Therapeutic Drug Monitoring

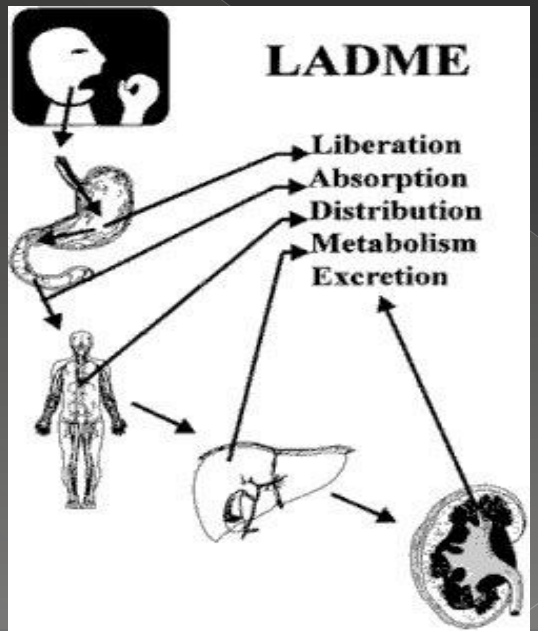
Hereafter TDM, you're welcome

Therapeutic Drugs

- Some drugs have different therapeutic and toxic doses (hard to OD on THC)
  - Therapeutic Range
  - Some drugs have narrow differences between therapeutic and toxic
- Drug-drug interactions for complex therapies
- Disease States may change levels

Definitions

- Pharmacodynamics
  - What the drugs do to the body
- Pharmacokinetics
  - What the body does to the drug
- CLADME
  - Compliance
  - Liberation
  - Absorption
  - Distribution
  - Metabolism
  - Excretion



Compliance

- Single largest reason for insufficient drug levels
  - Patients deciding to change dosage
    - Expensive drugs
    - Not seeing effects quickly enough
    - Complex dosage regimen

Liberation

- Release of drug from dosage form
  - Tablets, capsules, syrup etc is not immediately absorbable
    - Liberation allows for absorption of active compounds

Absorption

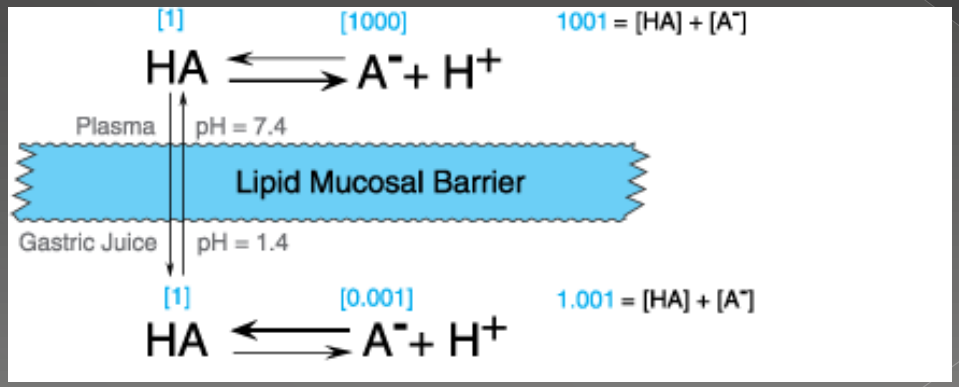
- Different depending on route of administration
  - Oral, IM, IV, topical, suppository
  - Factors affecting absorption
    - Solubility
    - Stability/pH
    - Drug-drug interactions
    - Nutritional status

Absorption

- If it has to go past the liver only some makes it
  - Bioavailability inversely related to hepatic extraction rate
  - Small intestine $\xrightarrow{\text{portal vein}}$ liver

Absorption

- A brief reminder about pH
  - pKa = ½ species is protonated
    - Above pKa drug isn't protonated
    - Below pKa drug is protonated
- In order to cross lipid bilayers, drugs must be UNCHARGED



Examples

- Aspirin (a weak acid)
  - At low pH is protonated
    - Neutral
  - Absorbed in the stomach
- Morphine (weak base)
  - At low pH is protonated
    - + charge
  - Cannot be absorbed in stomach

Distribution

- Binding to plasma proteins
  - Bound drugs exert no effect
  - Free drugs are active drugs!
    - Different drugs have different affinity for proteins
  - Disease states will affect this process

Distribution

- Capillary pores

	Pore diameter (Å)
Intestinal epithelium	**4**
Capillary endothelium	**40-80**
Muscle capillaries	**60**
Glomerular capillaries	**75-100**
Glomerular endothelium	**1000**
Liver capillaries	**1000**

Distribution

- Perfusion Rates where does most of your blood go?

