Final Exam (2 hours):

- 50 questions total, each worth 2 points (100 points total); 4 choices – answer options
  - 2 questions per Lecture (18 lectures) = 36 questions
  - 1-2 questions per Clinical Problem Set (10 cases) = 14 questions

- 40 questions (80%) – Must Know (understand and show ability to apply)
- 10 questions (20%) – Integrative (show ability to analyze and evaluate)

- 70% correct (35 questions – 70 points) – required to pass the course
- 92% correct (46 questions – 92 points) – required to receive an LOC

Know these equations (*will not be provided*):

$$Cp = \frac{Dose}{V_d}$$

$$Cp_{ss} = \frac{Dose\ Rate}{CL}$$

$$Loading\ Dose = \frac{target\ Cp \times V_d}{F}$$

$$Maintenance\ Dose\ Rate = \frac{target\ Cp_{ss} \times CL}{F}$$

$1\ t_{1/2}$ – **50%** drug is eliminated
$2\ t_{1/2}$ – **75%** (50% + 25%) drug is eliminated
$3\ t_{1/2}$ – **87.5%** (50% +25% + 12.5%) drug is eliminated
$4\ t_{1/2}$ – 93.75% (50% + 25% + 12.5% + 6.25%) drug is eliminated

Practice Questions (from Session 12/13):

1. Bradycardia is a likely effect of treatment with the following drugs, EXCEPT:
   a. Amiodarone – *anti-arrhythmic; side effect (associated with dose) = bradycardia*
   b. **Hydralazine** – *direct vasodilator; vasodilation = decreased BP; similar to nitrate, risk of increased HR due to baroreceptor mechanism = tachycardia (dangerous = increased risk of cardiac ischemia)*
   c. Propranolol – *anti-arrhythmic; side effect (associated with dose) = bradycardia*
   d. Quinidine – *anti-arrhythmic; side effect (associated with dose) = bradycardia*
   e. Sotalol – *anti-arrhythmic; side effect (associated with dose) = bradycardia*
2. Your patient is treated with: 1) Isosorbide dinitrate, 2) Sotalol, 3) Enalapril, and 4) Hydrochlorothiazide. The most comprehensive set of likely diagnoses is: (*Be familiar with this format for exam*)
   a. Angina pectoris, atrial fibrillation, bradycardia, congestive heart failure
      i. *Don't want to give Sotalol to a patient with Bradycardia*
      ii. *Angina pectoris = nitrate (Isosorbide Dinitrate)*
      iii. *Afib = Sotalol*

iv. *CHF = hydrochlorothiazide (diuretic), Enalapril (ACE inhibitor)*

b. Angina pectoris, atrial fibrillation, diabetes insipidus, hypertension
   i. *Diabetes insipidus = condition due to insufficient ADH (vasopressin) = wouldn't give diuretic*
c. **Angina pectoris, atrial fibrillation, hypertension, peripheral edema**
d. Bradycardia, congestive heart failure, diabetes insipidus, peripheral edema
e. Congestive heart failure, diabetes insipidus, hypertension, peripheral edema

Clinical Case Scenario:

PHC721 - CLINICAL PROBLEM SET # 10

Patient
Male, 62 years old
Chief Complaint
"Last week, I lost a filling in my lower tooth on the right side."
Background and/or Patient History
Atherosclerosis; Diabetes, Type 2, poorly controlled; Diabetic neuropathy; Myocardial Infarction (6 years ago); Obesity; Peptic Ulcer Disease; Alcohol abuse (> 10 years); Smokes tobacco, 40-pack-years Medications: Cimetidine (Tagamet®), H2 receptor antagonist Clopidogrel Digoxin Metformin, anti-diabetic, 500 mg twice daily Propranolol
Current Findings
Acetone smell in patient's breath. A missing filling in #30 – restorable. Temp: 98.8 F BP: 120/75 mmHg HR: 64 bpm 240 lb; BMI: 35

1. How would the patient's systemic health condition affect the local anesthesia administered for the tooth restoration procedure?
A. Upon contact with the extracellular fluid, is the ionized fraction of the local anesthetic expected to be larger or smaller?
B. Is the onset of the anesthesia expected to be normal, faster or slower?

2. Propranolol is a weak base, highly bound to plasma proteins (primarily alpha-1-acid glycoprotein), non-selective competitive antagonist of beta-adrenergic receptors. It is known to reduce hepatic blood flow.
If a poorly-trained dentist decided to use Lidocaine with Epinephrine for local anesthesia in this patient:
A. How would the efficacy, potency, Emax, and EC50 of Epinephrine acting through beta-adrenergic receptors be affected by Propranolol?
B. How would the risk of Lidocaine systemic toxicity be affected by Propranolol? Please explain the underlying mechanisms.

