Session 10: Diuretics and Blood Pressure (*4 questions – 2 questions ea. lecture)*

Common CV Health Conditions and Treatment Goals

- 1) Primary (a.k.a Essential, Idiopathic) HTN
  - Goal: **Decrease systemic vascular resistance (SVR) + extracellular fluid volume (EFV)**
    - Factors associated with edema:
      - Hydrostatic pressure directly related to cardiovascular work
      - Plasma colloid osmotic (oncotic) pressure related to protein content
    - Causes of edema = increased water in the interstitial space
      - Increased hydrostatic pressure (e.g., venous congestion due to heart failure)
        - Left heart failure = pulmonary edema
        - Right (and left-associated) failure = peripheral edema
      - Decreased plasma colloid (oncotic) pressure (e.g., hepatic cirrhosis, nephrotic syndrome)
    - Treatment of edema? **Decrease EFV**
  - Targets of treatment:
    - 1) **Peripheral circulation** – decrease systemic vascular resistance
      - Vasodilators (Blockers: alpha-1 receptors, Ca2+ ch, renin-angiotensin-aldosterone system; direct vasodilators)
      - Decrease blood volume (diuretics)
    - 2) **Kidneys** – renal regulation of water and sodium
      - Decrease extravascular volume
      - Decrease blood volume (intravascular volume) in order to decrease venous return -> preload -> cardiac output (= decrease blood pressure)

Overview of Diuretics

- **Diuretics**: increase the rate of urine flow (diuresis) and the rate of sodium excretion (natriuresis)
  - Primary clinical application is to reduce volume of extracellular fluid by **decrease total body NaCl** (sodium) -> **decrease water**
    - In a nephron, there are Na+ transporters that takes back Na+ into the blood circulation
    - Diuretics *block* Na+ ion transporters so that Na+ can be excreted via urine and *water will follow*
- Classes of Diuretics
  - 1) Inhibitors of carbonic anhydrase (***Acetazolamide***)
  - 2) Osmotic diuretics (***Mannitol***)
  - 3) Loop diuretics (***Furosemide***)
  - 4) Thiazide diuretics (***Hydrochlorothiazide***)
  - 5) K+ sparing diuretics (***Amiloride***)
  - 6) Antagonists of aldosterone (***Spironolactone***)

Overview of Drugs that Regulate the Systemic Vascular Resistance:

- Most common treatment of **primary HTN (uncomplicated, mild) = diuretics**
  - *Discussed last session*
  - Target: Blood volume, not the systemic vascular resistance
- 1) Sympatholytic Agents – inhibit sympathetic system
  - Sympathetic System:
    - Pre-sympathetic neurons – located in vasomotor center in medulla
    - Preganglionic sympathetic neurons
    - Postganglionic neurons – release NE and bind to receptors
      - **Alpha-1 adrenergic receptors** – when activated, cause vasoconstriction

        - Found on BVs
    - **Alpha-2 adrenergic receptors** – when activated, inhibit NE release
        - Found on the ends of postganglionic neurons (presynaptic) and in the vasomotor center (inhibit activity of pre-sympathetic neurons)
    - **Beta-1 adrenergic receptors** – when activated, cause increased HR and contractility
        - Found in the heart
- When these receptors are blocked? Vasodilation and decreased CO = decreased BP
    - **Alpha-1** and **Beta-1** antagonists
    - **Alpha-2** agonists
- Another target of drugs? **NE storage**
- *Note*: Catecholamines are released from the adrenal medulla, which is innervated by the sympathetic system (acts on alpha-1 and beta-1 receptors)
- Drugs to remember:
    - Centrally Acting:
        - **Clonidine** – selective alpha-2 adrenergic agonist
        - **Methyldopa** – adrenergic neuron inhibitor (its metabolite replaces central NE and likely activates alpha-2 receptors; mechanism isn't completely understood)
    - Centrally and Peripherally Acting:
        - **Reserpine** – NE-depleting agent
    - Peripherally Acting:
        - **Phentolamine** – alpha-adrenergic antagonists (non-selective alpha-blocker)
        - **Prazosin** – selective alpha-1 adrenergic antagonists
        - **Propranolol, Bisoprolol** – beta-adrenergic antagonists (beta-blockers)
            - Propranolol – non-selective
            - Bisoprolol – Beta-1 adrenergic antagonist
        - **Labetalol** – beta-antagonist with alpha-1 antagonist activity (used for medical emergencies)

- 2) RAA-System Inhibitors (renin-angiotensin-aldosterone)
    - RAA System:
        - Kidneys release **renin** – cleaves angiotensinogen to angiotensin I
        - **Angiotensin-converting enzyme** – converts angiotensin I to angiotensin II
        - Angiotensin II acts on **AT1 receptors** on BVs, leading to vasoconstriction
            - AT1 receptors found in BVs, kidneys, adrenal gland
                - Adrenal medulla – block release of catecholamines
                - Adrenal cortex – block release of **aldosterone**
    - Sympathetic System (*cross-talk*):
        - **Beta-1** adrenergic receptors found on juxtaglomerular apparatus; increase renin release
    - When these parts are blocked? Inhibit vasoconstriction at different levels
    - Drugs to remember:
        - **Captopril, Enalapril, Ramipril** = angiotensin-converting enzyme (ACE) inhibitors (most common)
        - **Losartan, Valsartan** = angiotensin II receptor (AT1) antagonists
        - **Aliskiren** = direct renin inhibitors
- 3) Ca2+ Channel Antagonists
    - Ca2+ channels found in BVs and heart – cause vasoconstriction, increased contractility (let more calcium in)
    - Antagonists = decrease vascular resistance and BP

- Drugs to remember:
  - **Nifedipine, Amlodipine** = dihydropyridines
  - **Verapamil**
  - **Diltiazem**

- 4) Direct vasodilators – act locally and directly on smooth muscle of BVs
  - Cause vasodilation rather than inhibition of vasoconstriction (*action of alpha antagonists*)
  - Drugs to remember:
    - **Hydralazine** – safe for pregnant women
      - No known mechanism
    - **Sodium Nitroprusside** – mechanism through nitric oxide (increased cGMP, relaxation)
    - **Minoxidil** – prodrug that needs to be activated (active metabolite)
      - Opens potassium channels = cause repolarization = relaxation
- *Clinical Implication*: **EPI + Non-selective beta-blockers**
  - Under normal physiological conditions, BVs have two receptors that EPI can act on:
    - Alpha-1 = vasoconstriction
    - Beta-2 = vasodilation
      - Also found in the lungs = bronchodilation
  - When EPI is applied with LA, under normal conditions, EPI is acting on both receptors = no effect
    - But, when patient is taking a non-selective beta-antagonist, the beta-2 receptors are blocked
    - So when EPI is applied, it will act primarily on alpha-1 receptors *only* = severe BP increase
- *Clinical implication*: **Triple Therapy**
  - Triple therapy with an NSAID, diuretic, and ACE inhibitor = acute renal failure
    - NSAIDs block COX = block prostaglandins = increased Na+ reabsorption
      - Normally, prostaglandins block Na+ reabsorption
      - Prostaglandins also normally cause vasodilation of afferent arteriole delivering blood to glomerulus
        - NSAIDs to block prostaglandins? Vasoconstriction of afferent arteriole = decrease GFR
        - Not bad if the RAA system is working = compensatory constriction of efferent arteriole = preserve pressure in glomerulus
      - + ACE inhibitor? = no constriction of efferent arteriole
      - + Diuretics? = decreased total blood volume -> decrease blood flow to the kidney

Session 11: Clinical Case Scenario #5 – Midterm Review (*1-2 questions)*

1. Assuming no interactions with other medication, would you switch from Acetaminophen (Tylenol) to an NSAID based on the lower dose of the NSAID?
   a. Yes, if the efficacy is higher and therapeutic index is lower for the NSAID
   b. **Maybe, if both the efficacy and the therapeutic index are higher for the NSAID**
   c. No, because a higher dose always means a higher efficacy and the efficacy is most important
   d. *Note*:
      i. Therapeutic Index = Median Toxic Dose/Median Effective Dose
         1. **Higher the index = safer the drug**
      ii. Higher dose doesn't mean higher efficacy; dose is associated with *potency*
         1. Potency increases when EC50 (Kd) decreases
            a. Lower concentration of the drug = higher potency

2. Pharmacodynamic interactions between drugs listed in the case include:
    a. **Epinephrine and labetalol – receptor-based antagonism**
        i. *EPI = catecholamine; Labetalol = non-selective beta-1 blocker with alpha-1 antagonist*
        ii. Effect of competitive inhibition = *EC50 increases (potency decreases), efficacy not affected*
        iii. Effect of non-competitive inhibition = *EC50 remains the same, efficacy decreases*
    b. **Hydrochlorothiazide and Ibuprofen (NSAID) – functional antagonism**
        i. *Hydrochlorothiazide = efficacy is lowered by NSAIDs = antagonism (functional)*
    c. **Fluoxetine (Prozac) and Tramadol – synergism**
        i. *Fluoxetine = selective serotonin reuptake inhibitor; Tramadol = inhibits reuptake of catecholamine*
        ii. *They do the same thing = synergism*
    d. **Clopidogrel and NSAIDs (Ibuprofen and Naproxen) – synergism**
        i. *Both have anti-platelet effects = synergism*
    e. **Clopidogrel and Warfarin – synergism**
        i. *Warfarin = anti-coagulant, but similar effect = synergism*
    f. **All of the above**
    g. Only A and D are correct
3. The following drug from the patient's medication list is known to be associated with the phenomenon of sensitization:
    a. **Labetalol** – *beta blocker receptor-based*
    b. Lithium
    c. Omeprazole – *proton pump inhibitor, but not receptor-based*
    d. Warfarin
4. The following drug from the patient's medication list is known to be associated with the phenomenon of pharmacodynamic tolerance:
    a. Hydrochlorothiazide
    b. Fluoxetine
    c. Naproxen Sodium
    d. **Tramadol** – *opioid analgesic; pharmacodynamic tolerance = receptor-based (decreased ability of drug to respond due to number of receptors)*
        i. *Pharmacokinetic tolerance = decreased level of the drug due to increased metabolism*
5. Please identify the correct pharmacokinetic drug interaction in this patient
    a. Distribution: Warfarin with Ibuprofen
        i. *Ibuprofen = highly protein bound = competition for protein = higher fraction of the drug becomes available = increased distribution due to more free drug*
    b. Metabolism: Omeprazole with Clopidogrel, Lidocaine and Tramadol
        i. *Omeprazole inhibits C19 and 3A4 – these enzymes metabolize the other drugs*
    c. Metabolism: Fluoxetine with Tramadol
        i. *Tramadol metabolized by 3A4 and 2D6, and Fluoxetine inhibits 2D6*
    d. Excretion: Lithium with Ibuprofen
        i. *Lithium excreted unchanged through glomerular filtration; Ibuprofen decreases GFR by blocking prostaglandins (compromise Lithium expression)*
        ii. *Lithium = low therapeutic index*
    e. **All of the above**
6. Please identify the correct patient-related pharmacokinetic drug action modifiers
    a. Physiological: Advanced Age-ADME; overweight-distribution
        i. *Advanced age affects all levels of pharmacokinetics*
    b. Psychological: Compliance and timing of drug administration