Organ	Perfusion rate (mL/min/mL of tissue)	Percent of cardiac output
Bone	**0.02**	**5**
Brain	**0.5-0.55**	**14-15**
Fat	**0.01-0.03**	**2-4**
Heart	**0.6-0.7**	**4**
Kidneys	**4.0-4.5**	**22-24**
Liver	**0.8-0.95**	**25-27**
Muscle	**0.025-0.030**	**15**
Skin	**0.04-0.05**	**5-6**

Distribution

- Recap of distribution
  - Lipid solubility
    - Must cross membranes
    - pH
  - Capillary permeability
  - Blood perfusion
  - Volume of distribution
    - $V_d = D/C_t$
      - D= dose in mg/g
      - C_t= concentration in mg/L or g/L

Metabolism

- Liver contains enzymes
  - Converts non-polar drug to polar contents of urine
    - Phase I: Modify Chemical Structure
    - Phase II: Conjugate to another species
    - Phase III: Take over the world
  - Metabolism affected by:
    - Age, weight, gender, genetics, disease, GI disorder, nutrition, other drugs

Drug vs. Drug

- Every drug has its own binding affinity for respective enzymes
  - Some drugs share enzymes (sharing is caring!)
  - This can lead to large amounts of the drug with lower affinity building up due to slowed metabolism

Elimination

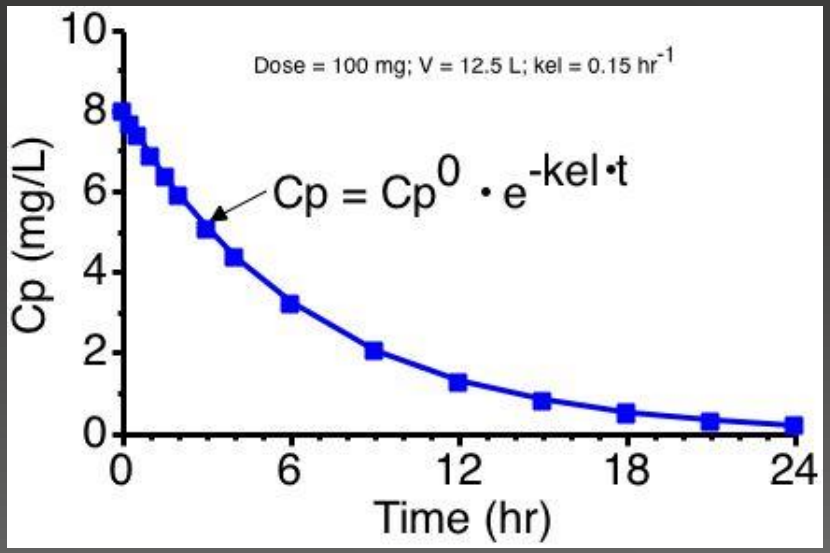
- Elimination of the actual drug
  - Only the free drug can be filtered
    - Hitching a ride on albumin is like hiding in the laundry cart to escape prison
  - Some drugs can be actively secreted
  - Some drugs can be reabsorbed by the tubules
- Polar conjugates are easily cleared by the kidney

Elimination

- Kinetics is back!
  - LOW drug concentration
    - Elimination depends upon drug concentration
      - ½ life is constant
      - Occurs when only some of the enzymes are occupied

