment

- Bisphosphonates
- Denosumab
- Calcitonin
- SERM (Raloxifene)
- Teriparatide
- Estrogen

Bisphosphonates

- Bone resorption inhibitors
- Administration Procedure
  - Before other meds/food
  - Glass of water
  - Remain upright
  - Try to avoid esophageal ulceration
- Osteonecrosis
  - Extremely rare, most occurrences surrounding oral surgery
- IV (zoledronic acid, ibandronate)
- Reassess use after 5 years

Denosumab

- SubQ injection every 6 months
- Hypocalcemia risk; monitor phosphorus and magnesium as well
- Rare osteonecrosis risk
- $$$

Calcitonin

- Nasal spray used most often
  - Rhinitis and nose bleed
- Potential compression fracture benefit
- Storage/Admin pearls
  - Store upright
  - Prime 5 times before use
  - Discard after 30 doses or 35 days

Raloxifene

- Breast cancer indication
- DVT/Cardiovascular disease warning
- Side effects
  - Hot flashes
  - Edema

Teriparatide

- Builds Bone (osteoblasts)
- SubQ – once daily
- $$$
- Warning – osteosarcoma in rats
  - Use longer than 2 years is not recommended

Other Considerations

- Vitamin D
- Calcium
- Exercise, strength building, weight bearing
- Fall risk

Classic Medication Contribution

- Steroids
- Anticonvulsants
- Thyroid supplements
- PPI's
- TZD's

Osteoarthritis

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Osteoarthritis Symptoms

- Pain after longer periods of use
- Stiffness after resting
- Potential change in the shape of ends of fingers (DIP)
- Not much inflammation (differentiator from RA)

Pain Impact

- Quality of life
- Sleep
- Function/ability
- Work/Volunteerism
- Appetite
- Exercise
- Mood

Treatment for OA

- Trial of hot/cold
- Massage
- NSAIDs
- Topicals
- Duloxetine
- Acetaminophen
- Opioids
- Steroid injections

NSAIDs

- Naproxen, ibuprofen, diclofenac, meloxicam, etc.
- More efficacious than acetaminophen for knee and hip OA
- Impact platelet function
  - May increase risk of bleeding with surgical procedures
- Avoid very high risk GI NSAIDs (i.e. indomethacin and ketorolac) for OA if possible
  - Ketorolac recommended for 5 days only (boxed warning)
- Naproxen dosed less often than ibuprofen which patients may like
- Possible increased risk of cardiovascular events
  - Naproxen typically considered safest with this adverse effect
- If localized pain, topical diclofenac gel may be an option for patients where minimizing systemic absorption is preferred

NSAIDs – Risk

- GI
- CKD
- CHF
- HTN
- Cardiovascular risk boxed warning

COX-2 Inhibitor

- Celecoxib
  - Same issues as NSAIDs
  - Exception: GI bleed is less
    - Remember that elderly patients are usually on antiplatelet/anticoagulant therapy
    - Risk similar if on baby aspirin

SNRI

- Duloxetine
  - Option for those with OA symptoms in multiple joints and those with contraindications to oral NSAIDs or non-responders
  - See depression for more information

Topical Medications

- Topical agents can be helpful especially if only a joint or two is affected by osteoarthritis
  - Topical NSAID – diclofenac gel (Voltaren)
  - Capsaicin (Salonpas)
  - Menthol type product, salicylate (i.e. Bengay)

Acetaminophen

- 4 gram max
- Lots of variation in dose
- Short half life
- Safest agent especially in elderly
- Combo products

Common Opioids

- Tramadol
- Tylenol #3
- Morphine
- Oxycodone
- Fentanyl
- Hydrocodone
- Methadone

Important Approximate Conversions

- Morphine (oral) 30 mg
- Oxycodone 20 mg
- Tramadol 300 mg
- Fentanyl (patch) 12 mcg
- Hydrocodone 30 mg

Opioid Adverse Effects

- GI
- Constipation
- Sedation
- Cough suppression
- CNS
- Itching
- Tolerance/Dependence/Addiction risk
- Avoid with other high risk agents (i.e. benzodiazepines)

Opioid Pearls

- Oxycodone
  - In combo with APAP or alone
  - Very commonly used
  - Long acting and short acting available
- Hydrocodone
  - Combo with APAP
  - Active metabolite is hydromorphone (created via CYP2D6)

Opioid Pearls

- Morphine
  - Gold standard for conversion (multiple dosage forms, i.e. oral, rectal, injectable etc.)
  - Caution in renal impairment
  - Possible interaction with reduction in P2Y12 inhibitors effectiveness
  - Metabolite morphine-3-glucuronide associated with neurotoxicity
  - Long acting and short acting available
- Codeine
  - CYP 2D6 converts to morphine
  - Rapid metabolizer of 2D6 will lead to more opioid effects
  - Drugs that inhibit 2D6 will lead to less opioid effects
  - Less potent than morphine, oxycodone etc.

Opioid Pearls

- Fentanyl patch
  - Long onset/long offset – not appropriate for acute pain relief or as needed use
  - Can cover with a Tegaderm patch or another adhesive
  - Heat can increase rate of absorption – avoid
  - Should NOT be used in opioid naïve patients
- Methadone
  - Conversion from or to methadone is a huge burden
  - Highest QTc prolongation risks of any opioids
    - Careful with other QTc prolonging meds
  - Role in managing opioid use disorder
  - Very long half-life compared to other opioids

Tramadol

- Max of 300mg in the elderly (differs from usual 400 mg)
- Be careful in elderly as they may have seizure disorder or condition that may predispose them to seizures
- Serotonin activity (caution in patients who are receiving high doses or multiple other serotonergic drugs
- Sedation, constipation, dizziness, CNS effects
- Risk of dependence/addiction, controlled substance
- Active metabolite formed via CYP2D6
  - Fluoxetine, paroxetine, and bupropion are examples of medications that may inhibit CYP2D6

Steroids

- Acute inflammation
- Benefit is usually transitory
- Injection to site of pain
  - Still has systemic effects

Glucosamine/Chondroitin

- Potential option for OA
- Takes time to work
- Be sure dose is adequate – target 1,500 mg
- If beneficial continue…if not, DC

Rheumatoid Arthritis

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Rheumatoid Arthritis

- Autoimmune disorder
- Inflammation
- Painful
- Joint Swelling (big difference with OA)
- Typically symmetrical
- Patients with RA may have elevated C-reactive protein (CRP) as well as elevated Erythrocyte Sedimentation Rate (ESR)

RA Versus OA

- RA
  - Onset middle age/anytime in life
  - Quick onset – Weeks to months
  - Inflammation/Swelling
  - Both sides of the body affected
  - Stiffness can last much longer throughout the day
  - Whole body symptoms possible (fatigue, feeling sick)

Goals of RA Therapy

- Minimize flares
  - Troublesome to patients
  - Reduce adverse effects from NSAIDs and steroids
- Early initiation of DMARD therapy
  - Reduces joint damage
- Minimize side effects
  - Infection risks

Flare Management - NSAIDs

- GI bleed risk (especially patients with history of GI bleed/issues, and those on anticoagulants or antiplatelet medications)
  - Celecoxib may reduce this risk but increase CV risk
- Impact platelet function
  - May increase risk of bleeding with surgical procedures
- CHF exacerbation risk
- Can contribute to resistant hypertension
- Possible negative impact on kidney function (especially in combo with ACE/ARB and/or diuretics)

Flare Management - Steroids

- Alternative to NSAIDs
- Minimize length of therapy if at all possible
  - Immune suppression risk
  - Exacerbates diabetes – causes hyperglycemia
  - Can cause GI upset, increase ulcer risk (generally try to avoid both steroids and NSAIDs together due to high GI risk)
  - Insomnia, anxiety
  - HPA suppression risk
  - Osteoporosis risk if used longer term
  - Heart failure risk
  - Increased hypertension
  - Possible increased risk of elevated intraocular pressure (monitor in patients on longer term use) – glaucoma
  - Increases the risk of cataracts

DMARDs

- DMARDs delay the progression and worsening of the disease
  - Examples: Methotrexate, hydroxychloroquine, sulfasalazine, azathioprine, leflunomide
  - Monitor CBC, LFT
  - Watch immunosuppression risk (WBC)
  - DMARDs do not work quickly, takes weeks to months
  - 3-6 month trial is typically done before declaring failure and switching agents unless side effects are incurred
  - Often started with NSAIDs or steroids in a new diagnosis, acute flare type situation; NSAID or steroid covers the acute pain and inflammation

DMARDs

- Methotrexate
  - Once weekly up to 20-30 mg
  - LFT's, CBC, immune system suppression
  - Folic acid
- Sulfasalazine
  - GI upset, rash, CBC, LFT's
  - Can impair folic acid absorption
  - BID dosing
- Hydroxychloroquine
  - CBC, LFT's, eye exams
- Leflunomide
  - LFT's, CBC, diarrhea, skin reactions, hair loss

DMARDs - Biologics

- Usually not used first line due to cost considerations
  - Oral DMARD first, then dual oral DMARDs, possibly even triple therapy with MTX, sulfasalazine, and hydroxychloroquine
- Etanercept (once weekly), adalimumab (every 2 weeks), infliximab (infusion), etc.
- Injection site reaction
- Infection risk

Biologics

- Infection warnings
- Malignancy warnings
- Screen for latent TB or hepatitis B/C as they may be activated by a suppressed immune system
  - If patients have a latent TB infection, they should be treated prior to initiation of the biologic agent
  - If taking a biologic when they are diagnosed with a new infection, they should stop therapy and receive treatment for the infection
- Cost/insurance often regulates selection
- Can be used with oral DMARDs, typically methotrexate

JAK Medications

- Tofacitinib (Xeljanz), baricitinib (Olumiant), upadacitinib (Rinvoq)
- Mechanism of Action: Inhibition of Janus kinase (JAK) enzymes which is critical to the function of immune system cells
- Numerous boxed warnings are concerning with their use so they are often reserved for patients who have failed other combinations of traditional DMARDs and biologics
  - Infection/malignancy
  - Cardiovascular events
  - DVT/PE risks

OB/GYN, Women's Health

Contraception

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Contraception

- Primary goal:
  - Reduce risk of pregnancy
- Options
  - Oral contraceptives (estrogen, progestin combination)
  - Progestin only
  - Vaginal option (ring)
  - Patch
  - IM injection
  - Implant/IUDs
  - Emergency contraceptives

Selection Factors

- Adherence
- Adverse Effects
- Cost
- Lifestyle
  - Patient preference
- Previous experience

Adverse Effects – Oral Contraceptives

- Weight gain
- GI (nausea)
- Mood changes
- Breast tenderness
- Variable spotting
- DVT
- CV events
  - Smoking, age (>35)

High Risk Patients – Oral Contraceptives (E/P)

- Age >35/smoking
- CVD risk factors (smoking, diabetes, hypertension, older age)
- Uncontrolled hypertension >160/100
- Clotting disorder
  - Hx of stroke/DVT
- Valve replacement/anticoagulation
- Breast cancer

Estrogen Component

- Higher estrogen
  - GI
    - May get used to this
  - More breast tenderness
    - May get used to/tolerant
  - DVT risk
- Less estrogen
  - Breakthrough bleeding

Progestin Only Pill

- "Minipill"
- Consistent administration key!
  - Take at same time every day
  - Risk of breakthrough bleeding or pregnancy
- Option for breastfeeding

Other Options

- Patch (E/P)
  - Weekly change
  - Higher clot risk?
  - Not as effective in obesity
- Ring (E/P)
  - Refrigeration
    - Insert once every 3 weeks, then off 1 week
- Medroxyprogesterone injection
  - Q 3 months
  - Weight gain
  - Warning – low BMD

Other Options (cont.)

- Subdermal implant – progesterone
  - 3 year implant
  - Irregular bleeding
- IUD
  - Non-hormonal (copper)
  - Heavy menstrual bleeding
- IUD
  - Levonorgestrel
  - 3-5 years

Emergency Contraception

- Levonorgestrel (progestin)
- "Morning after pill"
- Take ASAP after unprotected sex
- Best within 72 hours, possibly effective up to 5 days

Pregnancy and Medication Use

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Preeclampsia

- Increase in blood pressure late in pregnancy
- Hypertension drugs of choice
  - Nifedipine (CCB)
  - Methyldopa
    - Rare, notable precautions – edema, thrombocytopenia, liver issues
  - Labetalol
    - IV and oral option
  - Hydralazine
    - IV and oral option
- 100% Avoid
  - ACE, ARB, Aldosterone antagonists

Constipation

- Common complaint in pregnancy
- Non drug interventions first line
  - Fluids/fiber
  - Exercise
- Stool softeners generally considered safe
- Metamucil type products

Nausea/Vomiting (Morning Sickness)

- If serious enough, can lead to dehydration, nutritional concerns
- Non-drug interventions for mild to moderate
  - Small, frequent meals
  - Bland foods
  - Avoiding trigger foods/smells
- Pyridoxine (vitamin B6)
- Doxylamine
  - First generation antihistamine
- Other options – reserved for refractory cases
  - Chlorpromazine
  - Prochlorperazine
  - Diphenhydramine
  - Metoclopramide
  - Ondansetron

UTI's

- Rare case where asymptomatic bacteriuria treatment is indicated
- Drugs of choice
  - Cephalosporins
  - Penicillins
- Nitrofurantoin
  - Contraindicated at full term due to risk of hemolytic anemia in infant
    - 38-42 weeks
- Fosfomycin
- Sulfa – decent safety record early (1st and 2nd trimesters)
- Quinolones, Trimethoprim, Tetracyclines generally avoid

Heartburn

- Non-drug interventions
  - Small, frequent meals
  - Elevated head of bed if nighttime problems
- Antacids (calcium, magnesium based)
- Sucralfate
  - Minimal systemic absorption
- H2 blockers (i.e. ranitidine)
  - Generally considered safe, use for shortest duration possible
- PPI's – less data available compared to H2's; reserved for severe/refractory cases
- Metoclopramide – option if nausea and vomiting as well

Pain Management

- Non-drug
  - Heat, ice
- Acetaminophen
  - Drug of choice for pain/headache
- Educate to avoid NSAIDs
  - Risks>benefit
  - Ibuprofen, aspirin, naproxen, etc.

Depression/Anxiety

- SSRI's drug of choice if have to start one during pregnancy
  - Sertraline, fluoxetine generally have the most data
  - Avoid paroxetine
- Depression and/or anxiety can be detrimental to health of the mother and health of the baby too
- Weigh risk of treatment compared to benefit of treatment

Gestational Diabetes

- Risk of hypertension, high birth weight baby, early delivery
- First line
  - Diet management
- Insulin is typically first line if medication management is necessary
  - Most experience
    - NPH
    - Regular
- If patient refuses injections
  - May consider sulfonylurea/metformin

Lactation

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Use of Medications – Breastfeeding Mom

- Challenges
  - Chronic disease
    - HTN, Depression, Anxiety
  - Acute problems
    - Infections
  - Pain management
- Common sense principle
  - If baby can take it, breastfeeding mom should be able to take it

Meds that Impact Breast Milk Production

- Pseudoephedrine
  - Suspected suppression of prolactin
- Dopamine agonists
  - Remember that antipsychotics can cause elevated prolactin levels (and cause lactation)
- Estrogen
  - Birth control
  - May need to use progestin only BC

Mastitis

- Infection/inflammation of breast tissue
- If infected
  - Beta-lactam
    - Dicloxacillin
    - Cephalexin
    - **if baby can take it, mom should be able to as well

Baby Deficiencies

- Iron
  - Premature babies
- Vitamin D
- B12

Common Drugs Considered ”Generally Safe”

- Breastfeeding
  - Analgesics – APAP, ibuprofen
  - Antibiotics – PCN, Cephs, Macrolide
  - Big molecule drugs – heparin type products/insulin

What to do?