c. Genetic: CYP2C19/CYP2D6 polymorphisms
d. **All of the above**

7. Please identify the correct patient disease-related pharmacokinetic drug action modifiers.
    a. Atherosclerosis/DVT: Distribution
        i. *Associated with blood flow (similar to CHF) – decrease volume of distribution due to compromised blood flow*
    b. Bipolar Depression: Administration
        i. *Associated with patient compliance*
    c. CHF: ADME
        i. *All four levels are associated with CHF*
    d. Liver Cirrhosis: Distribution, Metabolism
        i. *Distribution compromised due to decreased level of proteins*
        ii. *Metabolism compromised since liver is site of metabolism*
    e. **All of the above**
8. The following drug from the patient's medication list is likely to lead to pharmacokinetic tolerance:
    a. Fluoxetine
    b. Omeprazole
    c. Both A and B are correct answers
    d. **None of the above**
        i. *Fluoxetine – inhibit enzymes*
        ii. *Omeprazole – inhibit enzymes*
        iii. *If inhibiting enzymes, the metabolism of drugs is compromised = higher level of free drug = patient responds to drug even stronger*
            1. *Pharmacokinetic tolerance caused by drugs that induce metabolism, not inhibit metabolism*
9. Allergic reactions to drugs:
    a. Are dependent on the drug dose (stronger reactions result from higher doses)
        i. *Allergic reactions are not dependent on drug dose – can be caused by really small doses (and have really large reactions)*
    b. Present as symptoms similar to the normal response to the drug, but of higher amplitudes
    c. **Require prior sensitization**
    d. All of the above
10. Rosuvastatin excretion is likely to be compromised in this patient by:
    a. Cholecystectomy – *Gall bladder removal doesn't affect the bile ducts (only storage associated); as long as bile ducts are clear, doesn't affect excretion of the drugs*
    b. **Liver cirrhosis**
    c. Peptic ulceration
    d. Both A and B are correct answers
11. What is a common cause of the disruption in drug enterohepatic cycling?
    a. **Enterohepatic cycling prolongs drug action** (e.g., oral contraceptives)
    b. **Antibiotics that wipe out gut flora = disrupt drug enterohepatic cycling**

Quiz for Session 10-11

1. In infarction of the left ventricle, the associated shortness of breath is most likely to be immediately relieved by:
    a. Acetazolamide – *Very weak diuretic; left ventricle infarction = pulmonary edema due to blood backing up in pulmonary veins; can fix pulmonary edema with diuretic, but this one is a very weak one*

b. Albuterol (beta-adrenergic agonist, rescue inhaler) – *Problem of ventilation, but this is a problem of perfusion/circulation*
c. Amiloride – *Very weak diuretic; can use for K+ sparing effects, but not for this problem*
d. Desmopressin – *Anti-diuretic; don't want to increase water content*
e. Epinephrine inhaler or injection (EpiPen)
f. **Furosemide** – *very strong loop diuretic; high ceiling effect, decreases pressure in venous system (immediate relief)*
g. Mannitol – *contraindicated in pulmonary edema*
h. Both B and E are correct answers
i. *How to solve:*
    i. *Problem of perfusion or ventilation? Perfusion (circulation)*

2. Identify the diuretic contraindicated in a severe chronic obstructive pulmonary disease (COPD).
    a. **Acetazolamide** – *Used to correct metabolic alkalosis; opposite of what we want*
    b. Furosemide
    c. Hydrochlorothiazide
    d. Mannitol – *Contraindicated for pulmonary edema/congestion*
    e. Spironolactone
    f. *How to solve:*
        i. *COPD = ventilatory problem (not circulation) = high CO2 levels (hypercapnia) = low pH = respiratory acidosis*
3. The most effective way to lower blood volume in a patient with Na-dependent hypertension due to an adrenal tumor is to:
    a. Decrease dietary sodium
    b. **Inhibit aldosterone receptors** – *Aldosterone is associated with increased sodium channels; The only way to treat this is with spironolactone (treatment of hyperaldosteronism)*
    c. Inhibit angiotensin-converting enzyme (ACE)
    d. Inhibit receptors for Angiotensin II (AT1)
    e. B, C, and D would be similarly effective
    f. *How to solve:*
        i. *Na-dependent HTN due to an adrenal tumor*
            1. *Medulla = EPI (pheochromocytoma)*
            2. *Cortex = aldosterone (associated with Na+ retention)*
4. The most likely treatment to result in an increased risk of cardiac arrhythmia due to ionic imbalance is:
    a. Amiloride and Ibuprofen (NSAID) – *Amiloride is K+ sparing = increase K+ levels; Ibuprofen = prevents diuretic action by blocking prostaglandins (which normally increase Na+ release), therefore NSAIDs would promote Na+ reabsorption*
    b. Furosemide and Ibuprofen (NSAID) – *Furosemide would lose K+*
    c. Hydrochlorothiazide and Diclofenac (NSAID) – *Hydrochlorothiazide would lose K+*
    d. Hydrochlorothiazide and Losartan – *Hydrochlorothiazide would lose K+; Losartan would block AT1 receptors would increase K+*
    e. **Spironolactone and Enalapril** – *Spironolactone is K+ sparing, Enalapril is also K+ sparing = too much K+ retention; K+ is what causes high risk of cardiac arrhythmias*

Session 12: MI, CHF, Anti-Arrhythmic Drugs (*4 questions – 2 questions ea. lecture*)

Angina Pectoris – chest pain/discomfort evoked by myocardial ischemia (oxygen supply < demand); activation of receptors by metabolites that are developing in an ischemic condition

- Types of Angina:

    - **Exertional (Stable)** – blood supply is sufficient under resting conditions, but insufficient upon exercise
        - Increased oxygen demand, decreased coronary blood flow (due to plaque)
    - **Unstable** – acute, unexpected (can be due to atherosclerotic plaque rupture, blocking blood flow)
        - Heightened risk of MI
- **"Coronary Steal" (*Dental Implications*)**
    - Inhalation anesthetics (i.e. **Isofluorane**) leads to systemic vasodilation and the resulting decrease in coronary blood flow
        - Includes **Nitrous Oxide** and **Hydrolazine**
    - In patients with angina pectoris, coronary vessels *distal* to the plaque are maximally dilated (i.e. unable to compensate for the decreased blood flow by vasodilation) -> increased risk of MI
    - What happens? The blood gets re-distributed *away* from the heart to the newly-dilated portions, but the blood volume doesn't change
        - The compromised area that was compensating for the decreased blood flow by vasodilation gets less blood = increased risk of MI
        - "Blood getting stolen *away* from the coronary circulation"
- Variant (aka Prinzmetal's) – occurs at rest (often at night), coronary artery spasm
- Microvascular – microvascular disease, vasospasms in microvessels
- Atypical – atypical and vague symptoms (chest discomfort rather than pain, back pain, etc.); more frequent in women

Treatment of MI (increase supply, decrease demand)
- Organic Nitrates – act through nitric oxide (direct vasodilators)
    - **Glyceryl trinitrate (Nitroglycerin)**
    - **Isosorbide dinitrate**
- Beta-adrenergic Antagonists (Beta-blockers) – increase oxygen supply by increasing diastole time and coronary blood flow, decrease oxygen demand by decreasing HR and contractility
    - **Propranolol, Bisoprolol**
    - **Labetalol**
- Ca2+ Ch Antagonists – increase oxygen supply by coronary vasodilation, decrease oxygen demand by decreasing contractility
    - **Verapamil**
    - **Dihydropyridines (Nifedipine, Amlodipine**)

Heart Failure – the heart is unable to pump the amount of blood that is adequate for the needs of the tissues
Congestion – volume overload (blood backs up in organs), leading to increased hydrostatic pressure -> increased filtration -> edema
- Pulmonary edema, hydroperitoneum (ascites), peripheral edema (swelling of feet, ankles, etc.)
- Types:
    - **Acute** (in MI, arrhythmia, etc.) – risk of sudden death
    - **Chronic** (in coronary artery disease, cardiac valve disease, etc.)
    - **Right Ventricle only (Cor Pulmonale)** – less common
    - **Left Ventricle of Both Ventricles** – more common
- Systolic Dysfunction: (Drug group targets in blue)
    - Decreased ventricular contraction -> decreased stroke volume -> increased end systolic ventricular volume (not all blood pushed out)-> compensatory sympathetic activation (due to BP drop) and stimulation of the RAA system ->