3. What are other patient-related factors or medications that would be likely to affect the severity of a potential systemic toxicity of Lidocaine?

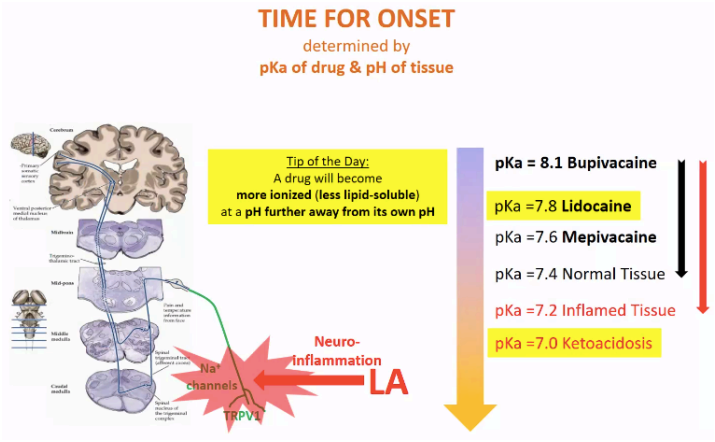
4. What are other potential drug interactions in this patient?

5. Metformin (CL 500 mL/min, Oral Bioavailability (F) 50%), is excreted unchanged by the kidney.
A. Assuming the patient takes Metformin as prescribed (no skipped doses or increased intervals between doses) and there are no patient- or drug-related modifiers, what is the expected plasma concentration of Metformin?
B. How would the plasma concentration of Metformin be affected by other conditions or medications of this patient?

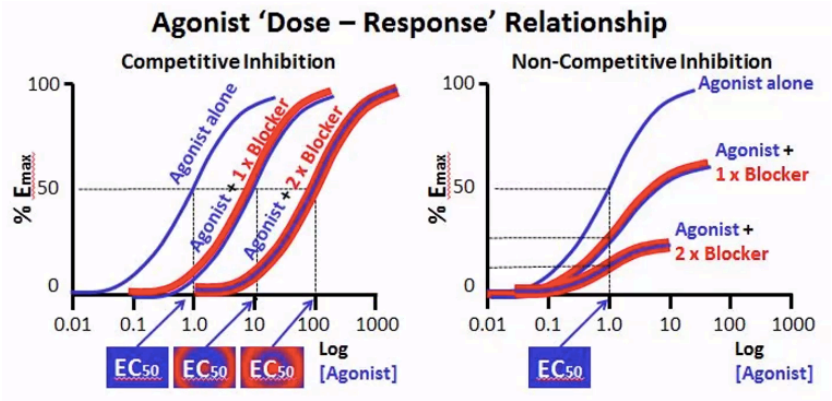
6. PHARMACODYNAMICS BONUS:
Imagine you have a full arsenal of agonists and antagonists (competitive and non-competitive) for: **1)** the receptor mediating desired (therapeutic) actions of a drug, and **2)** the receptor responsible for the drug's toxic effects. Which of the pharmacological tools would you use to **increase the Therapeutic Index** of that drug?

1. How would the ionized fraction of Lidocaine (pKa 7.8) and the onset change by pH drop from 7.4 to 7.0? (*Ketoacidosis*)
   a. Ionized fraction decreases; Faster onset
   b. Ionized fraction decreases; Slower onset
   c. Ionized fraction increases; Faster onset

d. **Ionized fraction increases; Slower onset** – *farther away from own pH = more ionized = slower onset*

i. 

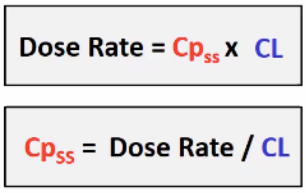
2. Propranolol is expected to have the following effect on Epinephrine acting through beta-adrenergic receptors:
    a. Decrease efficacy and Emax
    b. Decrease Emax and increase EC50
    c. Decrease potency and EC50
    d. **Decrease potency and increase EC50** – *Propranolol is a non-selective <u>competitive</u> antagonist = Emax doesn't change, but EC50 increases (potency decreases); Note that non-competitive antagonist = Emax (efficacy) decreases, but EC50 remains the same (potency doesn't change)*

    i. 