- If minimal data
  - Play it safe
  - Minimize dose
  - Minimize duration
  - Choose alternative agent
  - Factor in mother’s health
    - Anxiety/depression
  - Provide information to patient
  - Avoid breastfeeding

Neurology

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Neuropathy

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Neuropathy

- Painful
- Burning
- Tingling
- Needles/pinprick type pain
- Diabetes
  - Control blood sugars
  - Lower A1C
- Falls risk with loss of sensation

Treatment

- Gabapentin/Pregabalin
  - Sedation
  - Renally cleared
  - Cost concern with pregabalin
  - Edema/weight gain
    - Dose dependent
  - Gabapentin requires transporter in gut
    - Dose dependent absorption
  - 300 gabapentin – approx. 50 mg pregabalin
  - Multiple daily doses

Treatment

- SNRI's
  - Duloxetine with most evidence
  - Likely need higher doses of venlafaxine
  - Antidepressant effect can be nice
  - HTN possible at higher doses

Treatment

- TCA's
  - Generally avoid in elderly
  - Really nice inexpensive option
  - Highly anticholinergic
    - Retention, constipation, dry eyes, dry mouth, CNS effects
  - Nortriptyline possibly better tolerated in elderly

Topical Agents

- Capsaicin
  - Regular, frequent use
  - PRN generally not effective
- Lidoderm patch
  - Needs to be small areas
  - Expensive (limits use)
  - On/off 12 hours

Dementia

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Major Types of Dementia

- Alzheimer's
  - Plaques in the brain
  - Most common form of dementia
- Vascular
  - Loss of blood supply to certain regions of the brain
  - Damaged vessels - Stroke, atherosclerosis can contribute
- Lewy Body
  - Usually associated with Parkinson's
  - Abnormal clumps of protein found in the brain

Dementia-Like Causes

- B12 deficiency
- Hypothyroid
- Mental illness
- Medications associated with dementia symptoms: Tricyclic antidepressants, benzodiazepines, opioids, antiepileptic agents, beta-blockers, antihistamines, Z-drugs, incontinence anticholinergics, sleepers

MMSE

- *Higher = Better
  - 24-30 Normal
  - 20-23 Mild
  - 10-19 Moderate
  - <10 Severe

Medications

- Acetylcholinesterase Inhibitors
  - Donepezil, Rivastigmine, Galantamine, Tacrine
  - Used in mild to moderate Alzheimer's dementia
  - Option in dementia with Lewy bodies (DLB)
- NMDA Receptor Antagonists
  - Memantine
  - Used in moderate to severe Alzheimer's dementia
    - Less evidence in dementia with Lewy bodies, role unclear
- *Do NOT Reverse Dementia

NMDA Antagonists - Memantine

- Moderate to Severe
- XR and Immediate release
- 28 mg to 20 mg conversion
- CrCl
- Usually well tolerated
  - CNS Changes

Acetylcholinesterase Inhibitors

- All oral except rivastigmine patch option
  - Less GI ($$)
- Tacrine – liver toxicity
- GI (NVD)
- Weight Loss
- Low risk of bradycardia (think about Atropine)
- Mild-moderate

Aducanumab (Aduhelm)

- Anti-Amyloid Monoclonal Antibody
  - Indicated for mild Alzheimer's disease
  - Very expensive, IV administration every four weeks, MRI monitoring required adding more expense
  - One study noted benefit while another did not – most dementia patients are not receiving this medication at this time

The One Million Dollar Question

- When to DC?
- Questions to think about
  - Adverse Effects?
  - Function Left?
  - Family opinions?
  - What would the patient think?
  - Another problem identified?
- Risk of DC?
  - Deterioration
  - Increase in behaviors

Behaviors

- Wandering
- Restless
- Agitation
- Physical Aggression
  - Hit, bite, kick
- Hallucinations
- Delusions

Behavior Identification

- Contributing factors
  - Individual person
  - Time of day
- Rule Out Causes
  - Pain
  - Infection
  - Medication changes

Solutions

- Solve underlying problem
  - Rule out B12 deficiency, thyroid issues, and possible medication(s), environmental factors contributing to memory loss
  - Medications associated with dementia symptoms: Tricyclic antidepressants, benzodiazepines, opioids, antiepileptic agents, beta-blockers, antihistamines, Z-drugs, incontinence anticholinergics, sleepers
- Non-drug approaches
- Make sure problem is distressing to patient before treating
- Medications last resort
  - Drugs don't often "treat" behaviors effectively

Common Psych Medications Tried

- Trazodone
- Antipsychotics
- Mood Stabilizers
- Antidepressants
- Benzodiazepines

Seizures

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Causes of Seizures

- CVD
- Dementia
- Trauma
- Cancer
- Withdrawal
  - Benzo's
  - Barbiturates
  - ETOH

Medications that Increase Seizure Risk

- Bupropion
- Tramadol
- Cancer medications
- Hypoglycemia
- Antipsychotics
- Stimulants

Common Seizure Medications

- Phenytoin
- Levetiracetam
- Carbamazepine
- Lamotrigine
- Valproic Acid
- Topiramate

Phenytoin

- Complex Kinetics
  - Dose depending increase in concentration
  - Small doses can lead to disproportionately large increases in drug levels
- Free versus total levels
  - 1-2, 10-20
- Vitamin D deficiency
- General toxicity symptoms similar to alcohol
  - Vertical nystagmus
- Enzyme inducer
- Gingival Hyperplasia

Carbamazepine

- Enzyme inducer
- Hyponatremia
- Bipolar and trigeminal neuralgia
- Bone loss
- Levels
  - 4-12
- Cousin *oxcarbazepine

Levetiracetam

- Watch kidney function
- Drug levels not routinely done
- Adjust dose based upon SE's/seizures
- Less drug interactions
- SE's; sedation, confusion, GI, behavioral changes, increase in BP

Lamotrigine

- Very slow dose titration
- Interaction with Valproic acid and enzyme induces
  - Quicker titration with enzyme inducers like phenytoin
  - Slower titration with VPA
- Drug induced rash (SJS)
  - Life threatening

Topiramate

- Cognitive slowing
- Weight loss
- Migraine indication
- Metabolic acidosis
- Kidney stone formation

Valproic Acid

- Weight gain
- GI
- Hair loss
- Rare (ammonia elevations, LFTs, thrombocytopenia)
- Migraine, Bipolar indications, might also see off label for aggressive type behaviors versus use of antipsychotics

Parkinson's Disorder

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Parkinson's Symptoms

- Tremor (one-sided)
- Rigidity "stiffness"
  - Pain
  - Alters range of motion
- Akinesia (loss of movement)
- Postural instability
  - Unable to remain in a stable (generally upright position)
- Can be challenging to diagnose
  - Trial Sinemet

Complications

- Falls
- Hypotension
- Dysphagia/swallowing difficulties
  - Aspiration risk
- Bowel/bladder problems
- Sleep disorders
- Psychosis/anxiety/depression
- Sexual impairment

Drugs for Parkinson's

- Sinemet
- Dopamine Agonists
- MAOI's
- COMT's
- Anticholinergics

Sinemet (Carbidopa-levodopa)

- Gold Standard
- Frequent dosing
  - CR product available
- GI
- Psych AE's
  - Psychosis
- Orthostasis
- Drug/Food interaction – protein
- Unusual obsessive behaviors
  - I.e. gambling, eating

Inhaled Levodopa

- Only indicated for off period
- Quick onset
- PRN – up to 5X/day
- AE – respiratory, cough
  - Otherwise, similar to oral; hypotension, hallucination, dyskinesias GI etc.
- Avoid within 14 days of MAOI

Dopamine Agonists

- Ropinirole, pramipexole
- RLS treatment
- Orthostasis
- Edema
- Unusual obsessive behaviors
  - I.e. gambling, eating

Amantadine

- Can be used for drug induced EPS
  - Has antiviral action (influenza)
- Mechanism not well understood (dopamine effects?)
- Tremor benefit in Parkinson's
- Anticholinergic type SE's
- DI's – Antipsychotics, Anticholinergics, watch influenza (live) vaccine

COMT's

- COMT's
  - Preserve levodopa
  - Need to be dosed with Sinemet
  - May need to reduce dose of Sinemet
  - Entacapone, tolcapone
    - Tolcapone – liver toxicity

MAOI's (Type B)

- Selegiline, rasagiline
  - Possibly used alone in early disease where QOL is not impacted but symptoms are a nuisance
  - Reduce Sinemet dosing – 10-30%
  - Serotonin interaction concern
  - Tyramine interaction potential
    - Hypertensive crisis
    - As dose escalates, loss of selectivity may happen (MAO-Type A)
  - Increases Sinemet effects so may see side effect profile similar to Sinemet

Anticholinergics

- Most benefit in tremor
- Rarely used due to adverse effect profile
  - Constipation
  - Dry eyes
  - Confusion/CNS changes
  - Dry mouth
  - Urinary retention
- Trihexyphenidyl
- Benztropine

Pimavanserin

- Only indication is for Parkinson's disease psychosis
- Targets 5HT2A – inverse agonist/antagonist
  - Less risk for movement disorder exacerbation
- 'Boxed warning – increased risk of death in patients with dementia (unrelated to Parkinson's) related psychosis
- $$$
- 3A4 interactions, QTc prolongation risk, hypotension

Drug Induced Parkinson's

- Antipsychotics
  - Typicals – the worst
  - Quetiapine, clozapine – the best
- Metoclopramide
  - Used for GI problems, but DA blocking activity

Headache

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Types of Headache

- Tension
- Migraine
- Cluster
- Medication Overuse/Rebound

Tension

- Dull, constant pain
- Bilateral
- Milder pain/pressure
- Light and sound sensitivity
- Most common headache
- Usually relieved by OTC NSAID or acetaminophen

Migraine

- Intense, stabbing pain
- Typically one sided
- Aura (not all)
- High sensitivity to light/sound
- Nausea/Vomiting
- More common in females

Cluster

- Severe, recurrent
- More common in men
- Stabbing/burning pain around an eye
- Generally shorter in duration than migraine/tension
- "Attacks" – can happen multiple times per day and over a period of weeks to months

Medication Overuse

- Taking frequent analgesics (>15 days/mo)
- Symptoms can vary
  - Can be more tension type headache and/or migraine type symptoms
- Stopping drug is the intervention
  - Symptoms get worse for 1-2 weeks

Medication Overuse/Rebound

- Often precipitated by initial onset of headache
- Repeated use of medication over time to relieve headache
- Drug Causes
  - Caffeine
  - Opioids
  - Triptans
  - NSAIDs
  - Acetaminophen

Management of Tension Headache

- Non-pharmacologic
  - Reduce stress
  - Avoid triggers
  - Rest
- Pharmacologic
  - Acetaminophen
  - NSAIDs
  - Combination with Caffeine
  - Triptans
  - Opioids

Migraine Treatment

- Triptans (see next slide)
- Antiemetics can be used in patients with significant nausea/vomiting
  - Metoclopramide, prochlorperazine, chlorpromazine
- Dihydroergotamines
  - Generally avoided
  - Most dosage forms very expensive
  - Do NOT use if pregnancy is a possibility
- In general, avoid opioids and butalbital
  - Not that effective
  - Risk of dependence and medication overuse headaches
- Alternatives in patients with failure to triptans
  - Lasmiditan – selective serotonin 1F receptor agonist
  - Rimegepant, ubrogepant – CCRP antagonists

Triptans

- May be used in combination with simple analgesics
- Adverse effects – CNS changes, dizziness, chest pressure
- Meant for acute relief, not prophylaxis
- Potential for serotonin interactions (SSRI's, tramadol, MAOIs, etc.)
  - A patient being treated with an SSRI for depression is typically not a contraindication to triptan use
- Nonoral options for those with significant nausea and vomiting (i.e. nasal, injectable) – sumatriptan is the most commonly used agent and has oral, injectable (fastest onset), and nasal dosage formulations
- Zolmitriptan has a nasal option
- Generally avoided in patients with uncontrolled blood pressure, ischemic stroke or heart disease, Prinzmetal's angina, and pregnancy

Triptan Comparison Chart

Drug (Trade name)	Route	Typical dosing range (24 hr max dose)	Onset	Half-life	Tmax	Metabolizing enzymes
sumatriptan (Imitrex, Zembrace)	Oral tablet	25-100 mg x1, may repeat after 2 hours if needed (200 mg)	30 min	~1.5-3 hrs	2-2.5 hrs	MAO-A
	Nasal spray	5-20 mg x1, may repeat after 2 hours if needed (40 mg)	15 min	3 hours	10 min	
	Subcutaneous injection	1-6 mg x1, may repeat after 1 hour if needed (12 mg)	10 min	~1.5-3 hrs	12 min	
rizatriptan (Maxalt)	Oral tablet/orally disintegrating tablet	5-10 mg x1, may repeat after 2 hours if needed (30 mg)	30 min	2-3 hrs	1-2 hrs	MAO-A, CYP3A4
zolmitriptan (Zomig)	Oral tablet	1.25-2.5 mg x1, may repeat after 2 hours if needed (10 mg)	1 hr	3 hrs	1.5-3 hr	CYP3A4
	Nasal spray	2.5 mg x1, may repeat after 2 hours if needed (10 mg)	15 min	3 hrs	N/A	
naratriptan (Amerge)	Oral tablet	1-2.5 mg x1, may repeat after 4 hours if needed (5 mg)	1 hr	6 hrs	2-4 hrs	CYP3A4, MAO-A
almotriptan (Axert)	Oral tablet	6.25-12.5 mg x1, may repeat after 2 hours if needed (25 mg)	30 min	3-4 hrs	1-3 hrs	MAO-A, CYP1A4, CYP2D6
hovatriptan (Frova)	Oral tablet	2.5 mg x1, may repeat after 2 hours if needed (7.5 mg)	2 hrs	26 hrs	2-4 hrs	CYP1A2
eletriptan (Relpax)	Oral tablet	20-40 mg x1, may repeat after 2 hours if needed (80 mg)	30 min	4 hrs	1.5-2 hr	CYP3A4

Alternatives To Triptans

- Lasmiditan – selective serotonin 1F receptor agonist
  - 50-100 mg dose once every 24 hours (max)
  - Serotonin syndrome risk
  - Does not see same vasoconstriction effects due to 1000-fold affinity for 1F receptor – may be safe in patients with cardiovascular risk factors

Alternatives To Triptans

- Rimegepant, ubrogepant – CCRP antagonists
  - CYP3A4 drug interactions may be problematic with these agents
  - Dose reductions and/or avoidance of these agents in severe CKD
  - Rimegepant is the only medication in this class that is approved for both acute management and prophylaxis of migraines
  - May be considered when triptans are contraindicated

Alternatives To Triptans

- Antiemetics
  - Used to help control N/V symptoms and pain associated with migraine
  - In addition to antiemetic effects, IV prochlorperazine or metoclopramide may have the best evidence to help reduce pain associated with migraine
    - Dopamine blocking action may increase risk for dystonic reactions so diphenhydramine may be given in combination with these agents
  - Other agents that may be considered haloperidol, ondansetron, chlorpromazine
    - Watch QT prolongation risk

Alternatives To Triptans

- Dihydroergotamines
  - Generally avoided
  - Most dosage forms very expensive
  - Do NOT use if pregnancy is a possibility
  - Boxed warning on interaction with CYP3A4 inhibitors like protease inhibitors, azole antifungals, and macrolides
  - Potential adverse cardiovascular effects (increase in blood pressure)
- In general, avoid opioids and butalbital
  - Not that effective
  - Risk of dependence and medication overuse headaches

When To Use Migraine Prophylaxis?

- Severe, long duration of headaches
- Frequent headaches per month
- Can't tolerate acute therapies
- Impacting quality of life
  - Work
  - Family issues

Migraine Prophylaxis

- Topiramate
  - Cognitive slowing, weight loss, ammonia, metabolic acidosis, renal stones
- Propranolol
  - Sedating, pulse/BP monitoring, watch respiratory conditions
- Valproic Acid
  - Lab monitoring (CBC, LFTs), hepatic issues, weight gain, pregnancy risk, ammonia
- Tricyclic antidepressants
  - Highly anticholinergic
- SNRI's
- CCB's

CGRP Antagonists

- Calcitonin-gene related peptide antagonist
- Migraine prevention
- Erenumab, fremanezumab, and galcanezumab
- Minimal evidence in child-bearing aged females
- Monitor # of migraine days per month
- $$$
- Injection site reactions, constipation, antibody development – neutralize the drug?