    - Increased peripheral vascular resistance, Na+/H2O retention -> increased end diastolic volume (preload), increased oxygen demand -> compensatory cardiac hypertrophy -> eventually dilated cardiomyopathy
- Diastolic Dysfunction:
    - Decreased elasticity of the myocardium -> decreased filling during diastole -> decreased stroke volume
- Drug Targets for CHF: Decrease EFV and BP, increase contractility, decrease O2 demand, decrease ventricular stiffness
    - Cardiac glycosides – increase cardiac contractility by increasing Ca2+ levels in cardiomyocytes
        - **Digoxin**
    - Dopaminergic agonists – used only in very advanced cases (undesirable side effects)
        - **Dopamine**
    - Diuretics – **Furosemide, Hydrochlorthiazide, Spironolactone**
    - RAA- System Inhibitors
        - ACE Inhibitors – **Captopril, Enalapril, Ramipril**
        - AT1 Antagonists – **Losartan, Valsartan**
        - Direct Renin Inhibitors – **Aliskiren**
    - Beta-adrenergic Antagonists (Beta-blockers)
        - **Propranolol, Bisoprolol**
        - **Labetalol**
    - Vasodilators
        - **Hydralazine, Sodium Nitroprusside, Organic Nitrates (Nitroglycerin, Isosorbide Dinitrate)**

Arrhythmia – abnormal heart rhythm resulting from a perturbation of the normal sequence of impulse initiation or propagation

- Cellular mechanisms:
    - **Bradyarrhythmias** – slow heart rhythms
        - TX: Withdrawal of the offending drug/permanent cardiac pacing (no real pharmacological treatment)
        - Cause:
            - Failure of impulse *initiation* in the SA node -> sinus bradycardia
            - Failure in the *propagation* of action potentials from atria to ventricles -> dropped beats (heart blocks)
        - Types:
            - Supraventricular arrhythmias = AV conduction pathway deficits (heart blocks)
                - 1st degree = lengthened PR interval
                - 2nd degree = skipped “beats”; no QRS following P (heart didn’t pump)
                - 3rd degree (complete heart block; “skipped” heart beat) = atria and ventricles are no longer synchronized; atria follow the SA nodal rhythm whereas ventricles follow the AV nodal rhythm)
    - **Tachyarrhythmias** – rapid heart rhythms
        - TX: Anti-arrhythmic drugs (narrow therapeutic window -> easy to overdose)
        - Cause:
            - Sympathetic stimulation (B-adrenergic activation)/hypokalemia = increased automaticity (excitability of the cells)
            - *Digitalis* intoxication/genetic mutation (RyR) = increased Ca2+ overload = extra beats

        - MI/infarction = re-entry
- Examples of drug-induced arrhythmias:
    - Sinus tachycardia = <u>B-blocker withdrawal</u> after chronic therapy
    - Atria tachycardia with AV conduction block = <u>*Digoxin* overdose</u>
- Pharmacological approaches to suppress arrhythmias:
    - 1) Blocking flow through specific ion channels (Na+ Ch)
        - Decrease cell excitability, increase action potential duration = increased effective refractory period
            - Refractory period = period where cells cannot respond to stimuli
    - 2) Altering autonomic function (B-blockers)
        - Arrhythmias caused by emotion, stress = activation of sympathetic nervous system
        - TX = block the sympathetic nervous system

Re-Entry – the underlying mechanism of clinically important tachyarrhythmias

- Results from slow conduction in the heart, when impulses propagate between two points through at least <u>two pathways with different effective refractory periods</u> (ERP)
    - MI or ischemic condition causes decreased conduction velocity
    - When impulses pass the slow conduction area, they find another pathway that is re-excitable (already past recovery) = shorter ERP (i.e., faster recovery)
        - = The excitation wave "**re-enters**" this pathway since it's available
- Underlying conditions:
    - 1) Presence of an <u>accessory anatomical pathway made of conductive tissue</u>
        - Ex) Wolff-Parkinson-White Syndrome = #1 cause of ventricular tachycardia in children
    - 2) Tissue with electrophysiological characteristics <u>altered by disease</u> (e.g., ischemia, hyperkalemia)
- Anti-arrhythmic drugs suppress the initiating mechanism or alter the re-entrant circuit
    - In some cases, drugs suppress the trigger, but also promote re-entry

Examples of Tachyarrhythmias

- Atrial arrhythmias – excitation spreading from an independently discharging (ectopic) focus in the atria
    - Atrial extrasystole – additional contraction of atria
    - Atrial fibrillation – all atrial cardiomyocytes contract asynchronously
- Ventricular arrhythmias – premature beats that originate in an independently discharging (ectopic) ventricular focus
    - Ventricular fibrillation – asynchronous cardiomyocytes leading to no ejection of blood

Drugs to Remember (Anti-Arrhythmic)

- **Class I: Na+ Ch Blockers**
    - **Lidocaine**
    - **Quinidine**
- **Class II: B-Adrenergic Blockers**
    - **Propranolol, Bisoprolol**
    - **Labetalol**
    - **Sotalol** (also a K+ Ch blocker)
- **Class III: Drugs that Prolong Action Potential** (mostly K+ Ch blockers)
    - **Amiodarone**
- **Class IV: Ca2+ Ch Blockers**
    - **Verapamil**

Session 13: Clinical Case Scenario #6 (*1-2 questions*)

1. Acknowledging that even a common cold may become life-threatening, is any of the patient's symptoms the cause for a real concern and action by the dentist?

    a. Yes
2. In a short phrase: What is the non-dental worrisome symptom or a likely diagnosis?
    a. **Oropharynx is swollen. Wheezing during exhalation**.
    b. ACE inhibitors side effects/contraindications = angioedema (larynx, glottis)
        i. **Ramipril** was added 2 weeks ago
3. In a short phrase: Why would Sensodyne be potentially harmful for this patient?
    a. Increased risk/severity of **hyperkalemia** with **Ramipril, Spironolactone**
        i. Hyperkalemia would decrease the effect of **Digoxin**
    b. Potassium
        i. Potassium-sparing diuretic (Spironolactone)
        ii. RAA inhibitor (Rampril)
        iii. Digoxin
4. In one word: which class of analgesics should not be used to treat dental pain in this patient? What is the mechanism of the NSAID-diuretic interaction?
    a. **NSAIDs** – triple therapy (NSAID + diuretic + ACE inhibitor)
    b. Mechanism: NSAIDs = primary cause of resistance to diuretics
        i. 1) Prostaglandins increase blood flow to the kidneys (increased GFR) by dilation of afferent arterioles to glomerulus
            1. So, by blocking prostaglandins = constriction of afferent arteriole = **decreased GFR**
            2. Decreased GFR = decreased physical access of diuretic to site of action
        ii. 2) Prostaglandins decrease Na+ reabsorption
            1. So, by blocking prostaglandins = increase Na+ reabsorption = **counteract effect of diuretics which is trying to inhibit sodium reabsorption**
5. How would you modify the sedative dose for this patient?
    a. **Decrease**
6. If a standard dose is used, what level of sedation and recovery time do you expect?
    a. **Deeper sedation, longer recovery** – *relates to elimination half-life; patient has CHF so all levels of pharmacokinetics are affected; metabolism is decreased due to decreased perfusion, excretion is decreased due to decreased GFR due to decreased perfusion = deeper sedation + longer recovery*
    b. Deeper sedation, shorter recovery
    c. Lighter sedation, longer recovery
    d. Lighter sedation, shorter recovery
7. In one word or a short phrase: What are this patient's risk factors related to general anesthesia?
    a. **MI**
        i. **Isoflurane (inhalation anesthetics) should be avoided due to <u>coronary steal</u>**
            1. Leads to systemic vasodilation and the resulting decrease in coronary blood flow ("coronary steal")
8. In few words: What other drugs pose similar risks to this patient?
    a. **Hydralazine – or other systemic vasodilators** (mechanism above)

Quiz (+ Practice Problems) for Session 12-13

1. Patient with treated hypertension faints (syncope) when standing up from a chair. Which drug is likely to directly contribute to the mechanism of fainting?
    a. Aliskiren – *direct inhibitor of renin*
    b. Enalapril – *ACE inhibitor*
    c. Hydralazine – *direct vasodilator*
    d. Minoxidil – *direct vasodilator*

e. **Prazosin** – *selective a-1-adrenergic antagonist; baroreflex is through the alpha-adrenergic system*

2. Health consequences of "coronary steal" are likely to be alleviated by:
    a. Pre-treatment with hydrochlorothiazide – *would decrease total blood volume*
    b. Pre-treatment with Isoflurane – *would lead to "coronary steal"*
    c. **Oxygen supplementation**
    d. Oxygen supplementation and pre-treatment with Phentolamine – *Phentolamine is similar to Prazosin = non-selective a-1-adrenergic antagonist = peripheral vasodilation (so, no)*
    e. Oxygen supplementation and pre-treatment with Verapamil – *Verapamil causes peripheral vasodilation would additional effect of baroreceptor reflex activation (lead to increase in HR)*
3. 76 y/o patient: idiopathic hypertension, swelling ankles and feet, dentinal sensitivity to cold. "Sensodyne" is most likely to interact with:
    a. **Digoxin** – *Sensodyne has high levels of potassium; be careful of K+ sparing medications (includes Spironolactone and Ramipril)*
    b. Furosemide
    c. Hydrochlorothiazide
    d. Prazosin
4. 88 y/o patient: BP 105/65 mmHg, a good overall health, ankles swell in the evening. The best recommendation:
    a. **Decreasing sodium in the diet**
    b. Furosemide injections once a day in the morning – *Furosemide injections are dramatic, given in hospital setting for pulmonary edema*
    c. Furosemide tablets twice a day – *Blood pressure and health is okay; Giving a patient a diuretic will drop the BP even more (don't give to a patient who is not in an emergency situation)*
    d. Hydrochlorothiazide tablets twice a day
5. 45 y/o patient: BP 145/95 mmHg, hypokalemia, ankle edema. The best treatment:
    a. Furosemide – *Would cause patient to lose potassium (already has hypokalemia)*
    b. Hydralazine
    c. **Hydrochlorothiazide and Amiloride** – *Patient has hypokalemia so K+ sparing diuretic (Amiloride) is good*
    d. Low-sodium diet and exercise – *Want to treat HTN*
6. The most effective drug to treat HTN due to an overactive adrenal medulla is:
    a. Hydrochlorothiazide
    b. Losartan – *Target the AT1 receptor (RAA), but wouldn't be as effective as Spironolactone*
    c. **Prazosin** – *Adrenal medulla releases catecholamine which acts on alpha receptors, Prazosin is a selective alpha-1 adrenergic antagonist*
    d. Sprionolactone – *Target the last step of RAA, correct for adrenal cortex (not medulla)*
7. Chest pain due to esophageal spasm will most likely be relieved by treatment with:
    a. Amiodarone
    b. Digoxin
    c. **Isosorbide dinitrate** – *Organic nitrates provide relief of esophageal spasm*
    d. Spironolactone
8. Please identify the drug known to decrease the analgesic efficacy of Codeine.
    a. Amiodarone
    b. Lidocaine
    c. **Quinidine** – *Potent inhibitor of CYP2D6 (e.g., decreased codeine to morphine metabolism) = decreased opioid analgesia*
    d. Sotalol