3. List one mechanism of Propranolol-mediated risk of Lidocaine toxicity.
    a. ***Plasma protein binding***
        i. *Propranolol is basic – propranolol binds to alpha-1 acid glycoprotein; competes with lidocaine for binding sites*
        ii. *Leads to more lidocaine available in free form = more likely to cause toxicity*
    b. ***Decreased blood flow through the liver***
        i. *Lidocaine = fast metabolism through liver = rate limited by blood flow*
        ii. *Propranolol decreases hepatic blood flow*
            1. *Lidocaine metabolism decreased = increased toxicity*
4. List one patient factor/medication increasing the risk of Lidocaine toxicity.

a. ***Cimetidine*** *= potent inhibitor of enzymes*
b. ***Alcoholism*** *= liver damage (cirrhosis) = decreased capacity to metabolize drugs*
c. ***Digoxin*** *= most likely for CHF = decrease blood flow through liver*

5. List other potential drug interactions in this patient.
    a. ***Cimetidine =*** *affects enzymes (stated above)*
    b. ***Propranolol + Clopidogrel*** *= decrease blood flow through liver*
        i. *Impact clopidogrel since it is a prodrug that needs to be activated by the liver*
6. Patient takes Metformin, 500-mg twice daily. CL is 500 mL/min and oral bioavailability (F) is 50%. What is the expected plasma concentration? (*Be careful of oral bioavailability and units*)



Dose Rate = 500 mg x 2 tablets / 24h = 1000 mg/24h,
but 50% Bioavailability ⇒ 500 mg/24h

CL = 500 mL/min = 0.5 L/min = 30 L/h

Cp_{SS} = 500 mg/24h / 30 L/h = 0.69 mg/L

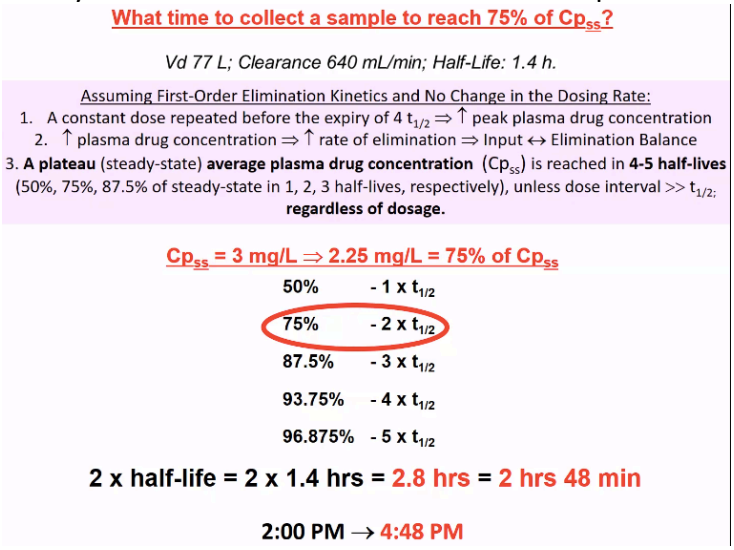
a.

7. The Therapeutic Index of a drug is most likely to be improved by adding a highly selective:
    a. Competitive antagonist of the receptor responsible for the drug's therapeutic effect
        i. *Therapeutic Index = Median Toxic Dose (TD50)/Median Effective Dose (ED50)*
        ii. *Competitive antagonist = increased EC50 (potency) = would decrease Therapeutic Index since larger drug dose is needed for same therapeutic effect*
            1. *Would also increase toxic effect*
    b. Non-competitive antagonist of the receptor responsible for the drug's therapeutic effect
        i. *Non-competitive antagonist = decrease Emax = decreased therapeutic effect per given dose; Therapeutic Index will only be improved if the dose is decreased but still have the same effect*
    c. **Competitive antagonist of the receptor responsible for the drug's adverse effects**
        i. *In order to get the same toxic effect, would need to increase the dose of the drug -> increased toxic dose*
            1. *Higher toxic dose (numerator) = higher Therapeutic Index*

d. Non-competitive antagonist of the receptor responsible for the drug's adverse effects
    i. *Wouldn't affect the TD50*
e. Both B and D are correct answers

Midterm Quiz Recap:

8. When treating a 5 y/o girl with a middle ear infection, the antibiotic dosage formulation most acceptable to her would likely be: (*Note: These types of question will not be on the exam*)
    a. Tablet
    b. Capsule
    c. **Oral suspension**
    d. IM injection
9. IV Lidocaine (Vd 77L; Clearance 640 mL/min; Half-life: 1.4 h); Cpss is 3 mg/L. The infusion started at 2:00pm. What time to collect a sample to see Cp 2.25 mg/L? (*Note: On the exam, the calculations won't be this complicated*)
    a. 3:40pm
    b. **4:48pm**
    c. 5:20pm
    d. It is necessary to know the dose of Lidocaine infused per unit of time
    i.