Cluster Headaches

- Acute
  - Oxygen
  - Triptans
- Prophylaxis
  - Verapamil

HIV/AIDS

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HIV/AIDS Pearls

- Drug resistance
  - Frequent mutations
  - Adherence CRITICAL
- Immune deficiency
- Rare, opportunistic infections
- Monitoring
  - CD4 counts
  - RNA

Medications for HIV/AIDS

- Nucleoside/nucleotide Reverse Transcriptase Inhibitors
- NNRTIs
- Integrase inhibitors
- Protease inhibitors
- CCR5-inhibitors
- Fusion Inhibitors

NRTIs

- Tenofovir disoproxil fumarate (TDF)
  - Adenosine analog (DNA component)
  - Osteoporosis risk
  - Renal toxicity
  - GI adverse effects
  - Lactic acidosis/fatty liver boxed warning
  - Elevation in cholesterol
- Tenofovir alafenamide (TAF)
  - Adenosine analog
  - Lower renal toxicity risk than TDF
  - Lower osteoporosis risk than TDF
  - Elevation in cholesterol, blood sugar
  - Weight gain

NRTIs

- Abacavir (ABC)
  - Guanosine analog
  - Must screen for HLA-B*5701 (contraindicated in patients who test positive due to increased risk for hypersensitivity reaction)
  - Generally avoided in patients with a history of coronary artery disease
- Emtricitabine (FTC)
  - Cytosine analog
  - Lactic acidosis/fatty liver risk
  - Hyperpigmentation
  - GI adverse effects
- Lamivudine (3TC)
  - Cytosine analog
  - Indicated for hepatitis B
  - Risk of HIV resistance if used for hepatitis B and HIV infection goes unnoticed
  - Lactic acidosis/fatty liver risk

HIV Medications

- Integrase inhibitor (raltegravir, dolutegravir, bictegravir, elvitegravir)
  - Elevated LFT's
  - Skin reaction risk/SJS (rare, but possible)
  - CNS changes possible
  - GI adverse effects
  - CPK increase/myopathy
  - Typically included in healthcare associated post-exposure prophylaxis
  - Bictegravir comes in a single pill combo with emtricitabine and tenofovir
  - Elvitegravir requires boosting with cobicistat

Starting Regimen

- Common starting regimen (if resistance testing is not available)
  - Tenofovir
  - Emtricitabine
  - Integrase inhibitor

Novel Agent – Long Acting Injectable

- Injectable integrase inhibitor and NNRTI
  - Cabotegravir and rilpivirine (Cabenuva)
  - Given every 1-2 months
  - Need to prove viral suppression and adherence on oral therapy for 6-12 months (significantly limits use)
  - Must be administered in a healthcare facility

HIV Medications

- Non-Nucleoside Reverse Transcriptase Inhibitors (efavirenz, delaviridine, etravirine)
  - CNS side effects, psychiatric changes
    - Hallucinations, abnormal dreams etc.
  - Hepatotoxic
  - Rash – can monitor if mild, but DC if severe
  - Potentially lowers seizure threshold

Protease Inhibitors

- Atazanavir, darunavir, fosamprenavir, lopinavir/ritonavir, cobicistat
  - Lipodystrophy (buffalo hump)
  - CYP3A4 interactions
  - Rash
  - Hyperglycemia
  - Ritonavir is a booster – increases concentrations of lopinavir
  - Atazanavir requires acidic stomach pH for absorption – watch PPI/H2 blocker use

HIV Medications

- CCR5-Inhibitors (maraviroc)
  - Boxed warning – hepatotoxicity
  - CNS effects
  - Orthostasis
  - Skin reaction risk
- Fusion Inhibitors (enfuvirtide)
  - Twice daily injection (so rarely used long term)
  - Injection site reactions
  - Possible increased risk in pneumonia, especially in patients already at risk (i.e. smokers, lung disease, low CD 4 count)

Opportunistic Infections

- PCP (Pneumocystis pneumonia)
  - Sulfa/TMP
  - Refractory treatment
    - TMP/dapsone
    - Pentamidine (severe)
  - Glucocorticoids
- Kaposi Sarcoma
  - Chemo or radiation
- Mycobacterium Avian Complex (MAC)
  - Macrolide
  - Ethambutol
  - Rifampin

Opportunistic Infections

- Cytomegalovirus – ganciclovir or valganciclovir
- TB – see TB
- Candidiasis – fluconazole
- Toxoplasmosis – pyrimethamine
- Cryptococcus – Ampho B, flucytosine, fluconazole

Lab Values

- RNA viral load
  - >100,000 copies/mL in early disease
  - Goal: undetectable (less than 50 or 20 depending upon lab)
- CD4 Count
  - 500-1500 is normal
  - Following trend
  - Lower = higher risk for infection
- If less than 200
  - PCP prophylaxis
- If less than 50
  - MAC prophylaxis

PrEP: Pre-Exposure Prophylaxis

- Patients who are HIV negative but at high risk of developing HIV
  - Sexual partners of HIV infected patients are the most common patients that may be impacted and candidates
  - High risk behaviors (i.e. multiple partners or sexual activity with a patient who has high risk behaviors)
  - IV drug users who share needles
- There is an extremely low risk of transmission in patients who are adherent to HIV therapy (highest risk or transmission is in patients who have a detectable amount of virus)
- Tenofovir and emtricitabine
  - Truvada – TDF; Descovy – TAF

Post-exposure prophylaxis (PEP)

- Initiate PEP for patients who have been exposed through needlestick or other means of puncturing the skin and has been working with a high risk patient
- Alternatively, PEP should be considered if a caregiver has an open sore or other nonintact skin and has been exposed to blood from a patient at risk for HIV
- Drug therapy should be offered even before HIV testing has been completed if the source of the blood is not known (i.e. ASAP drug initiation if there is potential for HIV risk)
- May offer PEP up to a week after exposure, but efficacy goes down over time (<72 hour is best)
- Tenofovir-emtricitabine, and integrase inhibitor
- Or substitute protease inhibitor for integrase inhibitor

Urinary Tract Infections

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UTIs

- Asymptomatic bacteriuria: >10^5 bacteria in the urine without symptoms
- Recurrent UTIs: culture confirmed UTIs with a frequency of >3 in 1 year or >2 in 6 months.
  - Relapse occurs within 2 weeks of treatment and is caused by the same pathogen
  - Reinfection occurs >4 weeks after an earlier UTI and usually involves a different pathogen
- Routine screening via urinalysis is rarely if ever appropriate
  - 10^5 bacteria in the urine and no symptoms is ASB (Asymptomatic bacteriuria) – In general this should NOT be treated with antibiotics
  - Urinalysis (aka follow up U/A) following a course of antibiotics is also not appropriate

Common Pathogens

- E. coli (70-80%)
- Proteus mirabilis
- Staphylococcus saprophyticus
- Klebsiella pneumoniae

Antibiotics

- Common treatment regimens include:
  - Trimethoprim/Sulfamethoxazole
  - Nitrofurantoin monohydrate/macrocrystals
  - Fosfomycin
  - Ciprofloxacin and other fluoroquinolones
  - Third-generation cephalosporins

Complicated

- Structural abnormality
  - Surgery
  - Urinary retention
  - Males
- Renal insufficiency
- Transplant
- Immunosuppression
- Diabetes

Treatment of Complicated UTIs

- Usually a 7-14 day treatment for mild cases
- Avoid Nitrofurantoin and Fosfomycin if suspected pyelonephritis
- Symptomatic cases require hospitalization and IV antibiotics
- Fluoroquinolones
  - Ciprofloxacin 500mg BID for 7 to 14 days
  - Levofloxacin 250 mg for 10 days or 750mg QD for 5 days
  - Can be used outpatient

Inpatient

- Extended-spectrum beta lactams
  - Ceftriaxone 1-2 grams IV/IM q24h or in divided doses twice a day
  - Ceftazidime 500mg IV/IM q8-12h
- Aminoglycosides
  - Ototoxicity
  - Nephrotoxicity
- If ESBL
  - Carbapenems

Trimethoprim-Sulfamethoxazole (TMP-SMX)

- Considered 1st-line for uncomplicated UTIs
- Good activity against many pathogens (except *Enterococcus* species)
- Growing resistance to *E.coli* (20%)
- Common side effects: GI upset and rash
- Crystalluria may occur- take with a full glass of water
- Contraindicated in patients with sulfonamide allergies
- Syrup available

Nitrofurantoin (Macrobid)

- Provides good antibacterial coverage
- Common side effects: N/V/D
- Take with food- increases serum concentrations
- Avoid in suspected pyelonephritis
- May discolor urine brown
- Rare respiratory, neuropathy, and CNS effects
- Contraindicated in patients with CrCl < 60ml/min
  - Some evidence now that it may be ok in CrCl 30-60 mls/min

Fosfomycin

- Studies showed equally effective to nitrofurantoin and TMP-SMX
- Can be given as a single dose
- Expensive
- Avoid in suspected pyelonephritis

Fluoroquinolones (ciprofloxacin and levofloxacin)

- Effective against gram (-) organisms, but only fair coverage against gram (+)
- Administer (oral) at least 2 to 4 hours before or 6 hours after antacids or other products containing calcium, iron, or zinc.
- Common side effects: N/V/D
- Rare side effect: tendonitis
- Avoid excessive exposure to sunlight
- Reduce the dose by half if CrCl< 30 ml/min
- Caution: may increase effects of warfarin/QTc prolongation

Prophylaxis

- Antibiotic prophylaxis of UTIs – recurrent infection considered two or more infections in 6 months or 3 or more in 12 months
- Continuous
  - Usually daily therapy with sulfa/tmp, nitrofurantoin, cephalexin, cipro
- Post-coital
  - Antibiotic use following intercourse
- Similar antibiotics used as continuous, but in patients whose UTI's seem to correlate with sexual activity

Pharmacologic Prophylaxis

- Regimens
  - Bactrim/Septra double strength 3x/week or single strength QD
  - Trimethoprim 100 mg QD
  - Macrobid (nitrofurantoin) 100mg QD
- Vaginal estrogen therapy
  - Used for prophylaxis
  - Helps maintain a normal flora to prevent infection

Non-Pharmacologic Prophylaxis

- Cranberry juice
- 300 ml/day of standard juice or 60 ml/day of concentrated juice
- 400 mg QD of cranberry extract
- Common side effect: calcium oxalate kidney stones

Miscellaneous

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Angioedema and Anaphylaxis

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Angioedema

- Signs
  - Swelling, tingling of mouth, lips, throat
  - Quick onset
  - Difficulty breathing is very concerning, medical emergency
  - Mild cases, limited to minor lip swelling can be managed outpatient

Anaphylaxis

- Respiratory distress
- Swelling/hives
- Hypotension
- Tachycardia

Goals of Therapy

- Medication treatment urgent
- 911
- Supportive care
- Identify cause
  - Avoidance to prevent future occurrence

Medications

- Epinephrine
  - Drug of choice in anaphylactic reaction
  - 0.15 mg dose in peds/0.3 mg dose in adults
  - Beta and alpha agonist activity constricts vessels
  - Beta/alpha blockers can blunt response
- Antihistamines
  - I.e. diphenhydramine
  - Used for allergic reaction in non-life threatening situation
  - Reduces reaction, can help with itch, hives

Medications

- Corticosteroids
  - Inflammation reduction
  - Alternative/add on to antihistamine in allergic reaction
  - Epinephrine used first line in anaphylaxis
- Glucagon
  - Possible option for those non-responsive to epinephrine
  - Helps avoid beta-blocker blunting effects
- Beta agonists
  - Inhaled – supportive care for continued breathing issues

Drug Induced Angioedema

- Generally not associated with urticaria
- ACE Inhibitors
  - African descent
  - Female
  - Age>65
  - Smoking
  - Seasonal allergies history
- NSAIDs
- Discontinue offending agent

Acne Vulgaris

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Acne Symptoms

- Hair follicles and their corresponding sebaceous glands that produce excessive oil
- Follicles get plugged
- Typically affects the upper part of the body, face, neck, trunk
- Whiteheads/blackheads
- Redness, papules
- Release of pus – pustules
- Scarring

Risk Factors

- Age
  - Puberty age
  - Excessive androgen production
- Medications
  - Exogenous androgens
  - Steroids
  - Lithium
- Diet
  - Chocolate
- Stress
- Family history

Drug Therapy

- Topical retinoids
  - Typically first line for most patients
  - Vitamin A derivatives
  - Tretinoin, tazarotene, adapalene
  - Can be used in combination with benzoyl peroxide and/or topical antibiotics
  - Do not apply at the same time as benzoyl peroxide
    - If using both, usually do one in the morning and one at night (may reduce effectiveness and/or increase peeling, adverse effects risk)
  - Dryness, irritation, flaking adverse effects

Drug Therapy

- Benzoyl peroxide
  - Can be used in mild cases as monotherapy or in combination for moderate to severe acne
  - Redness, irritation, dryness, flaking, burning are most common adverse effects
  - Can help reduce bacterial resistance risk especially when used in combination with oral or topical antibiotics
  - Alert patients that it can stain/bleach clothes, towels etc.

Drug Therapy

- Topical antibiotics
  - Clindamycin, erythromycin
  - Topical adverse effects possible, (i.e. irritation, redness etc.)
  - Bacterial resistance is a possible concern

Drug Therapy

- Salicylic acid
  - Alternative if topical retinoids or other agents are not tolerable
  - Available OTC
  - Inexpensive
  - Less robust evidence to support use

Drug Therapy

- Systemic antibiotics
  - Minocycline, doxycycline, erythromycin, sulfa/trimethoprim
  - Typically used in combo with other agents
  - Not first line due to potential for systemic adverse effects and antibiotic resistance risk
  - Most common adverse effects are GI for systemic antibiotics

Drug Therapy

- Tetracycline derivatives
  - Cation interactions (Fe, Calcium, etc.)
  - Educate patients of sunburn risk
  - Careful with women of child-bearing age – contraindicated for acne use; tooth discoloration
- Erythromycin
  - 3A4 inhibitor so drug interaction concerns
  - QTc prolongation risk
- Sulfamethoxazole/trimethoprim
  - Long term risks of bone marrow suppression
  - Rash/SJS risk (rare)
  - Trimethoprim can elevate potassium levels (exacerbated by other drugs, i.e. ACE/ARB/Aldosterone Antagonist)
  - Administer with full glass of water

AAD Recommendations

- Benzoyl peroxide or combinations with erythromycin or clindamycin are effective acne treatments and are recommended as monotherapy for mild acne, or in conjunction with a topical retinoid, or systemic antibiotic therapy for moderate to severe acne
- Benzoyl peroxide helps reduce resistance risk when used in combo with antibiotics
- Topical antibiotics (eg, erythromycin and clindamycin) avoid monotherapy because of the risk of bacterial resistance

AAD Recommendations (cont.)

- Topical adapalene, tretinoin, and benzoyl peroxide can be safely used in the management of preadolescent acne in children
- Azelaic acid is a useful adjunctive acne treatment and is recommended in the treatment of postinflammatory dyspigmentation
- Topical dapsone 5% gel is recommended for inflammatory acne, particularly in adult females with acne
- Generally avoid: sulfur, nicotinamide, resorcinol, sodium sulfacetamide, aluminum chloride, and zinc

AAD Recommendations (cont.)

- Systemic antibiotics are recommended in the management of moderate and severe acne and forms of inflammatory acne that are resistant to topical treatments
- Use doxycycline or minocycline (more effective than tetracycline)
  - Azithromycin and erythromycin as alternatives (pregnancy, younger children) but concerns of resistance
  - Bactrim last line
  - Reevaulate @ 3 months (minimize duration)
- Concomitant topical therapy with benzoyl peroxide or a retinoid should be used with systemic antibiotics and for maintenance after completion of systemic antibiotic therapy

AAD Recommendations (cont.)