Session 14: Hemostasis (*4 questions*)

Subendothelial Cells Exposed

- Within the subendothelial matrix proteins you have:
  - Von Willebrand Factor (vWF)
  - Tissue Factor (III)
- Injury -> damage to endothelial cells -> subendothelial proteins exposed

1st step: Vasoconstriction

- First step mediated by myogenic mechanisms
  - Smooth muscle contraction = vasoconstriction (but very short-lasting)
- Second step = disruption of NO/prostacyclin secretion
  - Normal conditions = endothelial cells release NO/prostacyclin which have vasodilatory effects
  - Upon damage = release of NO/prostacyclin disrupted = less vasodilatory effect = vasoconstriction
    - Tonic vasodilation partially removed (longer-lasting)

2nd step: Primary Hemostasis

- Key: Platelets
  - Adhesion -> Activation -> Aggregation
    - Activation = release of ADP, TXA2, serotonin (vasoconstrictive effect)
    - Aggregation = GP iib/IIIa, P2Y
- Von Willebrand Factor

3rd step: Secondary Hemostasis

- **Tissue Factor III** exposed = activation of Coagulation Cascade
  - Extrinsic Pathway (Initiator)
    - Tissue Factor III -> **VII** -> Common Pathway (**X** with **cofactor V**)
      - X -> **II** -> **I**
        - II converts **prothrombin -> thrombin**
        - Through the extrinsic pathway, it's not enough to cleave fibrinogen to fibrin
        - But the tiny amount of thrombin activates the platelets (which release more cofactor V) = more activation of X = activation of factors in intrinsic pathway
          - = **Amplification step**
          - Activates VIII and XI
  - Intrinsic Pathway (Propagator)
    - **XII -> XI -> IX -> VIII** -> X
    - As thrombin activates more XI and VIII, there is now enough thrombin to convert fibrinogen into fibrin
- Factor XIII (also activated by thrombin) converts soluble fibrin into insoluble fibrin = blood clot

4th step: Fibrinolysis

- **Tissue plasminogen activator (tPA)** = activates plasminogen into plasmin
  - Plasmin breaks fibrin and fibrinogen
- Thrombin activates plasmin as well = "negative feedback"/"suicidal"
- **Antithrombin III** = binds covalently to thrombin to block it (inhibition), but it's also activated by thrombin
  - Also prevents activation of Factor X

- Becomes efficient in presence of **Heparin** (increases the enzymatic activity of antithrombin III by 1000x)
    - Heparin is used as an anti-coagulant = used to prevent thrombosis/formation of blood clots

Treatment

- Topical Thrombin Application for blood clotting (bypass the pathway)
    - Need only platelets, fibrinogen, and factor XIII for clotting to work
- Fibrin Sealants (bypass the pathway)
    - One tube = thrombin
    - Other tube = fibrinogen + Factor XIII
- Collagen Sheets (beginning of pathway)
    - Work as subendothelial matrix proteins
    - Accelerate aggregation of platelets, but the effect is limited in patients with hemophilia (or any deficiencies in factors of coagulation cascade, or disorders of platelets)
- Gelatin Sponges
    - Matrix that traps platelets and RBCs = helps with clotting
    - Also facilitate disruption of platelets

Primary Hemostasis = Anti-Platelet Agents

- Indications for Anti-Platelet Therapy = Increased risk of thrombosis (Virchow's Triad)
- Topically applied Epinephrine = vasoconstriction
    - Can help stop bleeding
    - Needs to be applied in a restricted area and only for a short period of time due to risk of ischemia and tissue necrosis
        - There's also an increased risk of EPI entering systemic circulation (tissue is already inflamed)
- Drugs
    - **COX inhibitors = Aspirin, Ibuprofen**
        - Aspirin = anti-platelet treatment
        - Inhibit synthesis of thromboxane A2; irreversibly binds COX1
            - Thromboxane A2 is involved in platelet activation and vasoconstriction
    - **ADP receptor inhibitors = Clopidogrel**
        - Clopidogrel is a prodrug
        - Target P2Y1/P2Y12 which are critical for platelet aggregation
    - **GP IIb/IIIa inhibitors = Abciximab, Eptifibatide**
        - This complex plays a crucial role in the final step of platelet aggregation
        - Genetic deficiency in this receptor results in a strong deficiency in platelet aggregation
- **Von Willebrand Disease**
    - vWF deficient or defective means disturbance in:
        - Factor VIII stabilization
        - Platelet adhesion
        - Platelet aggregation (GP IIb/IIIa)
    - TX: Factor VIII/vWF replacement
- **Thrombocytopenia** – decreased number of platelets
    - Causes:
        - Liver cirrhosis (due to alcoholism)
        - Myelogenous diseases (leukemia), HIV
        - Drug-induced

Secondary Hemostasis = <u>Directly</u> Acting Anticoagulants

- Genetic Disorders
    - Hemophilia A (VIII), B (IX), C (XI)
    - vWF disease
    - Treatment:
        - Factor replacement products
        - Desmopressin
            - Prevents bleeding in patients with hemophilia as it causes endogenous VIII, vWF, and plasminogen activator to be replaced from storage sites in vascular endothelium
        - Factor VIIa (recombinant)
            - Used when patient develops antibodies against the factors that are supplied
            - Functions like endogenous VII, and stimulates X and IX after combining with tissue factor III
                - Risk of disseminated coagulation is small
                - Antithrombin III doesn't inactivate VIIa
            - But, it has a short half life = must be given in high doses with high frequency
- Directly Acting Anticoagulants
    - **Heparin** = catalyzes antithrombin reaction = decreases thrombin and Xa
    - Low molecular weight heparins = decrease Xa (no effect on thrombin)
        - **Enoxaparin, Dalteparin**
    - Antidote (reverse anticoagulation effect) = **Protamine Sulfate**
- Direct Oral Anticoagulants (DOAC)
    - Direct thrombin inhibitors
        - Hirudin, **Bivalirudin, Dabigatran-Pradaxa**
    - Antidote = **Idarucizumab-Praxbind**
- Direct Factor Xa inhibitors
    - **Rivaroxaban-Xarelto, Apixaban-Eliquis**
    - Antidote = **Andexanet Alfa-Andexxa**

Secondary Hemostasis = <u>Indirectly</u> Acting Oral Anticoagulants

- **Warfarin (Coumadin)**
    - Why take indirect over direct? Warfarin is inexpensive
        - What is the drawback? Difficult to maintain proper level of coagulation; drug is very sensitive to many outside factors
            - Related to the levels of **<u>VitK</u>**
            - Warfarin is a competitive inhibitor of Vitamin K epoxide reductase
                - Vit K is critical for activation of several clotting factors (II, VII, IX, X)
                - Warfarin prevents Vit K to be reduced so that it can serve as a cofactor in the synthesis of the clotting factors
            - <u>Warfarin = decrease amount of VitK = block activation of clotting factors</u>
    - Pharmacokinetic considerations:
        - 99% of Warfarin = plasma protein bound
            - If you have competition with other drugs that compete for plasma protein binding sites, or have decreased amount of plasma protein = increased amount of free Warfarin
                - = Stronger inhibition of enzyme = even less clotting factors = risk of bleeding (stronger anticoagulation effect)

        - Action of Warfarin depends on Vit K bioavailability
            - Diet (take a lot of VitK = lots of greens) = increased amount of VitK = inhibition of enzyme is not sufficient = anticoagulation effect goes down
            - Antibiotic therapy (Vit K made by intestinal microbiota) = wipe out gut microflora = decrease VitK = increased risk of bleeding
        - **CYP2C9-mediated metabolism**
            - Other drugs can induce or inhibit this enzyme
            - If the enzyme is induced, the level of Warfarin will go down = anticoagulation effect will not be sufficient
            - If the enzyme is inhibited, the level of Warfarin will go up = anticoagulation effect will be increased (increased risk of bleeding)
    - Other interactions:
        - Risk of uncontrolled bleeding with anti-platelet treatment (Aspirin, Ibuprofen, Clopidogrel)
    - Antidote = Vit K
        - Overdose of Warfarin or too much bleeding because of Warfarin, give Vit K
- How do we test the level of anticoagulation with Warfarin?
    - Most sensitive test = **depression of Factor VII** (half-life 4-6 hours; short)
        - Compared to 2-3 days for Factor II, Prothrombin
    - But, for actual testing, use **Prothrombin time**

Tests that evaluate coagulation (with regards to anti-coagulant treatment):
- The time it takes for blood clot to form after activation of…
    - **Extrinsic -> Common Pathway = Prothrombin Time (PT)**
        - How do we know it's only extrinsic pathway activated?
            - Citrated plasma with the addition of tissue factor (III)
        - Often presented as **INR**
            - PT (presented in seconds) can be varied
            - To normalize it, the lab establishes the PT for healthy subjects and using the same standards, they determine the PT for the patient = ratio is presented to eliminate lab to lab variability
            - General rule: Don't touch patient if INR > 3
    - **Intrinsic -> Common Pathway = Activated Partial Thromboplastin Time (aPTT, PTT)**
        - Citrated plasma + activator (e.g., silica)
- How do you interpret the data?
    - PTT increased, PT normal = problem with only intrinsic pathway (extrinsic and common pathway normal)
        - Deficiency in:
            - VIII (hemophilia A/vW)
            - IX (hemophilia B)
            - XI (hemophilia C)
        - Heparin treatment
            - PT is *not* a good measure for heparin treatment
    - PTT normal, PT increased
        - Factor VII deficiency (early stages; short half-life)
        - Decreased VitK acitivity (early; Warfarin treatment)
            - Picked up early
        - DIC (early/incoming stage)