10. Oral bioavailability of a weak base (pKa=8.0) that undergoes first-pass metabolism in the intestinal wall will be increased when: (*Key piece = intestinal wall = competition in the intestinal wall, not the liver*)
    a. pH in the intestine is lowered to 5.5
        i. *pKa = 8 = basic; So lowering the pH to 5.5, weak base will be more ionized = less likely to absorbed; bioavailability will decrease (not increase)*
        ii. *This is the opposite for acidic drugs (i.e. Aspirin)*
    b. **The drug is administered together with a drug undergoing the same type of first-pass metabolism**
        i. *Competition with drug with same type of first-pass metabolism*

c. The drug is administered together with a drug undergoing hepatic first-pass metabolism
    i. *Hepatic first-pass metabolism = no competition = less likely to increase the availability of the drug*
d. The patient has recently had a widespread MI of the left ventricular wall
    i. *When there's a question referring to MI think of CHF*
    ii. *Risk of CHF = edema in periphery (=intestines) = increased diffusion distance = decreased bioavailability*

11. A drug with LogP = 5 and 60% binding to plasma proteins is likely to have its Volume of Distribution DECREASED in:
    a. **Congestive heart failure** – *less ability for the drug to be "pushed" to peripheral tissues; more of it remains in circulation = VoD decreased due to decreased perfusion of drug to tissues*
    b. Liver cirrhosis – *No; liver cirrhosis = decreased plasma protein levels due to decreased protein synthesis; Decreased plasma protein = less drug binding to proteins, more free = VoD increased*
    c. Obese patients – *Lipophilic drug (high LogP) so VoD would increase because more of it would stick to lipophilic tissue*
    d. Patients chronically treated with Warfarin – *Competition for plasma proteins -> Warfarin would cause more free drug levels = increased VoD*
12. A highly water-soluble drug is excreted unchanged by the kidneys. Please identify the condition that is likely to increase the drug's clearance.
    a. Congestive heart failure – *Would decrease the clearance because of decreased perfusion through kidney*
    b. Kidney failure – *Since the drug is eliminated through the kidney, kidney failure would lead to decreased GFR*
    c. Liver cirrhosis – *No effect on clearance since drug is excreted unchanged (doesn't undergo metabolism in liver)*
    d. **Pregnancy** – *increased GFR*
13. The phenomenon of Pharmacokinetic Tolerance is likely to be evoked by:
    a. Drugs that inhibit hepatic first-pass metabolism – *Inhibited metabolism = active form stays longer = body would not be able to tolerate more of the drug*
        i. *Tolerance = need to add higher dose of the drug since the previous drug is "taken care of" by hepatic metabolism*
    b. Drugs that inhibit hepatic CYP450 enzymes
    c. **Drugs that induce hepatic metabolism** – *Induced metabolism = more quickly eliminated = can add more of the drug*
    d. Antibody binding to the drug – *considered Pharmaco<u>dynamic</u> Tolerance since Ab is binding to the drug receptor (can be considered a correct answer, but think of best answer)*
14. An advanced age of the patient is likely to be associated with:
    a. Enhanced drug absorption due to increased intestinal wall motility – *would decrease motility and drug absorption*

b. Increased drug metabolism due to upregulation of hepatic CYP450 enzymes – *would decrease drug metabolism due to decreased liver function*
c. **Decreased plasma protein binding of drugs** – *decreased protein binding is true due to decreased levels of proteins*
d. Decreased elimination half-life of drugs – *would increase elimination half-life*

15. Please identify the correct statement about Clopidogrel (an antiplatelet agent activated by hepatic metabolism)
    a. Its dose may need to be reduced in patients with advanced liver cirrhosis – *No, liver is working less effectively, want to increase dose*
    b. Its dose may need to be reduced in patients carrying CYP2C9 point mutation – *Mutation would decrease effectiveness of drug, want to increase dose*
    c. **Its potency is likely to be decreased in patients treated with Propranolol, which decreases hepatic blood flow** – *Decreased hepatic blood flow = less activation of drug = decreased potency*
    d. Its potency is likely to be increased in patients with congestive heart failure – *CHF decreases blood flow = decreased potency*