- Oral isotretinoin is recommended for the treatment of severe nodular acne
  - Treatment resistant moderate acne or scarring/psychosocial distress
  - Routine monitoring of liver function tests, serum cholesterol, and triglycerides at baseline and again until response to treatment is established is recommended
  - Birth defect risk
  - Special REMS program
    - iPLEDGE
    - Required pregnancy test being negative before issuing the medication every month
    - Only allowed to dispense within a given window
  - Adverse effects; dry lips, CNS effects, hair thinning, nose bleeds, swelling of eye lids or lips, sun sensitivity, and rarely SJS

AAD Recommendations (cont.)

- Oral contraceptives – useful for inflammatory acne in females
  - Remember precautions to OCs; smoking, age, hypertension, clot risk, etc.
- Spironolactone has show some benefit in females
- Severe inflammation – consider corticosteroids

Dermatologic Disorders

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Dermatitis

- Contact, Atopic (Eczema)
  - Inflamed skin
  - Redness
  - Itchy
- Treatment
  - Topical Steroids
  - Calcineurin Inhibitors (i.e. tacrolimus)

Common Steroids

- Determinants of potency
  - Drug
  - Percentage
- Table
  - https://www.psoriasis.org/about-psoriasis/treatments/topicals/steroids/potency-chart

Medication Causes of Skin Disorders

- Rash
  - Antibiotics
    - Sulfa
    - Penicillins
    - Macrolides
- SJS risk
  - Antiepileptic (i.e. carbamazepine, lamotrigine)
  - Allopurinol
  - Penicillins
- **Timing, Timing, Timing

Yeast Infection

- Candida albicans
- Risks
  - Diabetes
  - Antibiotics
  - Immunosuppression
- Treatment
  - Topical nystatin, clotrimazole
  - Systemic, fluconazole

Pressure Ulcer

- Staging:
  - 1 – red, no breaks in skin, potentially pain
  - 2 – skin broken open
  - 3 – deeper into the skin, fat potentially showing
  - 4 – deepest, possible visual presence of bone, tendon, or muscle
- Risk of osteomyelitis or sepsis with deeper stages (3 or 4 typically)

Dry Skin

- Xerosis
  - Common in the elderly
  - Cracks/Infection risk
  - Itching
- Common treatment
  - Moisturizers

Psoriasis

- Inflammation
- Excessive growth in the epidermis
  - Raised, rough skin
  - Scaly appearance
- Most common location
  - Elbows
  - Knees
  - Scalp
- Can result in pain in the joints (psoriatic arthritis)

Management

- Localized areas
  - Topical corticosteroids
    - Triamcinolone, betamethasone, etc.
  - Vitamin D analogs calcipotriene, calcitriol
  - Calcineurin inhibitors
    - Can increase risk of skin cancer
  - Coal tar
    - Messy

Management

- Moderate to Severe Disease
  - Systemic retinoids (acitretin)
    - Birth defect in females
  - Methotrexate
    - LFT, CBC
    - Similar dosing to RA – 10-25 mg per week
    - Folic acid
  - Cyclosporine
    - Immunosuppressive
    - HTN, nephrotoxicity, infection/malignancy risk
    - Tons of drug interactions
  - Biologics (etanercept, infliximab, etc.)
    - Risk of malignancy, infection
    - Injection/infusion
    - Expensive

Anemia

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Signs/Symptoms of Anemia

- Fatigue
- Low Hemoglobin/Hematocrit
  - Elderly often can feel normal despite levels below normal
  - WHO (men<14, women <12.3)
- Dizziness/Falls
- Skin pallor
- Weak
- Confusion

Classic Causes of Anemia

- Blood loss
  - Anticoagulants, antiplatelets, NSAIDs
- Iron
- B12
- Folic Acid
- Chronic Disease (esp. CKD)
- Chemotherapy

B12 Deficiency Causes

- PPI
- Metformin
- ETOH
- Intrinsic Factor - pernicious

Drug Causes – Folic Acid Deficiency

- Methotrexate
- Trimethoprim
- Phenytoin

Treatment of Anemia

- Transfusion
- ESA (i.e. darbepoetin)
- B12
- Iron
- Folic Acid
- No treatment (if asymptomatic)

Megaloblastic Versus Microcytic

- B12/FA
  - Megaloblastic
  - MCV>100
    - Homocysteine
    - MMA
- Iron
  - Microcytic
  - MCV <80
  - Ferritin
- *Elderly often present with mixed type of anemias and normal MCV

Pernicious Anemia

- Lack of intrinsic factor
- Poor oral B12 absorption
- B12 toxicity rare
- B12 shots
  - For replacement, most will do 1,000 mcg weekly until deficiency is corrected and then do once monthly maintenance

Oral Iron

- Ferrous fumarate (33%) has highest elemental iron > sulfate (22%) > gluconate (12%)
- Constipation, stomach upset (dose and elemental iron content dependent)
- Black stools
- Binding interactions can lower drug concentrations of levothyroxine, quinolones, and tetracycline antibiotics
- Vitamin C (acidic environment) may aid absorption
- PPIs, H2 blockers, and antacids may cause a reduction in iron absorption
- Polysaccharide iron complex may be an option if there is not enough absorption from standard therapy
- Target ferritin levels are not well defined and may vary based upon clinician experience and clinical response

ESA Pearls

- Boxed warning for cardiovascular events
- Can exacerbate hypertension
- Lack of iron stores is common reason for lack of response in hemoglobin – ensure adequate stores
- Use primarily in oncology or possibly CKD due to lack of endogenous erythropoietin
- Consider in patients with hemoglobin <10; may be used in patients with hemoglobin greater than 10, but anemia symptoms must be profound and risk for cardiovascular events must be weighed
- Goal hemoglobin may vary based upon symptoms, clinician discretion, risk of cardiovascular events
- Reduce dose 25% if Hb increases by greater than 1 g/dL in a 2 week period
- Increase dose by 25% if Hb does not increase >1 g/dL in a 4 week period

IV Iron

- Indications
  - Patients who cannot tolerate oral
  - Gastric surgery or other patients who may have challenges absorbing oral iron
  - Severe and ongoing blood loss
  - Absorption/GI disorders that may impair absorption of oral iron preparations (i.e. celiac disease)
- Disadvantages
  - More upfront expense
  - Anaphylaxis/allergic reaction risk (less common now with newer preparations)
  - Iron dextran has highest risk of anaphylaxis reaction (requires test dose)
  - IV infusion

Acute Blood Loss

- Blood Transfusion (PRBC)– way to quickly raise hemoglobin
- Risks are rare but significant
  - Allergic reaction
  - Donor matching
  - Iron overload with too many infusions

Acute and Chronic Kidney Disease

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Signs of Kidney Failure

- Rise in serum creatinine
  - Generally 30%
- Rise in Blood urea nitrogen
  - Both are removed by the kidney
  - In renal disease, both accumulate
- Hyperkalemia/cardiac changes

Cockcroft-Gault Formula for Estimating Creatinine Clearance

$$\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{Lean Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72} \quad (\times 0.85 \text{ if female})$$

Acute Renal Failure

- Prerenal
  - Inadequate perfusion
- Post renal
  - Blockage (stones, BPH)
- Intrinsic
  - Infection
  - Toxic agents
  - May be marked by elevated protein in the urine

Acute Kidney (Injury) Disease - Prerenal

- Common causes
  - Reduced blood flow to kidney
  - Caused by
    - Dehydration
    - Significant acute blood loss
    - Severe N/V/D
- Medications
  - ACE/ARB
  - NSAIDs
  - Diuretics

Classic Medication Causes - Intrinsic

- Aminoglycosides
- Cisplatin
- Amphotericin B

Treatment of ARF

- Supportive care
- Prerenal
  - Volume replacement with dehydration
- Intrinsic
  - Remove offending agent
  - Inflammation
    - Steroids
- Post renal
  - Remove blockage

Stages of Chronic Kidney Disease of all Types

Stage	Qualitative Description	Renal Function (mL/min/1.73 m²)
1	Kidney damage-normal GFR	≥90
2	Kidney damage-mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	End-stage renal disease	<15 (or dialysis)

Source: [illegible]

Problem: Dosing Medications

- Many drugs are dosed by CrCl
- Lab reports GFR
- Keep an eye on changes in kidney function
  - Drugs can accumulate
  - Cause toxicity

Incredible # of Medications Dose Adjusted

- Chronic medications
  - Use common sense
  - Check levels (i.e. digoxin)
  - Start low go slow
  - Should you change dose if no side effects
    - Gabapentin
    - Ranitidine
    - Allopurinol

Collateral Damage - CKD

- Fracture risk
  - Vitamin D deficiency
- Anemia
  - Kidney = source of EPO
- Fluid retention
- CVD
- Hyperkalemia

Preventing Kidney Problems

- Diabetes
  - Blood sugar control
  - ACE inhibitors
- Hypertension management
- Smoking cessation
- Obesity management

Medications for Organ Transplantation

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Calcineurin Inhibitors

- Cyclosporine, tacrolimus
  - Adherence is very critical
  - Change in dosage forms can result in changes in levels/bioavailability
- Monitoring
  - Immunosuppression/infection/cancer
  - Hypertension
  - Hyperglycemia
  - Hyperkalemia
  - GI side effects

Calcineurin Inhibitors

- Trough concentrations drawn
  - Goals can vary based upon:
  - Infection risk
  - Adverse effects
  - Risk of rejection
  - Time from transplant
  - 100-400 target levels
- Consistent timing of administration recommended
- CYP3A4 drug interactions
  - Monitor levels closely with changes

Corticosteroids

- Infection
- Cushing's
- Hyperglycemia
- Osteoporosis
- GI Risk

Mycophenolate

- Adverse effects
  - GI
  - Hypertension
  - Edema
  - Immunosuppressive effects
- Administer on empty stomach

Signs of Rejection

- Loss of function of organ – examples:
  - Jaundice (liver)
  - Worsening renal function
- Patient feeling poorly
  - Flu like symptoms
- Pain/swelling
  - Location of organ
- Acute rejection
  - Week to 3 months; chronic >3 months
- Review for adherence/interaction/adverse effect potential

Beers Criteria

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Beers Criteria

- POTENTIALLY Inappropriate medications
- Historically
  - Simply a list of medications, non-specific to patients
- More recently
  - List of medications inappropriate in specific situations
  - I.e. poor kidney function, drug-drug interactions

Cardiology

- Alpha Blockers
  - Non-selectives
  - Avoid for just hypertension
    - Possible role in BPH
- Central acting
  - Clonidine
- Digoxin – dose limit
- Antiarrhythmics
  - Flecanide
  - Propafenone
  - Amiodarone

Anticholinergics

- TCA's
- 1st Generation antihistamines
- Parkinson's disease

Analgesics/Antispasmotics

- Skeletal Muscle relaxants
  - Methocarbamol
  - Cyclobenzaprine
- NSAIDs
- Meperidine

CNS Medications

- Antipsychotics
- Sleepers
  - Z-drugs
  - Anticholinergics
- Benzo's
- Barbiturates

Endocrine/Women's Health

- Endocrine
  - Sliding Scale
  - Sulfonylureas
    - Chlorpropamide
    - Glyburide
- Women's health
  - Estrogen replacement

Gastrointestinal

- Metoclopramide
- Mineral oil
- Megestrol
- PPI's >8 wks

Beers Criteria Updates

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Antacid Medications

- H2 blockers
  - Historically recommended to avoid due to dementia/cognition concerns
  - Evidence insufficient/inadequate to continue that recommendation
  - Concern that recommendation led to excessive/overuse of PPI's
  - Still recommended to avoid in at risk delirium patients, but not dementia patients

Antacid Medications

- PPI's
  - Generally avoid long term (except in higher risk situations)
    - High-risk: Barrett's esophagus, GI bleed history, GI bleed risk medications and other risk factors
  - PPI risks
    - Fracture
    - C. Diff
    - Low magnesium
    - Low B12
    - Pneumonia

Practice Pearls on GI Medications

- Encourage an end date
- Review at least annually
- Taper for long time users
  - High incidence of rebound symptoms
- Consider step down (especially with new recommendation that H2's maybe aren't that bad)

Opioid Drug Interactions

- Drugs that increase risk of overdose and respiratory depression
  - Benzodiazepines
  - Pregabalin
  - Gabapentin
- Recognize other risk factors
  - Underlying respiratory disease (i.e. COPD)
  - Obesity
  - Sleep apnea

Antibiotics

- Trimethoprim/sulfamethoxazole
- Risk with dual use of ACE, ARB, or Aldosterone antagonists
- Risk of hyperkalemia
- "Use with caution"

Practice Pearls Sulfa/TMP Hyperkalemia

- Clinical options
  - Recognize at risk patients (renal disease)
  - Alternative antibiotic
  - Monitor K+
  - Alter ACE, ARB, or aldosterone antagonist

Antibiotics

- Warfarin Interactions
- Avoid concomitant use
  - Sulfamethoxazole/trimethoprim
  - Macrolides (excluding azithromycin)
  - Ciprofloxacin

Practice Pearls; Anbx and Warfarin

- Check INR if antibiotics are necessary
- Clinically monitor (bleed/bruise)
- Avoid warfarin in favor of newer anticoagulants

Ciprofloxacin and Theophylline

- Avoid together
- Cipro - CYP1A2 inhibitor
- Increases theophylline toxicity risk

Ciprofloxacin

- Caution with reduced renal function
  - Tendon Rupture
  - CNS adverse effects

Rivaroxaban

- "Use with caution" – 75 or older
  - GI bleed risk
- Lean toward apixaban
  - Understand dosing recommendations
  - Age, Weight, Creatinine
- Dabigatran age risk remains

Falls and Fractures

- SSRI's and SNRI's
  - Increased risk of falls
  - Minimize dose, titrate slowly
- Still going to mainstay in antidepressant selection for depression and anxiety

Hyponatremia

- Tramadol
  - Mechanism of action: binds to μ-opiate receptors
  - Also… inhibits the reuptake of norepinephrine and serotonin
- SSRI's, SNRI's are associated with SIADH and risk of hyponatremia
- Tramadol also can cause this
- Keep an eye out for at risk patients
  - On diuretics
  - SSRI's or SNRI

Hyponatremia

- Mirtazapine
- Oxcarbazepine
- Carbamazepine
- TCA's

Less Aspirin Use

- PRIMARY PREVENTION ONLY
- Age limit reduction from 80 to now 70
- Risks of bleed

Chemotherapy Agents

- Carboplatin
- Cisplatin
- Vincristine
- Cyclophosphamide
- *Removed – considered "highly specialized"

Dextromethorphan/quinidine

- Use with caution
- Limited efficacy in helping with dementia related behaviors in absence of pseudobulbar affect
- Fall risk
- Drug interactions
  - Anticholinergic
  - QTc prolongation
  - 2D6 implications (dextromethorphan)
  - 3A4 implications (quinidine)

Heart Failure

- Low Ejection Fraction
  - Avoid Non-DHP (diltiazem and verapamil)
- Use with caution in asymptomatic HF patients
  - NSAIDs
  - Celecoxib
  - TZD's
  - Dronedarone

Diabetes

- Glimepiride added to PIM
- Increased prolonged hypoglycemia risk
- Glipizide preferred

Antipsychotics in Parkinson's

- Avoid: Except,
  - Quetiapine
  - Clozapine
  - Pimavanserin

Start/STOPP Criteria

- STOP – Situations to review medications for discontinuation/taper
  - Long-term UTI prophylaxis – review after 6 mo/use, urology help
  - Non-cardioselective BB in asthma
  - Swallowing difficulties – oral bisphosphonates
  - Digoxin with eGFR<50 and dose >125 mcg/day
  - Thiazides in gout
  - SSRI with Na+ <130
  - Statins with life expectancy <6 mo
  - TCA in patient with dementia, glaucoma, constipation, retention

START Criteria

- ACE inhibitor
  - CHF, post-MI, DM nephropathy
- Antihypertensive therapy
  - SBP>160
- Statins
  - CVD, PVD, independent, life expectancy >5years
- Calcium/D
  - Osteoporosis diagnosis
- Laxatives
  - Patients on opioids

Eye Disorders

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Common Eye Disorders in the Elderly