    - PTT increased, PT increased
        - Decreased VitK activity (advanced)
        - Liver failure
        - DIC
        - Treatment with anticoagulants
            - Warfarin
            - Direct oral anticoagulants
                - *Note*: Main advantage of direct oral anticoagulants over Warfarin = don't need to test/measure
- **Thrombin time (TT)** = thrombin added for this test (in excess)
    - Want to measure the amount/function of fibrinogen
    - Increased TT:
        - Liver failure (where fibrinogen is made)
        - DIC (use-dependent)

Fibrinolysis

- Fibrinolytics – get rid of blood clots
    - Mechanism of action: Stimulate plasminogen -> plasmin
    - Indications: Relieving thromboses (e.g., acute MI, pulmonary embolism, ischemic stroke, DVT)
    - Drugs:
        - Recombinant tPA (**Alteplase**) – recommended in myocardial thrombosis
        - Mutant variation of tPA (Reteplase)
        - Streptokinase (exotoxin -> can trigger allergies)
- Anti-fibrinolytics
    - Mechanism of action
        - Competitive inhibition of plasminogen and plasminogen activators from binding to fibrin = limited fibrinolysis
    - Indications
        - Oozing sockets after dental extractions; post-surgery in hemophilics
    - Drugs:
        - **Aminocaproic acid**
        - **Tranexamic acid** (Cyklokapron, Lysteda)

Session 15: Clinical Case Scenario #7 (*1-2 questions*)

1. In ONE WORD: Which condition or medication would suggest compromised hemostasis?
    a. **Dabigatran** – direct oral anticoagulant
    b. **Aspirin** – anti-platelet agent
2. Should the dentist stop any of the prescription medications? What would be the best first step?
    a. **No**. They have significant cardiovascular problems
    b. Consult PCP, medical consult
3. In ONE WORD or a SHORT PHRASE, what is the additional risk with Ibuprofen (Advil)?
    a. **Acute renal failure** = ACE inhibitor (Ramipril) + Hydrochlorothiazide (diuretic) + NSAIDs
    b. + **Bleeding** (NSAID has anti-platelet properties)
4. In a SHORT PHRASE: Please list ONE local measure to improve coagulation.
    a. **Anti-fibrinolytic** = Aminocaproic Acid, Tranexamic Acid
    b. **Epinephrine** = hemostatic
    c. **Collagen sheets**
    d. Astringents and Styptics (same thing) – this is what we use as a hemostatic medication for gingival retraction cords

i. Iron salts (pH <3, irritating)
ii. Aluminum salts (pH <3)
iii. Zinc salts, silver salts (stains may be permanent)
iv. *These are only to aid hemostasis while retracting gingival tissue – avoid at all costs*
    1. Better not to use – mechanism of action = denature the tissue proteins = agglutination = plug formation
        a. Don't target any biological system or any step of hemostasis
        b. Leads to foreign body reaction and delayed healing (due to immune response)
    2. Use only briefly, with irrigation and debridement (remove the breakdown products)
        a. Do not apply to areas of exposed osseous material to avoid inflammation/retarded healing
        b. Patients with even a mild bleeding tendency = a risk of delayed oozing over a larger area

5. In ONE WORD and ONE NUMBER: With Warfarin, what test and value would assure an acceptable risk of bleeding?
    a. **INR between 2-3**
6. In a Warfarin-treated patient, how would the risk of intraoperative bleeding be affected by:
    a. Fluconazole, a CYP2C9 inhibitor, would make the risk of bleeding: **Higher**
    b. A drug that induces CYP2C9: **Lower**
    c. A drug that competes with Warfarin for CYP2C9: **Higher**
    d. A drug that is highly bound to plasma protein: **Higher**
    e. Hypoalbuminemia: **Higher**
    f. VitK-enriched diet (e.g., green leafy vegetables) **Lower**

Quiz (+ Practice Problems) from Session 14-15:

1. The following test would accurately determine the coagulation status of a patient taking Apixaban:
    a. aPTT
    b. **Factor Xa assay** – *Apixaban is a Factor Xa inhibitor, it is a direct oral anticoagulant*
    c. INR
    d. PT
    e. TT
2. Thrombocytopenia develops in a patient treated with unfractionated Heparin. Which parenteral anticoagulation is a viable alternative?
    a. Abciximab – *Anti-platelet agent, not an anti-coagulant*
    b. Alteplase – *tissue plasminogen activator (fibrinolytic), used for thrombosis treatment*
    c. **Bivalirudin** – *direct Thrombin inhibitor, used in parenteral form*
    d. Dalteparin – *Low molecular weight heparin; don't want to use another Heparin (worsens situation)*
    e. Intravenous Vitamin K – *VitK is a pro-coagulant, works opposite of Warfarin (anti-coagulant) as it inhibits VitK*
3. As a result of the pharmacodynamic action of Warfarin:
    a. Prothombin time (PT) and INR decrease – *No, with Warfarin (anti-coagulant) you would have increase, not decrease (time is how long it takes for blood to coagulate)*
    b. **The amount of active (reduced) form of Vit K decreases** – *Yes, Warfarin inhibits VitK epoxide reductase*
    c. The amount of coagulation factor XI decreases – *VitK affects II, VII, IX, X*

    d. The amount of coagulation factor VII increases – *False, Factor VII is decreased (not increased) due to reduced VitK*
    e. The amount of plasma protein available for drug binding decreases – *Yes and no, because this is a pharmacokinetic action, not pharmacodynamic*
4. Prothrombin Time (PT) is likely to detect deficiencies in:
    a. The number and/or function of platelets – *Platelets is 1st step of hemostasis; measured by bleeding time*
    b. The amount and/or function of coagulation factor III – *because you add tissue factor III, you cannot measure it*
    c. **The amount and/or function of coagulation factor VII**
    d. The amount and/or function of coagulation factor VIII – *No, part of intrinsic pathway*
    e. Both B and C are correct answers
5. Which of the following adverse effects is most likely to be associated with Tranexamic Acid (*anti-fibrinolytic)*?
    a. Hemorrhagic stroke – *This would be the opposite, caused by too much blood (no coagulation)*
    b. Acute renal failure – *Caused by blockage of renal artery*
    c. Pulmonary embolism – *Blockage of pulmonary artery*
    d. Ischemic stroke – *Blockage leading to lack of oxygen*
    e. **B, C, and D are all likely adverse effects of this drug**
6. 50 y/o with severe chest pain. History of moderate HTN, elevated blood cholesterol and smoking. ECG (ST elevation) and cardiac enzymes confirm the diagnosis of MI. Which drug is best for treatment:
    a. **Alteplase** – *Fibrinolytic used to relieve thromboses (acute MI)*
    b. Aminocaproic Acid
    c. Clopidogrel
    d. Dabigatran
    e. Heparin
    f. Warfarin
7. Please identify the serious adverse effect associated with the drug used in the case scenario from the previous question.
    a. Acute renal failure – *Associated with blocking an artery*
    b. Development of anti-platelet antibodies
    c. **Hemorrhagic stroke** – *Fibrinolytic can lead to too much blood flow (no clotting*)
    d. Ischemic stroke – *Associated with increased coagulation*
    e. Pulmonary embolism – *Associated with blocking an artery with increased coagulation*
    f. Skin rash – *Possible side effect of any drug*
    g. Thrombocytopenia
8. Suddenly stopping Apixaban (*Factor Xa inhibitor*) can lead to:
    a. Anaphylaxis
    b. Excess bleeding – *Would happen by Apixaban overdose*
    c. Increase in INR
    d. **Ischemic stroke** – *Stop Apixaban, increase coagulation*
    e. Thrombocytopenia
9. Statement 1: Relative to Aspirin 81 mg (aka, "Baby Aspirin"), Aspirin 325 mg is expected to have a significantly stronger inhibitory effect on platelet aggregation and should be prescribed instead of "Baby Aspirin" to patients with no GI problems. Statement 2: The dose of Clopidogrel should be reduced in patients with advanced liver cirrhosis in order to avoid drug toxicity and side effects.
    a. Both statements are true.

b. **Both statements are false.** – *81 mg is effective as 325 mg with regards to anti-platelet; Clopidogrel is a pro-drug, if you have liver cirrhosis would lead to less effective conversion of active form – so you wouldn't expect toxicity*
c. The first statement is true, the second is false.
d. The first statement is false, the second is true.

10. The mechanisms of interaction between Warfarin and Antibiotics involve:
    a. Increase in gut microflora-derived VitK; CYP2C9 inhibition
    b. **Decrease in gut microflora-derived VitK; CYP2C9 inhibition** – *Antibiotics clear gut microflora; Enzyme that metabolizes Warfarin is inhibited by some antibiotics (CYP2C9 catalyzes the oxidation of Warfarin) – Note that Warfarin interacts with NSAIDs and antibiotics/antifungals (Metronidazole, Fluconazole)*
    c. Increase in gut microflora-derived VitK; CYP2C9 induction
    d. Decrease in gut microflora-derived VitK; CYP2C9 induction
11. You have finished a tooth extraction, but the bleeding from the socket does not seem to stop. Best drug to aid in hemostasis is:
    a. Clopidogrel
    b. Dabigatran
    c. Enoxaparin
    d. **Tranexamic Acid** – *Anti-fibrinolytic*
    e. None of the above

Session 16: Local Anesthetics (*4 questions*)

Neuroscience Background

- Neuronal Fiber Classification:
    - A alpha/gamma – heavy myelination/large diameter/fast/high frequency = somatic motor neurons
    - A beta – heavy myelination/large diameter/fast/high frequency = tactile and proprioceptors
    - **A delta** – light myelination/smaller diameter/slower/lower frequency = **pain**, thermal, pressure
    - **C fibers** – unmyelination/smallest diameter/slow = **pain**, thermal, **postganglionic sympathetic**
- Three Classes of Somatic Nociceptors:
    - **A delta mechanosensitive** and **thermal** = first pain (sharp, shorter lasting)
    - **C polymodal nociceptors** = second pain (duller/burning, longer lasting)
- **TRPV1** = **nociceptor receptors** = voltage-sensitive + ligand-gated
    - Ligand = capsaicin, acid, anandamide (cannabinoid), 45 degrees C
- Tooth innervation:
    - Tooth = A beta, A delta (minority) + C fibers (majority)
        - Few penetrate into dentinal tubules (nociceptors), most terminate in pulp (nociceptors and some mechanoreceptors)
    - PDL = A beta (mechanoreceptors), A delta and C fibers (nociceptors)
- Membrane potentials
    - Voltage-dependent channels open upon depolarization (Na+ in) and further depolarization = action potential
        - Depolarizing stimulus = synaptic potential
        - Depolarization = Na+ rushes in down concentration gradient
        - Repolarization = Na+ closes, K+ opens
- Action potentials
    - Unmyelinated fibers

        - A low density of evenly distributed sodium channels
        - Continuous action potential propagation
    - Myelinated fibers
        - High density of sodium channels in Nodes of Ranvier
            - Saltatory ("jumping") action potential propagation
        - APs can propagate despite missing two nodes = **at least 3 consecutive blocked Nodes required to interrupt transmission**
            - Increased fiber diameter = increased distance between nodes
        - Partial blockade (with >70% Na+ channels blocked) = decreased AP amplitude = conduction failure if a sufficient nerve length is affected by the blockade
    - Nerve conduction readily disrupted (highly susceptible to block; blocked faster and longer to recover) =
        - **Small** fibers = **A delta** and **C fibers**; pain, sympathetic
        - *Not*: A alpha, beta; motor, proprioception, touch, pressure
            - Distance between nodes are greater = require wider range/dose of LA to block
        - Speed of LA block: unmyelinated > small > large

Review of pKa vs pH
- pKa = pH when 50% ionized, 50% unionized
    - pKa > pH = ionized > unionized
- Acidic = ionized = membrane impermeable
- Alkaline = unionized = membrane permeable

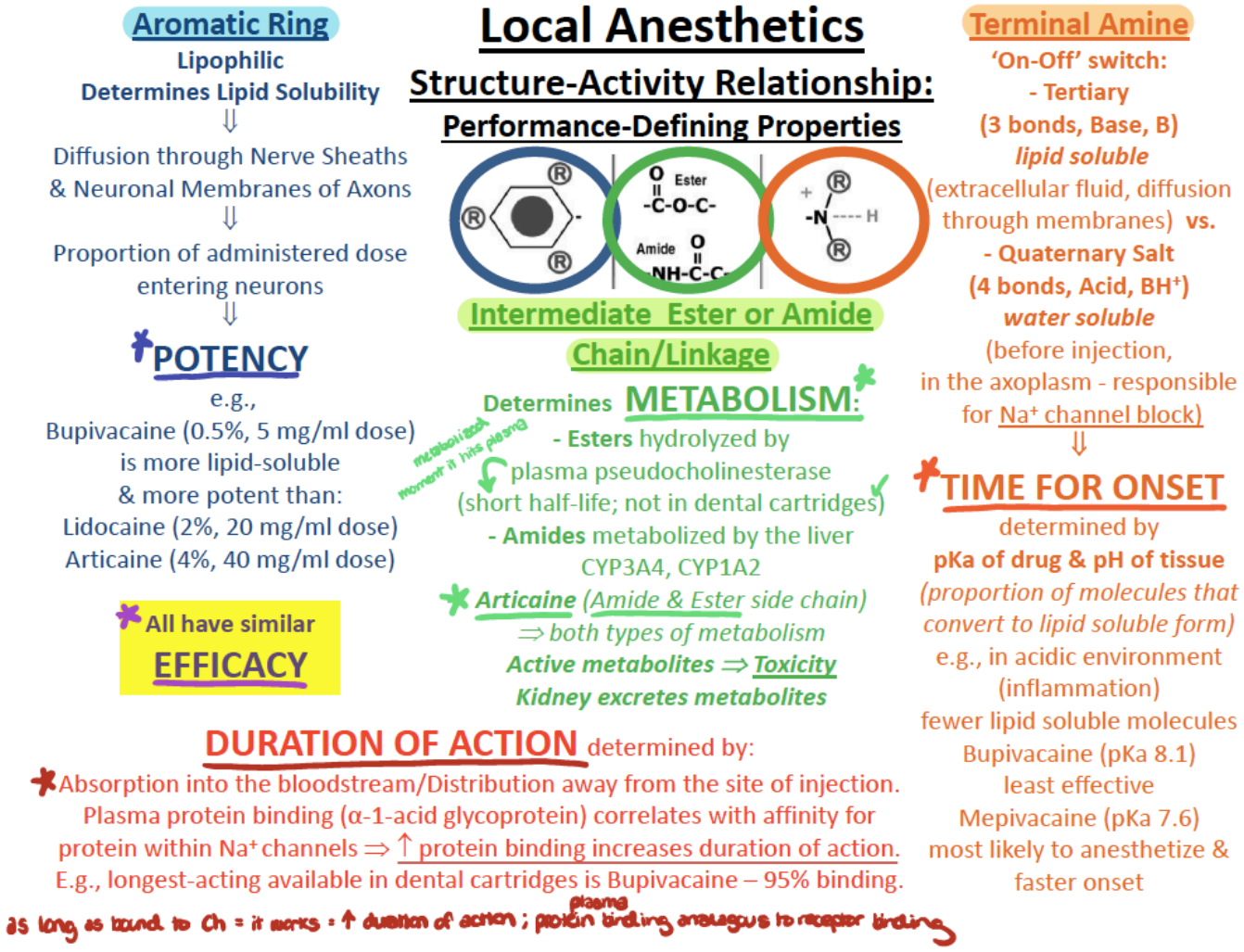
LAs bind reversibly to a specific receptor site within the pore of voltage-gated Na+ channels and block ion movement, thus inhibiting the generation and conduction of action potentials

Mechanism of Action of LAs
- 1) LA = free base-lipophilic
    - LA is prepared in **acidic** form to improve water solubility and stability
    - Upon injection, it quickly neutralizes into the free base form (non-ionized base)
    - As a weak base, their pKa is higher than the tissue pH (pKa > physiological pH)
        - The farther the pKa is from the pH, the more ionized it becomes
        - *A drug will become less ionized (more **lipid-soluble**) at a pH similar to its own*
- 2) Lipophilic LA = move through cell membrane
    - Intracellular pH < extracellular = LA converts to acidic form
        - Decrease in pH of environment = farther from pKa = greater proportion becomes ionized (acid form)
        - This form is critical for LA binding to voltage-gated Na+ channels
    - LA works from the **inside** = needs to be in **ionized form** (pKa >> pH)
    - Channel needs to be **open** = neuron needs to be active
        - LAs gain access to their receptor by traveling *up* an aqueous route within the Na+ channel, which must be open to permit their entry from the cytoplasm

Use (frequency) dependence: rapid firing increases exposure of the receptor site = increased drug action
- Increased activity of neuron = facilitates LA binding

Lipophilic molecules (e.g., Benzocaine, uncharged form of Lidocaine) can reach the receptor site by traversing the cell membrane lipid and hydrophobic portions of the Na+ channel (hydrophobic path)
- Charged anesthetics enter through TRPV1 receptor channels (hydrophilic path)
    - TRPV1 opens by capsaicin

- TRPV1 expressed only on nociceptors = more selective



KNOW THIS SLIDE WELL

Vasoconstrictors

- LAs = vasodilators; decrease sympathetic neuron and smooth muscle activity
  - Toxic response = hypotension
  - Vasodilatory potential (*exception* = ***cocaine = vasoconstrictor***)
    - Procaine > Bupivacinae > Lidocaine > Articaine > Prilocaine > Mepivacaine > Cocaine
- Vasoconstrictors inhibit systemic absorption of anesthetics by decreasing blood flow
  - Benefits of impeding systemic absorption of anesthetics and decreasing blood flow
    - Prolongs the duration
    - Improves the success rate and intensity
    - Minimizes systemic toxicity by reducing peak blood concentration
      - Less drug may be needed
      - Metabolism more likely to keep pace with drug absorption
        - Metabolism of lidocaine is blood flow limited
    - With infiltration, tend to reduce blood loss associated with surgical procedures (hemostasis)
- Use of EPI
  - For cardiac patients, minimizing EPI to <40 ug is appropriate

- Doses >200 ug can surpass titers associated with heavy exercise, surgery, pheochromocytoma = increased risk of MI and arrhythmias
    - **Levonordefrin** (1:20,000 solution with clinical efficacy ~1:100,000 EPI)
        - Indicated for cardiac patients because of fewer/less pronounced cardiac effects compared with EPI (predominantly alpha-adrenergic agonist; less effect on HR)

Overdose

- Mild-moderate = **loss of consciousness**
- Moderate-severe = **seizures**, general CNS depression, **cardiac arrest**
- Other
    - 1) Vasodilation = hypotension with large doses
    - 2) Potentiation of respiratory depression caused by sedatives/opioids (increased risk of seizures)
    - 3) Hypercarbia = decreased seizure threshold
    - 4) **Methemoglobinemia** caused by Prilocaine metabolite

Session 17: Clinical Case Scenario #8 (*1-2 questions*)