- Macular Degeneration
- Glaucoma
- Diabetic Retinopathy

Macular Degeneration

- Clinical Pearls
  - Central vision loss
    - Reading
    - Driving
  - Use of VEGF inhibitors (Bevacizumab)
  - Smoking can increase risk
  - Dry can progress to Wet (wet is worse)

Glaucoma Pearls

- Leading cause of blindness worldwide
- Peripheral loss
- Borderline Pressure 18-25
  - Assessment for damage
  - If damage, treatment
  - Some may argue >22
- Greater than 25 - treatment

Drugs

- Prostaglandins
- Beta-blockers
- Adrenergic agonists
- Carbonic Anhydrase Inhibits
  - Rarely oral used (acetazolamide)

Preventing Diabetic Retinopathy

- Blood sugar control
- Hypertension
- Regular Exams

Medications – Eye Problems

- Hydroxychloroquine
- Ethambutol
- Tamsulosin
  - Floppy iris syndrome
  - Concern in cataract surgery
- Dry eyes
  - Cornea scratch/damage
  - Anticholinergics
  - Diuretics
- Cataract
  - Steroid use

Vaccines

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Pediatric Vaccines

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Pediatric Vaccines

- Rotavirus
  - Rotarix: 2 doses given at 2 and 4 months
  - RotaTeq: 3 doses given at 2, 4, and 6 months
  - Do not start the series on or after age 15 weeks
  - Maximum age for the final dose is 8 months
  - Oral liquid
  - Live vaccine
    - Can be given on the same day as other live vaccines otherwise needs to be spaced 4 weeks apart
    - If the patient received antibodies must wait at least 3 months to give the vaccine
    - After vaccination must wait at least 2 weeks to receive antibodies

Pediatric Vaccines

- Hepatitis B
  - 3 doses
    - Given at birth, 1-2 months, and 6-18 months
  - Intramuscular injection
  - Inactive (non-living)
  - Engerix-B and Recombivax HB are available for use in children
    - Supplied as different concentrations and not interchangeable
  - Comes in combination with other vaccines if the patient is due for multiple vaccines
    - Pediarix: DTaP-HepB-IPV
    - Vaxelis: DTaP-IPV-Hib-HepB

Pediatric Vaccines

- DTaP: Diphtheria, tetanus toxoids, and acellular pertussis (Daptacel and Infranrix)
  - 5 doses
    - Given at 2,4,6, 15-18 months, and 4-6 years
  - Intramuscular injection
  - Inactivated (non-living)
  - Comes in combination with other vaccines if the patient is due for multiple vaccines
    - Example: Pediarix (DTaP-HepB-IPV)

Pediatric Vaccines

- Hib: Haemophilus influenzae Type B
  - ActHIB and Hiberix: 4 doses
    - Given at 2,4,6, and 12-15 months
  - PedvaxHIB: 3 doses
    - Given at 2,4, and 12-15 months
  - Intramuscular injection
  - Inactivated (non-living)

Pediatric Vaccines

- PCV13 or PCV15: Pneumococcal 13 or 15 Valent Conjugate Vaccine (Prevnar)
  - 4 doses
    - Given at 2,4,6, and 12-15 months
  - Intramuscular injection
  - Inactive (non-living)
  - Interchange OK per ACIP

Pediatric Vaccines

- IPV: Inactivated Polio Vaccine (IPOL)
  - 4 doses
    - Given at 2,4,6-18 months, and 4-6 years
  - Intramuscular or subcutaneous injection
  - Inactivated (non-living)
  - Comes in combination with other vaccines if the patient is due for multiple vaccines
    - Example: Pediarix (DTaP-HepB-IPV)

Pediatric Vaccines

- MMR: Measles, mumps, and rubella (M-M-R-II)
  - 2 doses
    - Given at 12-15 months and 4-6 years
  - Subcutaneous injection
  - Live vaccine
    - Can be given on the same day as other live vaccines otherwise needs to be spaced 4 weeks apart
    - If the patient received antibodies must wait at least 3 months to give the vaccine
    - After vaccination must wait at least 2 weeks to receive antibodies
  - Also comes in combination with Varicella vaccine
    - ProQuad: MMRV (measles, mumps, rubella, and varicella)

Pediatric Vaccines

- Varicella (Varivax)
  - 2 doses
    - Given at 12-15 months and 4-6 years
  - Subcutaneous
  - Live vaccine
    - Can be given on the same day as other live vaccines otherwise needs to be spaced 4 weeks apart
    - If the patient received antibodies must wait at least 3 months to give the vaccine
    - After vaccination must wait at least 2 weeks to receive antibodies
  - Comes in combination with other vaccines if the patient is due for multiple vaccines
    - ProQuad: MMRV (measles, mumps, rubella, and varicella)

Adolescent Vaccines

- Meningococcal A,C,W,Y serogroups vaccines (Menveo, MenQuadfi, and Manactra)
  - 2 doses
    - Given at age 11-12 and 16 years
  - Intramuscular injection
  - Inactivated (non-living)
- Influenza
  - Annual

Adolescent Vaccines

- Tdap
  - One booster shot 11-18 y/o
- HPV: Human Papillomavirus Vaccines (Gardasil 9)
  - 2 doses
    - Given at 9-14 years and 6-12 months later
  - 3 doses if initial vaccination is at age 15 years or older
    - Given at 0, 1-2, and 6 months
  - Routinely recommend first dose at age 11-12 years
  - Intramuscular injection
  - Inactivated (non-living)

HPV Vaccine - Indication for Ages >26

- OK to give in those >26 years of age
- Most will likely have been exposed
- Insurance may not cover
- May be indicated in those with no/minimal sexual exposure history
- Now more likely to have more sexual exposure

COVID-19 Vaccine*** - Subject to Change

- Moderna 2-shot course, 28 days apart (monovalent) or Pfizer 2-shot course 21 days apart
  - Approved for patients 6 months of age and older
- A one-time dose bivalent (Omicron coverage) booster is recommended for patients 12 years old and up
  - Pfizer product for ages 12-17
  - Moderna or Pfizer product for ages 18 and up
  - Can be given 2 months after previous vaccine dosages
  - Patients are eligible even if they have had a monovalent booster
  - Patients aged 5-11 not eligible for bivalent at this time but are recommended to have the monovalent booster
- Novavax
  - Monovalent recombinant protein vaccine for ages 12 and up
- May be given with influenza vaccine

Adult Vaccines

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COVID-19 Vaccine

- Moderna 2-shot course, 28 days apart (monovalent)
  - Approved for patients 6 months and older
- Pfizer 2-shot course, 21 days apart (monovalent)
  - Approved for patients 6 months of age and older
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  - Can be given 2 months after previous vaccine dosages
  - Patients are eligible even if they have had a monovalent booster
  - Patients aged 5-11 not eligible for bivalent at this time but are recommended to have the monovalent booster
- Novavax
  - Monovalent recombinant protein vaccine for ages 12 and up

Shingrix

- Recombinant Zoster Vaccine (Shingrix)
  - Stronger evidence/response compared to Zostavax
  - Age 50+
  - Wait to give if active shingles episode
  - Give even if they have had shingles before
  - 2 dose course, 2-6 months apart
  - Give even if they have had Zostavax in the past
  - Inactive

Pneumococcal Vaccination

- Pneumococcal Conjugate Vaccine – PCV15 (Vaxneuvance), PCV20 (Prevnar 20)
  - One time lifetime dose
  - Injection
  - Inactive (non-living)
  - 1 year separation from Pneumococcal Polysaccharide 23 valent vaccine if both are to be given (8 week separation may be considered for immunosuppressed/high risk patients)
  - If PCV13 and PPSV23 had previously been received, revaccination with PCV15 or PCV20 is not recommended
  - If only PPSV23 has been given, give PCV product one year after

Pneumococcal Vaccination

- Pneumococcal Polysaccharide 23 Valent Vaccine (PPSV23) - Pneumovax
  - Up to 3 lifetime doses (only 1 after the age of 65)
  - Injection
  - Inactive
  - Indicated for all patients 65 and older (wait at least 5 years between doses if the patient received a dose prior to age 65)
  - Indications for younger individuals
    - CHF, lung diseases, smoking, diabetes, alcoholism, liver disease, cochlear implant, cerebrospinal fluid leaks, asplenia, sickle cell disease, immunocompromised condition (20 mg of prednisone for >2 weeks)
  - If 19 years of age and patient has an immunocompromising condition, give PPSV23 and may do a repeat dose 5 years later

Pneumococcal Vaccination

- ACIP Recommendations – Pneumococcal Vaccination
  - PCV20 (Prevnar 20) or PCV15 (Vaxneuvance) is recommended in patients who are 65 years of age or older or in patients 19-64 who have specific underlying conditions (PCV13 no longer recommended)
  - If PCV15 is used, it should be followed by PPSV23 1 year later
  - PCV20 does not require a follow up PPSV23 dose per ACIP, but some may consider this based upon clinical decision making
  - If PCV13 and PPSV23 had previously been received, revaccination with PCV15 or PCV20 is not recommended

Influenza Vaccination

- All flu vaccines are quadrivalent
- Given annually
- CDC does not state a preference as to which influenza vaccine is best; but the vaccine should be indicated and studied for use in specific patient populations
  - ACIP recommends specific products for elderly (65 y/o and above)
- Inactivated vaccine (injection) - Indicated for all patients greater than or equal to 6 months of age
- Live, attenuated (LAIV) nasal indicated for patients age 2-49 (possibly less effective, but remains an option)
  - Numerous contraindications exist for LAIV: immunocompromised patients, children aged 2-4 with an asthma diagnosis, close contact with immunocompromised patients, pregnancy, CSF leak, cochlear implants, recently received antiviral therapy such as oseltamivir, baloxavir, etc.

Influenza Vaccination

- High dose (Fluzone)
  - A little more expensive
  - Many clinicians are using it for all >65
  - Some are reserving for higher risk populations (i.e. smokers, lung disease etc.)
  - ACIP gives preference to adjuvanted or high dose in patients 65 years of age or older
- FLUAD – Adjuvanted for higher immune response, indicated in 65 y/o+
- Typically takes 2 weeks to form antibodies
- Start giving vaccine in Fall (September/October) timeframe
- Give vaccine until influenza is no longer circulating
  - Usually April-May timeframe
- May be given with COVID-19 vaccine

Influenza

- High dose (Fluzone) available
  - A little more expensive
  - Many clinicians are using it for all >65
  - Some are reserving for higher risk populations (i.e. smokers, lung disease etc.)
  - CDC does not give preference as to which flu vaccine should be selected in the geriatric population
- FLUAD – Adjuvanted for higher immune response, indicated in 65 y/o+
- Typically takes 2 weeks to form antibodies
- Start giving vaccine in Fall (September/October) timeframe
- Give vaccine until influenza is no longer circulating
  - Usually April-May timeframe
- May be given with COVID-19 vaccine

Tdap/Td

- Tetanus, Diphtheria, Pertussis (whooping cough)
- Revaccination
  - Every 10 years (one time dose of Tdap)
  - Td for all other doses
- Inactivated
  - Immunosuppressed patients ok

Pharmacogenomics

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Clinical Basis

- Understand 2 clinical principles that pharmacogenomics can help with
  - Safety
  - Efficacy
- CPIC – Clinical Pharmacogenetics Implementation Consortium
  - Resources/guidelines

Critical Concepts

- Rapid/extensive metabolizer – most often going to result in lower concentrations (lack of efficacy)
- Slow/poor metabolizer – most often going to result in higher concentrations (risk of toxicity)
- Prodrugs – opposite effects

Drug Examples – Genetic Variations

- Clopidogrel (prodrug)
  - Genetic variation in CYP2C19
  - Slow/poor metabolizer – risk of reduced clinical effects
  - Risk of MI/ACS
  - In treatment failure, consider alternative antiplatelet agent (prasugrel or ticagrelor)

Drug Examples – Genetic Variations

- Codeine (prodrug)
  - Converted to morphine via CYP2D6
  - Rapid metabolizer – increases risk of opioid overdose
  - Slow metabolizer – increases risk of non-response
- Warfarin – 2C9
  - Rapid metabolizer – higher dose needed to achieve therapeutic concentrations
  - Poor metabolizer – Lower doses needed, increased risk for bleed

Drug Examples – Genetic Variations

- Allopurinol – HLA-B*58:01 positive
  - Increased risk of skin reaction
- Carbamazepine – HLA-B*15:02 positive
  - Increased risk of SJS
- Irinotecan
  - UGT1A1 Gene alteration – risk of neutropenia
- Tacrolimus
  - CYP3A5 – extensive metabolizer; going to need higher dose
  - Monitor target concentrations
- 6-mercaptopurine
  - TPMT Gene variation carries an increased risk for myelosuppression

Drug Examples – Genetic Variations

- Metoprolol – 2D6
- Phenytoin – 2C9
- Abacavir – All patients should be screened for HLA-B*5701 prior to starting (hypersensitivity reaction)
- Simvastatin
  - Gene variation SLCO1B1 – increased risk for myopathy/AE's
- Rasburicase
  - Do NOT administer to patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency – risk of hemolysis
  - African/Mediterranean populations at higher risk for genetic deficiency

Notable Psych Drugs Affected By 2D6

- Atomoxetine
- Methylphenidate
- Amitriptyline
- Nortriptyline
- Doxepin
- Paroxetine
- Fluoxetine
- Sertraline
- Bupropion
- Venlafaxine
- Duloxetine
- Mirtazapine
- Aripiprazole
- Olanzapine
- Risperidone
- Clozapine

Others 2D6

- Propranolol
- Tolterodine
- Quinine
- Tamoxifen (prodrug)
- Tramadol (prodrug)
- Oxycodone

Pediatrics

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Premature Baby Issues

- Developmental and intellectual challenges
- Anemia
- Infection risk
- Jaundice
- Lung development

Ear Infection

- Symptom management
  - APAP or Ibuprofen for pain management
  - Avoid topical "caines" in patients <2 due to risk of methemoglobinemia
- To treat or not?
  - <6 months – likely yes
  - 6 months – 2 years and mild pain, symptoms <48 hours, lower grade fever (<39C, 102.2F) – consider watch and wait
  - >2 years – mild symptoms, no discharge, consider observation
- Drugs
  - Amoxicillin 90 mg/kg/day or amox/clav in 2 doses
  - Cefdinir, cefuroxime, cefpodoxime, azithromycin are alternatives

Cough and Cold

- Upper respiratory viral infections are self-limiting
  - Milder symptoms
  - Symptoms should start to get better after about 2-4 days
- Educate to avoid excessive treatment, risk of overdosing
  - Minimize use of OTC medications in patients <6
  - Avoid medications if symptoms are mild
  - Supportive options are used first: saline spray, suction, hydration, humidifier
  - Other considerations – cough drops (in those old enough), honey (>1 y/o)
- Warning signs; extended time of illness with no improvement, wheezing, violent coughing (i.e. vomiting), SOB, higher fever

Respiratory Syncytial Virus Prevention

- Palivizumab
  - Costly
  - Reduces hospitalization in high risk patients
  - Initiated at the start of RSV season and monthly during the RSV season (fall/winter)
  - Max 5 doses
- Indications
  - <32 weeks with chronic lung disease
  - Up to age 23 months
- Those without lung disease
  - <29 weeks and under 12 months old at start of RSV season
  - 29-32 weeks – clinically controversial

Teething

- Symptoms
  - Fussy, drooling, chewing, fever, diarrhea
- Management
  - Cool teething ring
  - Avoid anything that might break and be a choking risk or that could wrap around the baby's neck such as a necklace
  - Analgesia (i.e. acetaminophen)
  - Avoid "caines"
    - Lidocaine – boxed warning for risk of seizures, CV concerns, death in patients <3
    - Benzocaine – warning for methemoglobinemia (MetHb)
      - Reduces hemoglobin's ability to release oxygen in the tissues