1. What are the expected systemic effects of…
    a. Lidocaine – CNS depression, vasodilation (hypotension)
    b. Epinephrine – Vasoconstriction (alpha and beta-adrenergic receptors affected), increased HR
    c. Phentolamine – Vasodilation (alpha 1 and 2 adrenergic receptors)
2. Please list two factors/drugs involved in the mechanism of the patient's heart block
    a. Direct effect = **Lidocaine**
    b. What makes it worse?
        i. **Congestive heart failure** (decreased blood flow to the liver = decreased metabolism of lidocaine)
            1. Risk of systemic toxicity increases
        ii. **Alcoholism** (leads to liver damage = decreased capacity to metabolize drugs)
        iii. **Propranolol** = decreases blood flow through the liver (similar to CHF) + basic (binds not to albumin (acidic drugs), but to alpha-1 acidglycoprotein (?); competes with lidocaine for binding sites)
            1. Less alpha-1 acidglycoprotein available for lidocaine binding = more lidocaine available in free form = more likely to cause toxicity
    c. Indirect effect = **Phentolamine**
        i. Leads to release of massive amounts of lidocaine = higher risk of toxicity
3. What is a potential link between the dental treatment this patient received and the dizziness, chest pain, and shortness of breath that he is experiencing?
    a. Heart function compromised = decreased blood flow to the brain (cardiac depression)
4. The decision to lower the concentration of EPI likely resulted from the following patient's condition:
    a. Congestive Heart Failure
    b. Narrow-Angle Glaucoma
    c. Treatment with Propranolol
    d. All of the above
        i. Patient has cardiac problems and takes propranolol (B-blocker) = dangerous effect with EPI in LA
5. Could any of the patient's other medications have evoked, or contributed to, the incident? If so, please indicate which medication and explain the underlying mechanism of interaction.
    a. Direct = **Quinidine** – reversal of LA (w/ Phentolamine) can result in dangerous cardiac depression, particularly in patients with liver or kidney disease that may significantly increase the elimination half-life of Lidocaine

    b. Indirect:
        i. **Propranolol** – decreases blood flow through the liver, increased free levels of lidocaine
        ii. **Cimetidine** – strong metabolism inhibitor; higher levels of free lidocaine
6. How would physical exercise affect the duration of LA in a healthy individual? What is the underlying mechanism?
    a. **Decreased duration and increased absorption of the LA**
7. Which of the patient's medications are expected to affect the LA pharmacokinetics and/or pharmacodynamics?
    a. **Quinidine** = increase elimination half-life of Lidocaine for patients with liver or kidney disease = decreased metabolism
    b. **Propranolol** = decreases metabolism
    c. **Cimetidine** = strong metabolism inhibitor; higher levels of free lidocaine

Quiz (+Practice Problems) from Session 16-17

1. Characteristic properties of local anesthetics include all of the following, EXCEPT one. Please identify the EXCEPTION.
    a. Blockade of voltage-dependent sodium channels
    b. Effects on vascular tone
    c. Preferential binding to closed (resting) channels – *LA are more active when channels are open*
    d. Inhibition of axonal impulse conduction
    e. Depression of Central Nervous System (CNS) neurons
2. Relative to a local anesthetic whose LogP is 2.8, a local anesthetic with LogP of 4.5 is expected to have:
    a. Longer time for onset – *determined by pKa, determine how quickly drug switches from lipophilic to hydrophilic form; if it doesn't switch quickly = longer time for onset*
    b. Shorter duration of action – *determined by how long the drug sticks to ion channels, measured by plasma protein binding (measured in correlation with ion channel proteins)*
    c. Shorter plasma half-life – *about metabolism*
    d. Higher potency – *LogP is a measure of lipophilicity; lipophilicity determines potency; Greater LogP = more lipophilic = higher potency*
    e. Lower risk of CNS toxicity – *higher lipophilicity = higher risk of toxicity*
3. Local anesthetic (LA)-A is 55% plasma protein-bound, whereas LA-B is 95% plasma protein-bound. Relative to LA-A, LA-B is expected to have:
    a. Higher risk of cardiotoxicity – *this is about ease of drug to go to heart, 95% bound means it remains in circulation = lower toxicity*
    b. Longer duration of action – *increased plasma protein bound = relates to amount bound to ion channels = longer duration of action*
    c. Lower potency – *determined by lipophilicity*
    d. Shorter plasma half-life – *determined by structure (amide vs ester)*
    e. Shorter time for onset – *determined by pKa*
4. Please identify the anesthetic with the strongest ability to diffuse through both soft and hard tissues.
    a. Articaine – *diffuse through soft and hard tissues; only LA that has amide and ester features = most quickly metabolized (metabolized in the plasma, doesn't have to go to liver)*
    b. Bupivacaine – *highly lipophilic*
    c. Lidocaine
    d. Mepivacaine
    e. Prilocaine
5. Prilocaine is relatively contraindicated in patients with cardiovascular or pulmonary disease because:
    a. It acts as an agonist at beta-adrenoceptors in the heart and the lung – *Doesn't act as a beta-adrenoreceptor agonist*

   b. **It causes decompensation through formation of methemoglobin** – *Methemoglobinemia caused by Prilocaine metabolite*
   c. It inhibits cyclooxygenase in cardiac and pulmonary cells – *Doesn't inhibit cyclooxygenase*
   d. It is a potent bronchoconstrictor – *Prilocaine is a vasodilator = bronchodilator (like most LAs – except Cocaine)*
   e. None of the above because Prilocaine does not have any contraindications
6. Which local anesthetic is expected to have the shortest plasma half-life?
   a. **Articaine** – *both an amide and ester, can be metabolized in plasma*
   b. Bupivacaine
   c. Lidocaine
   d. Mepivacaine
   e. Prilocaine
7. Relative to Mepivacaine, Bupivacaine is characterized by:
   a. Lower lipid solubility – (*similar to B)*
   b. Lower potency – *Potency determined by lipophilicity; if drug has lower lipid solubility, it will have lower potency; so both cannot be correct; In this case, Bupivicaine has higher lipid solubility and higher potency*
   c. Shorter duration of action – *(similar to E)*
   d. **Stronger cardiotoxicity** – *More lipophilic, more distribution = longer half-life; Bupivicaine has specific affinity for heart muscle*
   e. Weaker binding to sodium channel protein and neuronal membrane – *Bupivicaine is highly bound to plasma proteins, it's strongly bound to sodium channel proteins = longer duration of action*
8. Which drug has intrinsic vasoconstrictor actions (e.g., for nasopharyngeal procedures)?
   a. Bupivacaine
   b. **Cocaine** – *uniquely vasoconstrictor*
   c. Lidocaine
   d. Mepivacaine
   e. Procaine
9. A vasoconstrictor added to lidocaine for a peripheral nerve block will:
   a. Decrease the risk of a seizure
   b. Increase the duration of anesthetic action of the LA – *Vasoconstrictor will increase the duration by keeping the LA in the site of action*
   c. Decrease the peak plasma concentration of lidocaine
   d. **All of the above are correct** – *Without vasoconstrictor, there will be higher concentration of lidocaine in the plasma (increased plasma concentration), and will travel to the brain (increased risk of a seizure due to stronger diffusion*
   e. Only A and B are correct
10. The most important effect of inadvertent intravenous administration of a large dose of lidocaine is:
   a. Bronchoconstriction – *Would expect bronchodilation with lidocaine; Lidocaine = vasodilation = bronchodilation*
   b. Methemoglobinemia – *Unique feature of prilocaine (metabolite)*
   c. Renal failure – *Drop in blood pressure can affect, but kidneys are resistant to short-term changes of blood pressure*
   d. **Seizures**
   e. Tachycardia – *LA used as anti-arrhythmic = decrease HR (bradycardia)*
11. MRD of Lido is 500 mg, MRD of Mepi is 400 mg. Administered 6 cartridges 2% Lido with Epi. Max # of cartridges of 3% Mepi is: (Assume 2 mL per cartridge)
   a. **3**

i. *2% Lidocaine = 2 g/ 100g or mL = 20 mg/mL = 40 mg/cartridge = 240 mg/6 cartridges*
ii. *Approximately one-half of the MRD of Lidocaine has been injected*
iii. *Approximately one-half of the MRD of Mepivacaine can be injected*
iv. *3% Mepivacaine = 3g/100g or mL = 30 mg/mL = 60 mg/cartridge*
    1. *Half of 400 mg (MRD) = 200 mg; 200 mg/60 mg = 3 cartridges*

Session 18: Analgesics (*4 questions*)

Somatic Component of Pain

- Primary receptor responsible for transduction of nociceptive information = **TRPV1**
    - Voltage-sensitive = permeable to Na+ and Ca2+
        - Different from the Na+ channels of LAs
            - Transmission of nociceptive stimulus from periphery to the brain = propagation of action potentials mediated by voltage-gated Na+ channels
                - Na+ channels expressed throughout the entire membrane of the axonal membrane of the neuron – from free nerve ending to next order neuron (SC)
            - TRPV1 let Na+ through, but located only at the terminals of the free nerve endings
    - Ligand-gated = **capsaicin (hot peppers), acid, anandamide (cannabinoid), 45 C (temperature)**
        - Capsaicin = "spicy, burning tingling" = activation of TRPV1 channels
            - Capsaicin activates the TRPV1 channels, opens and initial depolarization of free nerve ending = leads to opening of voltage-gated Na+ channels responsible for propagation of information to the brain
- "Burning" sensation of LA anesthetic upon injection = mediated by TRPV1 receptors
    - LA delivered in a vehicle of low pH (acidic)
        - LA's are weak bases, so being an acidic environment = highly ionized = more stable
    - Ligand for TRPV1 = acid
        - The vehicle of the LA activates TRPV1 receptors = "burning pain" upon injection
    - Then the LA starts working, and blocks and binds to voltage-gated Na+ channels
        - The TRPV1 receptors may be activated and working, there is no more transmission of information as the LA is blocking the voltage-gated Na+ channels

Trigeminal Pain Pathway

- 1) Noxious stimulus activates **free nerve endings** (thermoreceptor or nociceptor)
    - Free nerve ending = primary afferent with **TRPV1** receptors at the end
- 2) Free nerve ending -> **trigeminal nerve** -> **trigeminal ganglion** (cell bodies of 1st order neuron)
- 3) Trigeminal ganglion -> **spinal trigeminal tract** (mid pons) = collection of primary sensory neurons
    - Upon entering the pons, the neurons travel caudally to the second order neurons = ***subnucleus interpolaris*** *and* ***caudalis*** (cell bodies of 2nd order neurons)
        - Subnucleus caudalis = important for nociceptive information = in the SC
- 4) Decussation (cross over to the contralateral side) at the same level of where information is received
    - Travel up **contralaterally** through the **trigeminothalamic tract**
- 5a) **Thalamus**
    - **VPM nucleus** – for the trigeminal system
        - Travels to the **somatosensory cortex** (post-central gyrus) = sensory, discriminative aspect of pain
            - Tells you where the pain is coming from, where it is located
            - Not important in terms of treatment and patient's perception

- **Midline nuclei**
  - Travels to the **cingulate and insular cortex** = affective-motivational (aversive) aspect of pain
    - This is what we to eliminate = good for chronic pain conditions ("not feeling well" aspect)

Opioid Targets – most efficacious *analgesics* (don't influence underlying cause/mechanism)
- **Cingulate and insular cortex** = **primary site** with most opioid receptors*
- Trigeminal complex in the brainstem, specifically **Subnucleus Caudalis**
- **Free nerve endings**
- **Periaqueductal Grey** = contains neurons critical for descending control of pain
  - Collection of neuronal cell bodies (gray matter) around the aqueduct (= connection between the 3rd and 4th ventricle, CSF)
  - Send signal to first order synapse, affect interneurons at the level of the subnucleus caudalis = block the transmission of nociceptive information

NSAID Targets – influence the ***mechanism*** of pain (anti-inflammatory)
- **Free nerve endings** = primary site of action
- **Trigeminal complex in the brainstem** = 2nd order neurons

Acetaminophen – not an NSAID, but analgesic
- Site of action is unknown

Sensitization
- 1) Noxious stimulus
  - Tissue damage
    - Release of inflammatory mediators = **prostaglandins** (target of NSAIDs)
      - Prostaglandins cause **neuroinflammation** (inflammation of peripheral nociceptive endings) = basis of **peripheral sensitization**
        - Neuron more sensitive to stimuli = responds more than it would
          - Change in type of Na+ channels and increase in density
          - Changes in TRPV1 receptors
  - Stimulation of nociceptor endings
    - Drives upper order neurons to increased activity
    - Activation of axon collaterals that release neuropeptides in the periphery (axon reflex)
      - Results in vasodilation, increased BV permeability, histamine release
      - Drives the release of inflammatory mediators (increased neuroinflammation)
- 2) High level of activity in 1st order neurons
- 3) Increased excitability of 2nd order neurons
  - **Central sensitization**
- 4) Activation of nociceptive pathways (**ALS** = body) by nociceptive inputs and non-nociceptive inputs
  - **Allodynia** – patient feels pain in response to non-painful stimulus
- 5) As a result of peripheral and central sensitization = **hyperalgesia**
  - Increased sensitivity to pain
- How to stop vicious cycle?
  - Stop peripheral sensitization = stop the drive of the system
    - This is due to inflammation (prostaglandins)

Targets of Non-Opioid Analgesics = **Prostaglandins**

- Tissue injury activates phospholipases -> release of arachidonic acid
    - Arachidonic acid metabolized by
        - Lipoxygenases
            - Leukotrienes – vasoconstriction, bronchospasm, increased vascular permeability, chemotaxis
            - Lipoxins – vasodilation, decreased neutrophil adhesion, decreased chemotaxis
        - **Cyclooxygenase**
            - **Prostaglandins** (target = smooth muscle)
                - Vasodilation, increased vascular permeability = symptoms of inflammation
                    - EDEMA
            - **Prostacyclin** (in the endothelium)
                - Vasodilation
                - Decreased platelet aggregation
            - **Thromboxane A2** (in platelets)
                - Vasoconstriction – aids hemostasis
                - Increased platelet aggregation
- Treatment: **Steroids**
    - Target = phospholipases
- Treatment: **NSAIDs**
    - Target = **Cyclooxygenase**
        - COX-1 = constitutively expressed
            - GI tract = PGE1 = protective effect on gastric mucosa
                - This is why NSAIDs are irritating for the stomach (block COX-1)
            - Kidney = Prostaglandins modulate GFR, effect on afferent/efferent arteriole
                - Decrease the efficacy of diuretics – interfere with normal effect of prostaglandins
            - This is why NSAIDs have adverse effects in addition to anti-inflammatory effects
        - COX-2 = inducible (e.g., inflammation)
            - This is the one we want to block; desired effect
    - *Not responsible for names of individual NSAIDs*
        - Know that they differ in potency with COX-1 vs COX-2
            - COX-1 = protects gastric mucosa = NSAIDs not good for gastric irritation
- *Note*: Opioids simply block transmission of pain, nothing about the mechanism of pain
    - NSAIDs target inflammatory response
    - Steroids work higher up in pathway

NSAIDs

- Mechanism of action and therapeutic effects:
    - **Anti-inflammatory**
    - **Anti-pyretic**
    - **Analgesics** – related to sensitization mechanism (prostaglandins)
    - **Anti-platelet**
- Dental indications
    - Acute pain, mild to moderate post-procedural pain, TMJ disorders
- Adverse effects (*Note:* selectivity of COX-1 vs COX-2)
    - **GI bleeding**

        - Side effect because this is *dose-dependent* (higher risk of GI bleeding with increased dose)
    - Interactions with other drugs (diuretics and triple therapy and B-blockers)
        - *Note*: Previous lectures in more detail

Acetaminophen (Not an NSAID)

- Compared with Aspirin
    - Anti-pyretic = equivalent potency and efficacy
    - Analgesic = equivalent potency and efficacy
    - ***Anti-inflammatory = very weak (if any)***
    - ***Anti-platelet = no effect***
- Indications
    - Antipyretic analgesic of choice when NSAIDs cannot be used due to contraindications
    - Antipyretic of choice in children
    - Post-operative dental pain (less likelihood of inflammation)
        - Same effectiveness of aspirin
- Adverse effects (few side effects compared to NSAIDs) = but **toxic effects** (when recommended dose is exceeded)
    - Overdose: Liver damage

Session 19: Clinical Problem Set #9 (*1-2 questions*)

1. How would you manage this patient's acute pain needs? **Managing the tooth problem with LA**
    a. "The best set of therapies to offer:"
        i. **1-LA and pulpectomy/extraction, 2-NSAID, 3-Opioids, 4- Acetaminophen**
            1. *Treat the cause – manage the tooth problem with LA*
            2. *There are some contraindications to NSAIDs, but they treat inflammation (acute pulpitis)*
                a. *This is why Acetaminophen won't help (4th choice)*
    b. Would you prescribe opioids that she is asking for? If so, what interactions do you expect with Codeine?
        i. No, the patient is taking **Quinidine**
    c. Which class of analgesics should be used with caution in this patient? Why?
        i. **NSAIDs** – taking Warfarin, Valsartan, Sotalol
    d. The patient reports being in pain despite treatment with Tylenol. How efficacious do you expect Acetaminophen to be for this condition?
        i. **Acute pulpitis = inflammation**
            1. **Tylenol is not an NSAID** and does not have anti-inflammatory effects
2. Why is the patient taking Warfarin? If the doctor prescribed an NSAID, what mechanisms of interaction between the NSAID and Warfarin do you expect? Please list at least three. What would be the clinical consequence of each interaction if Warfarin dose remain unchanged?
    a. Taking Warfarin because need **anti-coagulation for DVT**
    b. "The following are the consequences of NSAID-Warfarin interactions EXCEPT:"
        i. Increased INR due to competition for CYP2C9
        ii. Increased risk of peptic ulcer due to competition for CYP2C9
        iii. **Increased blood coagulation due to increased binding of Warfarin to plasma alpha-1 acid glycoprotein**
        iv. Increased risk of bleeding due to impaired primary and secondary hemostasis
        v. Increased anti-platelet effect due to decreased binding of NSAIDs to plasma Albumin
    c. Warfarin + NSAID

        i. 1) NSAID block COX = decrease prostaglandins and thromboxane = reduced platelet aggregation = increased risk of uncontrolled bleeding
        ii. 2) Increase the INR
        iii. 3) Compete for protein binding = higher fraction of the drug becomes available (more free Warfarin = increased distribution)
3. What other drug interactions with NSAIDs do you expect in this patient?
    a. **Renovascular HTN** = stenosis of renal artery = increased risk of renin
        i. RAA inhibitors = **Valsartan** (AT1 blocker), **Lisinopril** (ACE inhibitor)
        ii. Interaction = blunted effects = increased blood pressure with addition of NSAID
        iii. **Sotalol** (B-blocker) = risk of lesser effect of CV drugs
4. A sedative dose for this patient should be:
    a. Higher
    b. Lower
    c. The same (i.e. standard dose)
        i. *Drug dose doesn't have to be modified unless the drug is highly bound to proteins (i.e. Benzodiazepine)*
        ii. *If highly bound to proteins, the dose has to be modified*
            1. *Patient is taking Warfarin = need to look at interaction/competition for Albumin*
            2. *If benzodiazepine is highly protein bound, need less dose*

Quiz from Session 18-19:

1. The primary target of Opioids in the Trigeminal Pain Pathway is/are:
    a. Na channels in free nerve endings
    b. Subnucleus Caudalis of the Spinal Trigeminal Nucleus
    c. **The Insula** – *Cingulate and Insular Cortex; also targets Subnucleus Caudalis and free nerve endings*
    d. Trigeminothalamic Tracts
    e. TRPV1 receptors in free nerve endings
2. The burning sensation that your patient may experience during the injection of a LA is most likely mediated by:
    a. **Activation of TRPV1 receptors by the acidic medium of LA**
    b. Transient activation of voltage-gated Na channels on trigeminal nociceptor endings
    c. Psychological factors
    d. Sensitization of trigeminal nociceptors by mechanical stimuli, such as poking with a needle
    e. Vasodilation caused by the LA and the resulting increase in the blood flow through the area
3. Which of the following is an analgesic and antipyretic drug that lacks an anti-inflammatory action?
    a. **Acetaminophen**
    b. Apixaban
    c. Clopidogrel
    d. Codeine, an opioid analgesic – *Codeine is an analgesic without an anti-inflammatory action, but it is not an antipyretic*
    e. Ibuprofen, a non-steroidal anti-inflammatory drug
4. The direct, well-established action of non-steroidal anti-inflammatory drugs (NSAIDs) targets the following mechanism(s) of nociception:
    a. Allodynia
    b. Central sensitization
    c. **Peripheral sensitization**
    d. All of the above are correct answers
    e. Only A and B are correct answers