Pharmacokinetics

- Drug Absorption
  - Higher stomach pH until age 2 (gradual)
    - Reduces absorption of weakly acidic medications (i.e. phenytoin, barbiturates, acetaminophen) and increases absorption of weak bases (i.e. opioids, amphetamines)
  - Slower GI motility in neonates
  - "Thin-skinned" – transdermal absorption is quicker and greater in pediatrics
- Distribution
  - Higher water content in newborns versus adults
  - Need higher dose to get equivalent concentration for water soluble drugs (vancomycin)
  - Less protein in newborns – less protein binding (phenytoin)
  - BBB may be more permissible

Pharmacokinetics

- Metabolism
  - Reduced liver function at birth (i.e. CYP enzymes)
    - Many developed by age 2
- Elimination
  - Varies greatly as age changes
    - GFR around 40 mls/min at birth and may approach and exceed normal adult values at 3 months
    - Penicillins and cephalosporins

Pharmacokinetics

- Pediatric patients are NOT mini-adults; processes can vary greatly in the first few years of life!
  - Extreme caution with NTID (i.e. phenytoin)
- Neonates and infants (age 0-1) are typically more sensitive to medications
  - Immature means of metabolism and elimination
  - Higher risk for ADRs than adults
- Tremendous variability in pharmacokinetics as a child ages

Dosage Forms and Safety

- Measuring mistakes and dose verification
  - Avoid teaspoon/tablespoon measurements
  - Provider dosing errors based upon calculation
  - Inaccurate weight (kg/lbs.)
  - Shaking suspension
- Abbreviations
- Communication
- Route of administration
- Greater risk of AEs due to altered kinetics
- Multiple Rx's (i.e. amoxicillin, acetaminophen)
- Accidental overdose – childproof caps, blister packaging

Medications to Avoid in Pediatrics (KIDs List)

- Aspirin and other salicylates for pain/fever with recent viral infection– Reye's syndrome; hepatic, CNS swelling
- Benzocaine, Lidocaine for teething
- Codeine (unless pharmacogenomic testing is done)
- Lomotil – respiratory depression, death
- Many first generation antipsychotics – acute dystonia
- Mineral oil – lipid pneumonitis
- Nitrofurantoin in neonates – hemolytic anemia
- Fleets enema in infants - electrolyte disturbances
- Tetracyclines – tooth discoloration
- Topical steroids for diaper rash <1 y/o; increased absorption
- TCAs – cardiac risks
- Valproic acid – hepatic issues, pancreatitis

Regulatory, MTM Practice, Statistics, and Patient Advocacy

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Ambulatory Care – Billing Codes

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MTM Billing Codes

- 99605, 99606, 99607
- Medicare part D benefit (pharmacy benefit)
  - Part B is clinic benefit
  - State Medicaid and private insurance may recognize these in a non-pharmacy setting
- 99605 – new patient, 15 minute increment
- 99606 – follow up with established patient, 15 minutes
- 99607 – Each subsequent 15 minutes

Medicare Eligibility

- Patient eligibility requirements
  - Must meet all 3 criteria to be eligible OR be considered as an "at risk beneficiary
    - Drug spend, # of chronic diseases, # of medications
- 3 Criteria for MTM eligibility
  - Annual drug spend at least
    - $4,696 in 2022
  - May be set at minimum of 3 chronic disease
  - May be set at a minimum of 8 medications (Part D covered medications)
  - If eligible, the patients have to request to not be in this program (i.e. opt-out)

At Risk Beneficiaries

- "At Risk Beneficiaries" are designated by CMS as a patient who may be at higher risk for opioid overdose based on opioid prescribing guidelines – these patients will be automatically eligible for MTM services regardless of whether or not they meet the other three criteria

Example Billing MTM Codes

- New patient
- 15 medications, 7 diagnosis
- 45 minutes spent working with patient for education and identification of drug therapy problems
- Billing codes
  - Bill 99605 – quantity 1
  - Bill 99607 – quantity 2

Comprehensive Medication Review

- "CMR"
- Component of MTM
- Interactive F2F, telehealth, or telephone (may require prior authorization) med review
- Done annually
  - Increase patient education
  - Identify drug therapy problems
  - Plan to resolve problems

Targeted Medication Review

- TMR
- Quarterly (3 months)
- Focuses on a specific (targeted) problem
  - May be follow up from an initial CMR
- Suggestions for changing drug therapy
  - I.e. high risk medications in the elderly
  - Statin therapy for eligible patients

Billing Codes

- "Incident to" Codes
  - Billed under a Medicare part B eligible provider (MD, NP, etc.)
  - 99211-99215 (Evaluation and Management Codes – E&M)
    - Physician based clinic
  - 99211 is less complexity and 99215 is most complex ($$$)
  - Pharmacist scope of practice tasks
    - Diabetes, osteoporosis collaborative practice agreements

Billing Codes

- Hospital based outpatient clinic
  - G0463
  - "Facility fee"
  - Set amount

Transitional Care Management

- 99495, 99496
- Billed under provider "incident to"
- F2F visit with provider needs to happen with 7 days to bill 99496 or 14 days for 99495
- Transitions of Care
  - Emphasis on medication reconciliation

Chronic Care Management

- Payments shifting for quality care, preventative services
- CCM – 99490
- 20 minutes of services provided/month
  - Nurse, pharmacist, or other "clinical staff"
  - Examples
    - Disease state education (COPD, HTN, Diabetes, etc.)
    - Medication education

Diabetes Education

- G0108 (individual visit)
- G0109 (group visit)
- Need an accredited diabetes self-management program (ADA)

Annual Wellness Visits

- G0402 – Initial welcome to Medicare visit; CANNOT be done by a pharmacist
- G0438 – First visit after initial welcome
- G0439 – AWV
- G0438, G0439 can be done by nurses or pharmacists under direct supervision of provider

Comprehensive Medication Management (CMM)

- Patient Centered Care
- Working in close collaboration with physicians/patients
- Access to EHR, notes, labs
- May be able to make changes/orders via collaborative practice agreements
- Most often pharmacists embedded within the healthcare institution

Cost of Prescription Medications

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Cost Concerns

- Adherence issues
- Rationing
- Leads to;
  - Poor outcomes
  - Excessive use of other medications
  - Increased need for care/risk of ED/hospital stays
  - Use of "natural" OTC therapies

Patient Strategies to Avoid High Costs

- Take less
- Don't take at all
- Buy them in another country
- Ask pharmacist or prescriber for cheaper alternative
- Shop around at different pharmacies
- Drug Savings Card

Pharmacist Strategies to Improve Affordability

- Ask, Ask, Ask – if patients can afford their medications
- Review insurance coverage with patient
  - I.e. understand if they have deductible/donut hole problems
- Formulary review
- Cost effective generic alternatives
- RxAssist and NeedyMeds
  - Non-profit, searchable database for coupons
- Company coupons/rebates for brand name meds
  - Patients with private insurance only
- Patient assistance programs offered by drug companies
  - Uninsured

Cultural/Religious Barriers to Medication Use

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General Beliefs by Ethnicity

- Whites
  - Technology/drugs can cure/manage their disease
  - Expectation that pain is treated with medication, not a part of normal life
  - Generally want aggressive treatment that is effective
- Japan
  - Greater emphasis placed on safety of medication versus effectiveness
- Hispanics, Asians, Chinese
  - Expect quick relief
  - May be challenging to manage chronic disease

Medication Adherence

- Native/African Americans
  - Tend to stop medications when symptoms have resolved
  - Antidepressants, antibiotics
- Diabetes is not common in Asia
  - Misconceptions may exist
- Islamic, African cultures
  - Avoid vaginally inserted medications
- Latin Americans
  - Used to injections and may believe that they are better

Religious/Social Concerns

- Jehovah's Witnesses
  - Against use of blood products
- True Vegans
  - Against use of any animal product
  - Many capsules contain gelatin (bovine/porcine derived)
  - Conjugated estrogen (pregnant horses)
- Hindu
  - Avoid bovine products (cow)
- Jewish, Muslim
  - Porcine (pork) products
  - Heparin derivatives

Example Medication Products

- Horse derived – Premarin
- Porcine – heparin based products, gelatin
- Bovine – gelatin
- Non-specific animal derivation
  - MMR

Take Home Message

- Be aware
- Work with patients
- Determine what alternatives exist
- Acuteness of the situation

References

- https://www.ismp.org/newsletters/acutecare/articles/20030904.asp
- http://onlinelibrary.wiley.com/store/10.1002/psb.1524/asset/psb1524.pdf;jsessionid=A60D76E263E51BE22C556A4873206A42.f01t04?v=1&t=jbyzayhd&s=0f900527c68b221793e7a72264d98bb345e7e045

MACRA

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Medicare Access and CHIP Reauthorization Act

- MACRA
- Slowly phasing out of fee for service
- Phase in – pay for performance
  - Financial payment tied to keeping patients healthy
- Focus
  - Quality
  - Value
  - Accountability

MIPS

- Merit based Incentive Payment System
  - Determines payment structure surrounding MACRA
- Negative payments/penalties
  - Poor performers
- Payments based on
  - Quality metrics
  - Resources used
  - Clinical improvement activities
  - EHR use

Physician Quality Reporting System

- PQRS
- Must report data to CMS
- Penalties exist for not reporting quality data
- Mandatory participation to receive CMS payment (Medicare)

Why do Pharmacists Care?

- Pharmacists role
  - Quality based system
  - Less based on fee-for-service as providers
  - Pharmacists are not providers (at this time)
- Expensive patients are often non-adherent and have numerous medication related problems

Example Quality Metrics

- % of patients at goal A1C
- Statin use in appropriate patients
- % of patient at hypertension goals
- Aspirin use in appropriate patients
- ***Pharmacists can play a huge role in ensuring that quality measures are being met and also to get the clinic at those goals
- ***Financial performance of the clinic is tied to meeting these metrics

Medication Reconciliation

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Definition

- **Medication reconciliation** is a formal process in which healthcare providers work together with patients, families and care providers to ensure accurate and comprehensive medication information is communicated consistently across transitions of care. - ISMP

Important Components of Med Rec

- Collaboration
- Participation
- Something to compare with
  - Home list
  - Discharge list
  - Pill bottles
  - Patient/family report
- Time

Critical Steps

- Having an accurate pre-visit/preadmission medication list
- Correctly adding/updating AND removing medications from visit/hospital stay
  - Reason for starting new medication
  - Adequate documentation for next HCP in line
- Accurate list at discharge time/end of visit
- Communication to patient/caregiver

Patient Interview

- Combination of open/closed ended questions
- Inquire about what they take their medication for
- Solving the OTC mystery
  - Heartburn
  - Headaches
  - Allergies

Patient Interview

- Ask patients about their disease
  - What do you take for pain/blood pressure?
- Be approachable
  - Looking for honesty, most accurate list possible
- Patients forget about irregular, non-oral medications
- Involve caregiver/family as necessary

Motivational Interviewing

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Motivational Interviewing

- Stimulate the patient's desire to make a change
  - Done through identifying patient's own intrinsic desire to change
  - Legs hurt due to neuropathy
    - Blood sugars are out of control and could worsen this
- Historic medical relationship
  - Parental
    - Do this because I said so…

Motivational Interviewing

- Relationship building
- Empathy
- Learning to assess patient desire to change
- Allowing patient to self reflect on failures and/or why they don't want to change
  - Use open-ended questions
  - "Why?"

Goal Setting

- Generally patient driven
- Self-directed
- Celebrate success
- Builds confidence

Challenges/Barriers

- Time
- Setting
  - Busy pharmacy not ideal
- Interviewer skills
- Patient attitudes

Point of Care Testing

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Clinical Laboratory Improvement Amendments

- "CLIA"
  - Regulates lab testing
- CLIA Waived tests
  - Simple
  - Low risk for incorrect result
- Contact state health department for process of obtaining CLIA certificate of waiver

Point of Care Testing

- Diagnostic test with reliable result
  - Screening
    - Infectious disease (strep and influenza)
  - Disease monitoring
    - Glucose and cholesterol are common examples
- Patient advantages
  - Easy access pharmacy
  - Don't have to pay for office visit
  - Early detection

Point of Care Testing

- Pharmacy Advantages
  - Allows a larger role in patient care
  - Revenue generation
  - Enhance patient relationship/trust
  - Raising pharmacy's standing as a leader in healthcare
  - Many patients don't go in for regular check-ups
  - Improve Medicare part D Star Ratings (ex. better DM management)

Point of Care Testing

- Challenges
  - Motivational health coaching
    - Stimulating patient to take action for actionable results
  - Workflow
  - Training
  - Getting results (chronic disease) to primary care provider
  - Patient perceptions (dispensary only)
  - Embrace by medical community (competition)
  - Financial incentives
  - Documentation/regulatory agencies

Regulatory

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CMS – Centers for Medicaid and Medicare

- Falls under HHS umbrella
- Medicare part A – Hospital/skilled nursing/hospice
- Medicare part B – Medical/clinic/labs/imaging healthcare benefits
- Medicare Advantage (Part C) – puts everything together; part A, part B, and often vision, hearing, and possibly prescription coverage
  - Often require "networks"
- Medicare part D – outpatient dispensing pharmacy benefit

HIPAA

- Standards for handling patient information
- Protects patients personal information
- Also provides access to healthcare professionals who need the information to make informed decisions with the patient
- No restrictions of de-identified data/info

Common Sense Violations - HIPAA

- Anything that could possibly reveal a patient's identity/condition/etc.
- Discussion PHI in a public area
- Obtaining more information than is necessary to treat the patient
- Releasing information about minors without parental consent
- Leaving computer screen up/not logging off

Food and Drug Administration

- Regulatory Agency
- Role in Drug Approval
- OTC
- Prescription
- Role in Drug monitoring after approval
- Supplements
- Food

Center for Drug Evaluation and Research

- CDER
- Part of FDA
- Monitors drugs for safety/effectiveness
- Reviews New Drug Applications (NDA's)
- OTC approvals
- Rx approvals
- Removal from the market
- Ensures Good Manufacturing Practices (GMP's)

Division of Medication Error Prevention and Analysis

- DMEPA
- Under CDER umbrella (which is under FDA umbrella)
- Review medication error reports
- Work closely with
  - Institute of Safe Medicine Practices (see later slide)
  - United States Pharmacopeia (USP)

Institute of Safe Medication Practices

- ISMP – Non-profit organization
- Medication Errors Reporting Program (MERP)
  - Voluntary
  - Reports forwarded to FDA
  - Identify trends (look alike, sound alike, dosing concerns)
- Send out reports to HCP's
- ***my favorite – do not crush list

ISMP - Vaccines

- Separate from MERP
- Voluntary
- Vaccine errors
- Good catches can be reported as well
  - I.e. similar labels etc.

Vaccine Adverse Event Reporting System

- VAERS
- Part of Department of Health and Human Services
- Post marketing vaccine reporting only
  - May be hard to identify rare reactions in clinical trials due to # of patients
- Non-preventable adverse reactions
- Analyze reports
  - Identify trends
- NOT mandatory

Process for New Drug Approval

- Discovery
- Development
- Study in non-humans (pre-clinical research)
- Apply/receive IND approval
- Three phases of clinical trials***see next slide
- Phase 4 – post-marketing monitoring

Human Clinical Research

- After receiving Investigational New Drug application approval
- Phase 1 Clinical Trials
  - 20-100 healthy volunteers
  - Safety/dosing
  - Usually at least a few months
- Phase 2
  - Up to several hundred people (have disease being studied)
  - Months to years
  - Efficacy and adverse effects

Human Clinical Research

- Phase 3
  - Hundreds to 1,000's of study participants
  - Often up to a few years
  - Efficacy, adverse drug reactions
- Drug approval after Phase 3
- Phase 4
  - Post Marketing Surveillance
  - Safety and efficacy
  - Rare adverse events
  - Drugs removed from market or have restrictions
    - Rosiglitazone
    - Darvocet

Generic Drug Approval

- Do NOT require clinical trials
- Simply have to prove bioequivalence
  - This is why they are a lot cheaper!
- ANDA
  - Abbreviated New Drug Application is what generic medication manufacturers submit

MedWatch

- FDA program
- 3500B form for consumers
  - Report serious reactions from medications
  - Quality concerns/product malfunction problems (i.e. devices0 etc.
- MedWatch goals
  - Ensure availability of safe/effective drugs
  - Ensure integrity of drugs on the market
  - Promote safe use of available drugs

Center for Biologics Evaluation and Research

- CBER
- Under FDA umbrella
- Biologic medication approval
- Biosimilar approval
- Monitoring of these products

Risk Evaluation and Mitigation Strategy (REMS)

- Ensure the benefit>risk of medication
- Used for certain medications that pose a significant risk of problems (or a small risk of VERY serious problems)
- Above usual Rx designation
- Examples
  - Clozapine registry (WBC monitoring)
  - Isotretinoin (iPLEDGE – fetal risks in pregnancy)

REMS Program

- Drug sponsor designs program
  - FDA reviews/approves REMS program
- Program is generally developed based upon the risk of the medication (clozapine, isotretinoin is pretty intensive)
- Can be class effect or just a specific drug
- May be required with initial approval
  - OR may be due to post-marketing surveillance
- REMS Medication Guides
  - Given to patient in patient friendly language

ETASU

- Elements to assure safe use (may be part of REMS program)
  - Tasks that need to be completed before Rx/dispensing
  - Time consuming
  - May require
    - Special training
    - Special administration (maybe in a controlled setting by HCP)
    - Lab testing
    - Patient may have to enroll in registry

National Institute of Health

- Government agency
  - Biomedical research
- Under HHS umbrella
- Clinical trials funded via taxpayer expense
- Goal is to improve understanding/knowledge in the medical community

Institute of Medicine

- Agency that released "To Err is Human" report
  - Opened discussion about medical/medication errors
  - Fostered environment for care improvement
  - Development of safeguards
- Shifted focus to system problems
  - Versus blaming humans (staff) for errors

Agency for Healthcare Quality and Research

- AHQR
- Under HHS umbrella
- Fosters evidence based medicine in making healthcare more accessible, affordable, safe, and equitable
- Improve delivery of healthcare
- TJC will often incorporate research from AHRQ information

ACO's

- Accountable Care Organization = ACO
- Group of physicians, hospitals, healthcare professionals who voluntarily commit to provide high quality, highly coordinated care to Medicare patients
- Attempt to reduce costs
  - Avoiding duplicate services
  - Minimize excessive care (delivering care in least expensive way) – I.e. avoiding expensive ED/hospital care
- Payment models shifting to quality of care reimbursements, not fee for service

National Quality Forum

- Agency that provides guidance on standards/quality measures
  - Endorses
  - Makes recommendations on quality measures that should be incorporated into payment models
- Source for provider/healthcare tools
  - Reports
  - Guidance on how to improve quality
  - Guidance on how to meet standards

Meaningful Use

- Electronic health record use
  - Improvement of quality, safety, sharing information, care coordination
- Benefit to population health
  - Vaccine tracking
  - Sharing between organizations
  - Allows patients to access their own records in efficient manner
  - Allows streamlined communication with healthcare professionals
  - Allows for better tracking, reporting, and analytics

Presenting Materials

- Who's the audience
  - Ensure presentation matches education level
- What is the objective
  - Is there a need?
  - Weakness to be improved?
- Assessment of education delivered
  - Testing
  - Improvement in practice
  - Teach back

Barriers to Providing Education

- Language
- Cultural
- Educational
  - Non-healthcare professionals
- Hearing problems
  - Written materials
- Visual problems
  - Audio materials
- Cognition concerns

OSHA

- Occupational Safety and Health Administration
- Protects workers safety
- Reviews standards for risky medication handling by HCP's
  - Handling
  - Administration
  - Storage
  - Disposal
  - Transportation

Pharmacy Legislation

- Biologics Control Act of 1902
  - Ensured safety and purity of products that were used to treat and prevent diseases
- Food and Drugs Act of 1906
  - Prohibited interstate commerce of adulterated and misbranded drugs
- 1938 Food, Drug, and Cosmetic Act
  - New drugs approved must be proven safe
  - Factory inspections began

Pharmacy Legislation

- Durham-Humphrey Amendment of 1951
  - Delineates categories for two types of drugs
    - OTC versus prescription
- Kefauver-Harris of 1962
  - Ensure efficacy and enhance safety
  - **thalidomide use in pregnancy
- Tamper Resistant Packaging 1982
  - Tylenol/cyanide poisoning

Pharmacy Legislation

- Orphan Drug Act of 1983
  - FDA promoted research for drugs for rare diseases
  - Conditions affecting 200,000k or less
  - Financial incentives
- Prescription Drug Marketing Act
  - Required wholesalers be licensed
  - Restricted reimportation of drugs
  - Bans sale/trade/purchase of drug samples
  - Bans diversion of Rx drugs from commercial channels

Pharmacy Legislation

- Medwatch initiated – 1993
- DSHEA - 1994
  - Dietary Supplement Health and Education Act
  - Classifies dietary supplements as food (not medication)
  - Allows FDA to encourage GMP for supplements
- FDA Modernization Act of 1997
  - Regulated off label advertising

Pharmacy Legislation

- Medicare Prescription Drug Improvement and Modernization Act of 2003
  - Medicare part D
  - Implemented in 2006
- Affordable Care Act 2010 (Obamacare)
  - Allowed children to remain on plan until age 26
  - Set up fee for not having insurance
  - CMS Innovation Center
    - Developed to test healthcare models to reduce cost, maximize service
    - MTM model received expanded testing

Institutional Review Board

- Responsible for monitoring, reviewing, approving research within an entity
- Protects the rights and looks out for human research participants
- Reviews planned research process
  - Informed consent
  - Proposed study
  - Patient education

Institutional Review Board

- IRB – needs to register with HHS if doing FDA research
- Doesn't have to be set up by institution
  - Can use an outside IRB
- IRB members can be paid
- Conflicts of interest should be considered when selecting members
- IRB Members
  - At least #5
  - Varying backgrounds (need more than one profession)
  - Mix of men and women – recommended but not required
  - One member – scientific background
  - One member – non-scientific background

Pharmacy and Therapeutics Committee

- P&T
- Interdisciplinary Team
  - Nurses, pharmacists, physicians, administration, quality personnel
- Responsibility
  - Creating drug formulary
  - Updating formulary
  - Review of evidenced based medicine, safety, as well as cost effectiveness of drug therapy
  - Review ADR's, errors, processes, risks, guidelines, etc.

Medication Use Evaluation

- MUE sometimes called Drug Utilization Reviews (DUR)
- Analysis of medication use process
  - Prescribing, ordering, preparing, dispensing, administration, monitoring
- Prevent errors, injuries
- Supports ideal use of medication therapy
- Best practices
- Continuous improvement
- Identify areas of weakness
- Minimize costs
- Regulatory requirements

SWOT Analysis

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Development of MTM Practice

- Strengths
- Weaknesses
- Opportunities
- Threats

Strengths

- Board Certified staff members
- Solid community involvement/outreach
- Asthma educator
- Only pharmacy within 5 mile radius
  - High percentage of patients in the community come here

Weaknesses

- Physician's historically not collaborative
- Staffing/time
- Patient reception

Opportunities

- High number of COPD patients/smokers
- High percentage of elderly patients
- Expanding MTM programs of Medicare patients

Threats

- Expanding clinical pharmacy services being done by clinics
  - Employing nurses to do this
- Lack of payment from underinsured or uninsured
- Insurance based telehealth programs

URAC Standards

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Utilization Review Accreditation Commission (URAC)

- Nonprofit
- Independent
- Advance healthcare quality through leadership, accreditation, measurement, and innovation
- Accredits: Healthcare organizations, pharmacies, healthcare plans, and other entities

Why Accreditation?

- Demonstration of high standards
- Accountability to best practices, patient care, and consumer protection
- Focus on patient health
- Regulatory requirement
- Financial reimbursement

Accreditation Process

- Application
- Information submission
- Review process
- Ongoing monitoring
- Every 3 year review

Pharmacy Core Standards

- Organizational Structure
- Regulatory Compliance
- Inter-Departmental Coordination
- Oversight of Delegated Functions
- Marketing and Sales Communications
- Business Relationships
- Clinical Staff Credentialing and Oversight
- Healthcare System Coordination
- Information Management
- Quality Management
- Staff Qualifications
- Staff Management
- Consumer Protection and Empowerment

Drug Therapy Management Mandatory Measures

- Call center performance (% of calls answered by live voice within 30 seconds as well as abandoned calls
- Drug-drug interactions
- Opioid and Benzodiazepine use
- High dose opioids
- Statin use in diabetes patients

Drug Therapy Management Mandatory Measures

- Proportion of days covered – percentage of patients who received their medications on a routine basis (threshold of 80% for the proportion of days covered)
  - Medications included in this requirement
    - Oral diabetes medications
    - Statins
    - Blood pressure medications (Beta-blockers, RAS drugs, and CCB's)
    - Antiretrovirals (90% threshold)
    - Long acting COPD meds
    - Biologic agents for RA
    - MS agents
- Adherence to non-warfarin anticoagulants (80% threshold)

Drug Therapy Management Exploratory Measures

- High risk medication avoidance in the elderly (i.e. cyclobenzaprine, amitriptyline, hydroxyzine, etc.)
- Benzodiazepine, sedative hypnotic use in the elderly
- Turnaround time for prescriptions
- Consumer experience (surveys)

URAC PDF's

- https://www.urac.org/sites/default/files/basic_page/file_attachments/DTM_Measures-at-a-Glance_FINAL-20161118.pdf
- https://www.urac.org/sites/default/files/standards_measures/pdf/Pharmacy%20Core%20Accreditation%20v3.1%20Standards%20at-a-Glance.pdf

Biostatistics

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Hypothesis Testing

- Ho – null hypothesis
  - No difference between groups
  - Example: comparing new drug to placebo
    - People studying new drug will want p-value less than 0.05
  - If the p-value is low (<0.05), null hypothesis must go
- Ha – alternative hypothesis
  - Ha is accepted when the null hypothesis is rejected

P-Value

- Also referred to as alpha (α)
- Represents the probability that your study is wrong
- The lower the p-value, the less likely your study is incorrect
  - <0.05 (5%) is set by convention as a statistically significant study
- Type 1 error
  - Detecting a difference when one doesn't actually exist

Beta

- Beta (β) represents the probability of type 2 error
  - Type 2 error is the inability to detect a difference and one actually exists
  - Underpowered studies
    - Inadequate sample size
- Power = 1-Beta
  - Target power is 80% or greater (0.8)
  - Target Beta is 0.2

Variables

- Independent
  - What the researches set as variables
  - Drugs, doses, etc.
- Dependent
  - They depend upon the independent variables
  - Drop in blood sugar, blood pressure, etc.
- Control variable
  - No intervention is made
  - Comparison group

Types of Variables

- Nominal "name"
  - Placing patients in groups/categories
  - Those with MS, those without
- Ordinal
  - Order
  - No specific distance between variables
  - Subjective scales/surveys are included in this group
    - Staging of pressure ulcer
    - Pain scale
    - Rating a speaker
  - Ordinal and Nominal are also called discrete variables (only take on a limited # of values within a range

Types of Variables

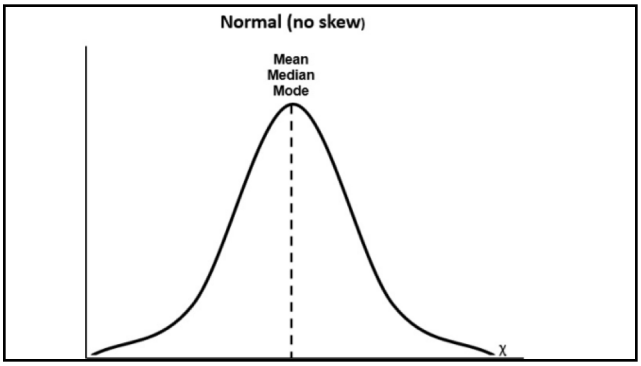
- Continuous (can have fraction of numbers)
  - Ratio
    - Has an absolute zero
    - Example: height
  - Interval
    - Similar to ratio
    - No absolute zero
    - Fahrenheit/Celsius temperature scale

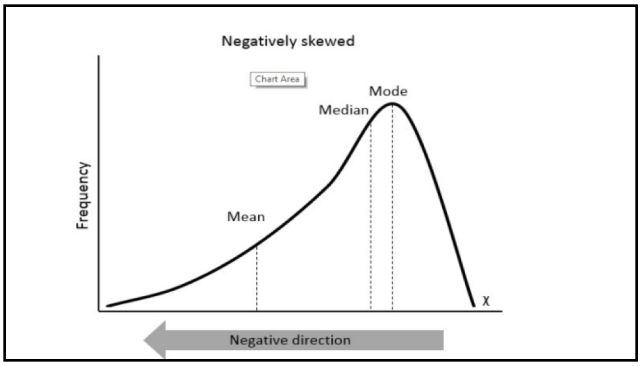
Confidence Intervals

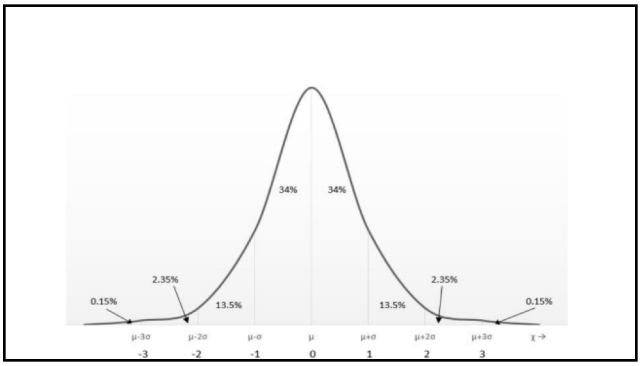
- Range of values that you believe the true value lies between
  - Traditionally set at 95%
  - I.e. you are 95% confident that the values lie between two values
- If you are looking for a change, does your confidence interval contain "0"
  - Change in blood sugar on prednisone; 95% CI = 4-25
- If you are looking for a deviation from normal comparing two confidence intervals (groups), do they overlap?
  - Comparing two different dosages
  - Drop in systolic blood pressure (2.3-6.8) vs. (4.5-8.1)

Normal Distribution – Continuous Variables

- Also termed parametric data
- Mean = Median = Mode
- Mean – average
- Median – middle number
- Mode - # (or value) that occurs most often
  - Bell Curve
- ***Do NOT use for ordinal data
  - Ordinal, nominal are considered nonparametric data







Statistical Testing – Paired/Unpaired Groups

- Paired
  - Data measured from same subject
  - Before and after treatment
    - Washout period when using drugs
- Unpaired
  - Two different groups being compared
  - Assume a normal distribution in the population
    - No before and after comparison for an individual research participant

Statistical Testing

- Ordinal
  - Sign test
  - Wilcoxon test
    - Used for two paired samples
  - Unpaired Samples (two)
    - Mann-Whitney
  - Three or more unpaired samples
    - Kruskal-Wallis test
  - Spearman correlation
    - Correlation for two paired samples

Statistical Testing - Continuous

- Continuous (t-test or sometimes called Student's t-test)
  - Paired t-test
    - Two paired continuous groups
  - Unpaired t-test
    - Two unpaired continuous groups
- ANOVA (analysis of variance)
  - Three or more samples
- Pearson correltation

Nominal Data

- Chi-squared χ^2
  - Unpaired samples
- Paired samples
  - Sign test
- Correlation comparison
  - Contingency coeffecients

	Dataset		
	Nominal	**Continuous**	**Ordinal**
Example of Variable	Separation of patients into Afib and non-Afib groups	Readings of blood pressure from several patients	Pain Scale
Is mean (average), standard deviation applicable?	No	Yes	No
Example of appropriate Statistical Test (dependent upon samples)	χ^2 (chi-squared)	One-sample t test	Sign test or Wilcoxon test
Compare two paired samples	Sign test	Paired t test	Sign test or Wilcoxon test
Compare two unpaired samples	χ^2 square Fisher's exact test	Unpaired t test	Mann-Whitney test
Compare three or more unmatched samples	χ^2 test	One-way ANOVA	Kruskal-Wallis test
Quantify association between two paired samples (correlation)	Contingency coefficients	Pearson correlation	Spearman correlation

Absolute Risk

- Simply take the difference between the raw %
  - 60% of smokers develop lung cancer
  - 20% of non-smokers develop cancer
- Absolute risk reduction
  - Not smoking is 40% (0.4) absolute risk reduction

Number Needed to Treat

- NNT
  - Good comparison of agents/pharmacoeconomics
  - Also good to compare risks (adverse effects) versus benefits of medication therapy
- Lower NNT = more effective treatment
  - How many people will get benefit
- NNT = 1/ARR
  - Difference between groups is 5% MI rate versus 10% MI rate
  - ARR = 0.05
  - NNT = 1/0.05 = 20

Number Needed to Harm

- Similar to NNT
- Demonstrates tolerability/risk of ADR's in medication studies
- Higher NNH is better
  - Less likely that an adverse effect will happen
- Risk of renal failure is 1% in placebo group and 2% in treatment group
  - NNH = 1/Absolute risk
  - NNH – 1/0.01 = 100 patients treated, 1 patient will have renal failure from the medication

Relative Risk

- RR = ART/ARC
- Relative Risk = 1 means that there was no difference between the groups
- If RR is >1 it means that events are more likely in the treatment group
- If RR is <1 it means that events are less likely
- If confidence interval (CI) contains 1, it means that there is not statistically significant difference between the groups
  - i.e. CI = 0.7 – 1.4
- Relative Risk Reduction = RRR = ARC-ART/ARC = 1-RR

Sample

- 8% in treatment group developed osteoporosis
- 16% in placebo group developed osteoporosis
- ARR: 0.16-0.08 = 0.08 = 8%
- Relative Risk: 0.08/0.16 = 0.5
  - Protective effect in treatment group
- Relative Risk Reduction: 1-RR
  - 1-0.5 = 0.5 or 50% in the treatment group compared to placebo
- NNT = 1/0.08 = 12.5

Odds Ratio

- Most often presented as 95% CI
- CI containing 1 will not be considered statistically significant
  - 0.7-1.31
- Range less than 1
  - Demonstrates that outcome is less likely to happen
- Range greater than 1
  - I.e. 1.23 – 1.61
  - Demonstrates that outcome is more likely to happen

Hazard Ratio

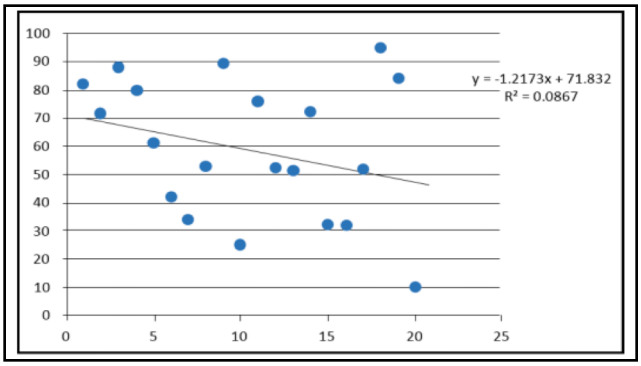
- Often related to adverse events
  - CI less than 1 and doesn't contain 1
  - Protective effect
- Adverse effects more likely
  - CI that doesn't contain 1 and is greater than 1

Correlation

- Association
- Negative
  - Variables go in opposite direction
- Positive
  - Variables go in the same direction
- Correlation does not mean causation***
  - Patients with COPD develop lung cancer

Correlation Coefficient

- Correlation coefficient = r
  - Value ranging from -1 to 1
- R-squared
  - Lies between 0-1
  - Tells us how accurately we can predict where values fall
  - 0 = no correlation
  - 1 = perfect predictability of the model



Clinical Literature

- Primary
  - Clinical trial/study
- Secondary
  - Review article breaking down a particular topic
- Tertiary
  - Large compilation of information
  - Textbook

Bias in Studies

- Selection
  - Study participant groups differ
- Observation
  - Investigator "seeing" something or exaggerating the response
- Recall
  - Memory recall
- Misclassification
  - Incorrect incorrect classification of a study participant
  - Misdiagnosis
- Publication bias
  - Outcome of trial influences whether it is published/distributed
  - May exaggerate body of evidence in favor of positive outcomes

Confounding Variables

- A variable that is impacting your study results
  - Known or unknown
- Confounding Variable
  - Lead to incorrect assumptions/association
  - Kind of similar to correlation does not mean causation

Study Design

- Single Blind
  - Study participants do not know if they are receiving the treatment
- Double Blind
  - Study participants and researchers do not know who is receiving the treatment
- Non-inferiority
  - Prove equivalence to standard of care
  - Agent being studied may have a clinical advantage (less drug interactions, simpler dosing, etc.)
- Placebo controlled
  - Unethical in some situations (i.e. seizures)
  - Comparison against doing nothing

Study Design Strength

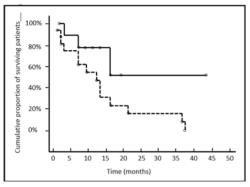
- Randomized Controlled Trials
  - Direct comparison under controlled environment to identify
  - Gold Standard
- Meta-Analysis
  - Comparison of similar studies to draw conclusions
- Cohort
  - Following a group of patients over time on a drug/with a disease etc. and monitor some effect (done prospectively)
- Case Control series
  - Look back (retrospective) at information to identify trends/associations
- Cross Section Surveys
  - Snap-shot in time
- Case Studies
- Expert opinion

Meta-Analysis

- Benefits
  - Allows for a way to summarize numerous clinical trials about a specific problem or question
  - Increases the number of subjects (sample size)
  - May aid in identifying minor but clinically significant effects
- Limitations
  - Subjectivity – which trials are selected
    - Publication bias risk
  - Variable inclusion/exclusion criteria
  - Secondary/tertiary outcomes may be difficult to compare
  - Conflicting data
  - Need to include high quality studies

Kaplan Meier

- Estimation of survival over time



Testing Terminology

- Positive predictive value
  - Positive test for patients who actually have the disease
  - Higher is better
- Negative predictive value
  - Probability that a patient with a negative test actually does not have the disease
  - Higher is better
- Ideal test: Positive when patient has the disease and negative when the patient doesn't

Testing Terminology

- Sensitivity
  - "True positive" rate
  - How often the test provides a positive result for people who have the disease
- Specificity
  - "True negative" rate
  - Ability of the test to provide a negative result for people who do not have the disease

Testing Terminology Example

- Influenza test is has high sensitivity and low specificity
  - High sensitivity: If the patient has influenza, there is a high likelihood that the test will provide a positive result
  - Low specificity: If the patient doesn't have influenza, there may be a high likelihood of false positives

Oncology

Breast Cancer

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Risk Factors

- Genetics
  - BRCA1 and BRCA2 genes
    - Increase risk of breast and ovarian cancer
- Estrogen excess
  - HRT
- Female
- Age
- Obesity
- No children

Targeted Medications

- Targeted therapy
  - Estrogen receptor positive (ER+)
    - SERMs
    - Aromatase inhibitors
    - Fluvestrant
  - Human Epidermal Growth Factor Receptor 2
    - Trastuzumab, pertuzumab, lapaptinib

SERMs

- Tamoxifen
  - Prodrug via CYP2D6 (inhibitors can decrease effectiveness)
  - Side effects
    - Hot flashes, increase clot risk, vaginal atrophy, night sweats
- Raloxifene
  - Useful in osteoporosis
  - Hot flashes, vaginal atrophy, blood clots

Estrogen Targeting Drugs

- Anastrazole, letrozole, exemestane (Aromatase inhibitors)
  - Prevent production of estrogen
  - Use only in postmenopausal women
  - Hot flashes, osteoporosis risk, vaginal atrophy
- Fulvestrant
  - Disables estrogen receptors
  - Menopausal type side effects
  - Post menopausal indication only

HER2

- Human Epidermal Growth Factor Receptor 2 targeted drugs
  - Trastuzumab, pertuzumab, lapatinib
  - Only used in HER2 overexpression
  - GI/flu like side effects
  - Increase stroke, heart failure risk

Cervical Cancer

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Human Papilloma Virus

- Most common cause of cervical cancer
- HPV subtypes
  - 16 and 18 – most common for cervical cancer
    - 6, 11 associated with genital warts
- Sexual transmission

Vaccination

- Gardasil-9 (9 subtypes)
  - Includes 6,11, 16, 18
- 2 dose schedule approved
  - Patients <15
  - Target patients before sexually active
- Vaccination recommended in immunocompromised
  - AIDS patients may be at higher risk (i.e. AIDS is often sexually transmitted)
- Males benefit as well
  - Cancer, warts protection

Chemotherapy

- Platinum drugs
- 5-FU
- Taxanes
- Bevacizumab
- Topotecan
- ***Agents selected may vary based upon many factors; common chemo agents discussed in separate section

Colon Cancer

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Symptoms

- Bowel pattern changes
  - Weeks/months
- Blood
- Pain
- Weight loss
- Fatigue

Screening Options

- 50 is the magical age (American Cancer Society, looks at age 45) – patients at average risk
- Colonoscopy every 10 years
- Colonography or sigmoidoscopy every 5 years
- Annual fecal occult blood test – take home
- Q 3 Year DNA stool test
- Risk factors may increase recommended screening frequency
  - Genetics
  - History of polyps
  - Smoking

Management

- Prevention
  - Aspirin may have some evidence as reducing the risk
- Early stages
  - Polyp removal
- Radiation, surgery (colectomy)
- Targeted agents
  - Bevacizumab, ramucirumab, aflibercept
    - Vascular endothelial growth factor (VEGF)
    - Boxed warning on GI perforations, wound healing and bleeding
    - HTN, DVT/PE

Management

- Cetuximab
  - Epidermal growth factor
  - Boxed warning for cardiac arrest, infusion reaction
  - Rash, hypomagnesia
- Metastatic disease
  - Irinotecan
  - Oxaliplatin
  - 5-FU
  - Capecitabine
  - Leucovorin

Leukemia

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Leukemia

- Cancer impacting bone marrow
- Abnormal/dysfunctioning WBC's
- Infection risk
- Bone pain
- Fatigue
- Bruising/bleeding

Leukemia

- Subtyping of leukemia
  - ALL (Acute Lymphoblastic Leukemia)
  - AML (Acute Myeloid Leukemia)
  - CLL
  - CML

Treatment

- Radiation
- Stem cell transplantation
- Chemo regimens
  - Know side effects versus selection – see chemo agents section
- Imatinib (Gleevec)
  - CML
  - Tyrosine kinase inhibitor
  - Precautions
    - Bone marrow suppression
    - Heart failure
    - Moderate emetic potential
    - Hepatotoxicity
    - Tumor lysis syndrome

Lung Cancer

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Lung Cancer Stats

- US – 200,000+ new cases
- US – 150,000+ deaths
- Leading cause of cancer death
- Non-small cell lung cancer (NSCLC)
  - 80-85% of lung cancer
- Small cell lung cancer
  - 10-15% of lung cancer
- Staging; 1-4
  - 4 being the worst

Lung Cancer Risk Factors

- Smoking
  - Don't forget about second hand smoke
- Radon
- Asbestos or other carcinogenic toxin
- Family history

Agents

- EGFR inhibitors
  - Erlotinib, afatinib, gefitinib
  - Fatigue, rash, GI
  - 3A4, 1A2 metabolism
- ALK protein
  - Crizotinib, certinib, alectinib
  - Edema, neuropathy, GI
  - Immunosuppression risk
  - Elevated LFT's
  - QTc prolongation
  - Eye/pulmonary toxicities
- See Chemo agents

Chemotherapy Agents

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Anthracyclines

- Doxorubicin, daunorubicin
- Cardiotoxicity
  - Dexrazoxane may be used to help prevent this
  - Beta-blockers may also be utilized
- High risk of N/V when used in combination with cyclophosphamide
- Neutropenia
- Anemia
- Hair loss

Taxanes

- Paclitaxel, docetaxel
  - Neutropenia risk is high compared to other agents
  - Neuropathy risk is high compared to other agents
  - N/V (low risk agents)
  - Bone marrow suppression
  - Anaphylaxis type infusion reaction

Cyclophosphamide

- N/V/D
  - Highest risk if dose greater than 1,500 mg/m2
- Appetite suppression
- Bladder cystitis
  - Fluids and mesna for prevention
- Hair loss
- Myelosuppression

Platinum Drugs

- Cisplatin, Carboplatin
- Cisplatin
  - highest risk category for CINV
  - Amifostine to prevent ototoxicity and renal toxicity
- Carboplatin – moderate risk
- Class effects
  - Neutropenia
  - Neuropathy
  - Hair loss
  - CNS changes

Vinka Alkaloids

- Vincristine
  - Very significant neuropahty
  - Vesicant warning – avoid extravasation
  - Elevations in uric acid
    - Can cause nephropathy
  - Minimal CINV

5-fluorouracil

- Stomatitis
- Neutropenia
- Photosensitivity
- Diarrhea

Methotrexate

- Myelosuppression
- Hepatotoxic
- Renal elimination
  - Increased risk of toxicity in CKD
- Pneumonitis
- Tumor lysis syndrome
  - See next slide
- Leucovorin rescue (folinic acid)
  - Administer within 24-36 hours of methotrexate

Tumor Lysis Syndrome

- Cells destroyed, release contents into blood stream
- Laboratory assessment (Cairo-Bishop)
  - Elevated uric (>8mg/dL)
  - Potassium >6 mEq/L
  - Phosphorus >4.5 mg/dL
  - Calcium <7 mg/dL
- Prevention
  - IV hydration
  - Allopurinol
  - Rasburicase
    - Avoid in glucose-6 phosphate dehydrogenase

Prostate Cancer

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Prostate Cancer

- Slow growth
- Symptoms
  - Flow issues
  - Pelvic pain
  - ED
  - Blood in urine
  - Incontinence

Prostate Cancer

- Prostate specific antigen
  - Can be elevated in any type of damage
    - Infection
    - Cancer
    - Inflammation/damage
  - Not necessarily specific to cancer

Management

- Considerations for monitoring
  - Slow growth nature
  - Age
  - Symptoms
- Radiation

Medications

- Luteinizing hormone-releasing hormone (LH-RH) agonists
  - Leuprolide, goserelin, triptorelin, histrelin
  - Reduce testosterone production which feeds the cancer
  - ED, hot flashes, decreased BMD, weight gain
  - Vitamin D deficiency, calcium monitoring; OP treatment may be necessary
- Anti-androgen
  - Bicalutamide, flutamide, nilutamide
  - Similar SE profile to LH-RH
- Metastatic disease
  - Docetaxel, cabazitaxel, mitoxantrone, estramustine

Skin Cancer

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Skin Cancer Stats

- Most common 5+ million cases
- 1/5 develop skin cancer
- Actinic keratosis
  - Precancer (58+ million affected)
- 90% caused by UV radiation
- Most treatable/least serious
- Melanoma (<1% of skin cancer)
  - Majority of deaths

Types

- Basal cell
  - Bump on skin, brown/flesh color
  - Usually only occurs on sun exposed areas
- Squamous Cell
  - Red nodule or scaly type surace
- Melanoma
  - Not necessarily on sun exposed areas
- Kaposi's Sarcoma
  - Red/purple patches
  - AIDS defining illness

Increased Risk of Sunburn

- Drugs
  - Tetracyclines
  - Diuretics
  - Quinolones
  - Sulfa drugs
  - Retinoids
- Fair skin
- Lack of sunscreen and excessive exposure
- Immunosuppressed

Prevention

- Long sleeves
- Avoiding tanning
- Sunscreen
  - SPF 30 or greater
  - 30 minutes before exposure and every 2 hours thereafter

Management

- Cryotherapy
- Surgery
- Radiation
- Phototherapy
- Electrosurgery
- Drugs

Topical Agents

- 5-FU
  - Apply to localized area
  - Clean/wash area, wash hands before and after application
  - Hazardous medication
  - Increased sunburn risk on application area
  - SE – dry, scaling, pain, redness, burning
- Imiquimod
  - Local SE's similar to 5 FU
  - Photosensitivity
  - $$$