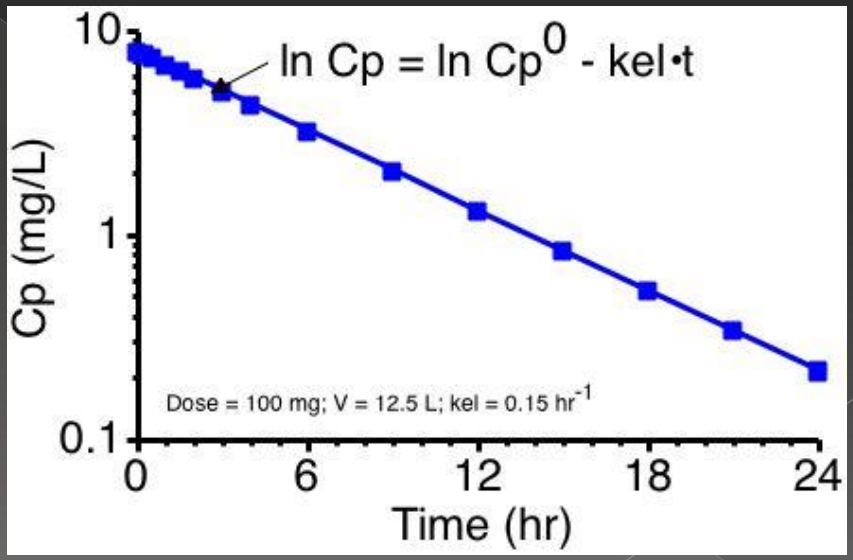
First Order Elimination

Concentration vs. time



Concentration falls **exponentially** with time

LOG Concentration vs. time



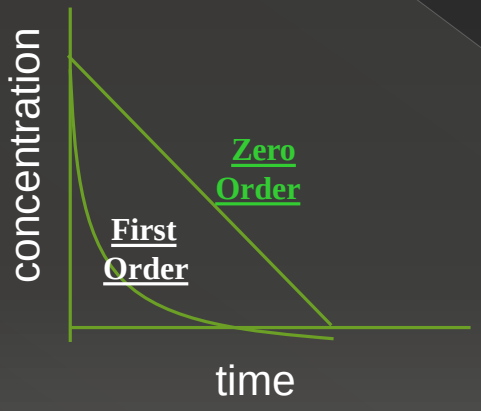
Log of concentration is linear

Elimination

- Kinetics is back!
  - HIGH drug concentration
    - Elimination is independent of drug concentration
    - ½ decreases with decreasing concentration
    - Common with drugs that are extensively metabolized
      - Enzymes become saturated, limited cofactors available

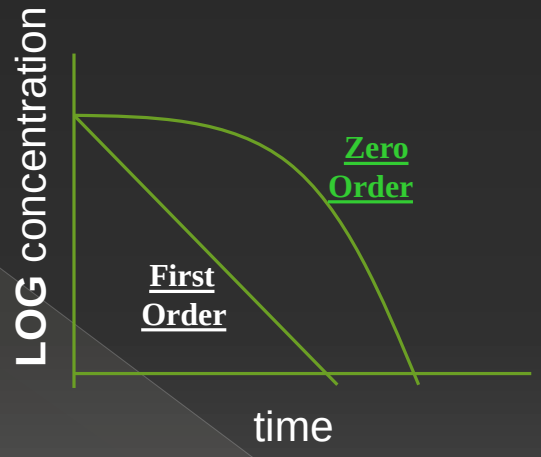
Zero Order Elimination

Concentration vs. time



Zero order plot is linear

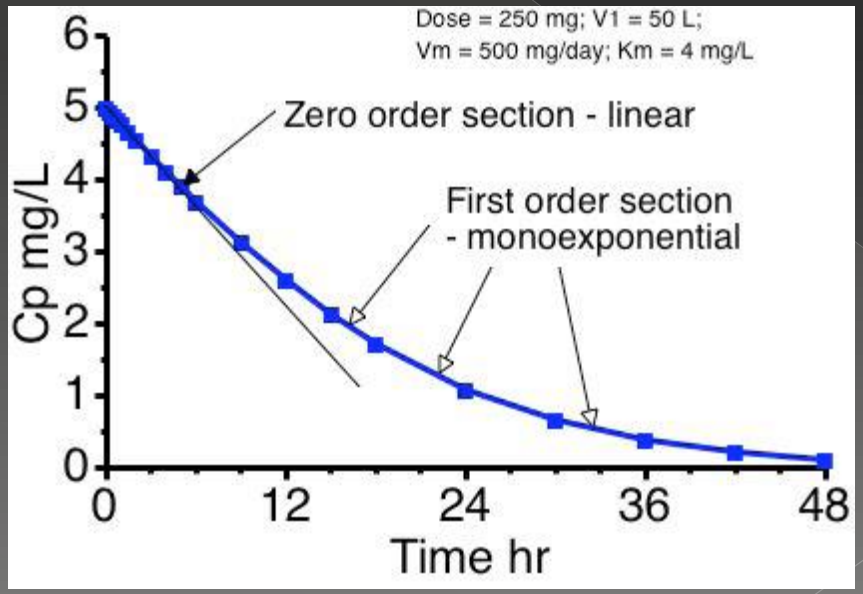
LOG Concentration vs. time



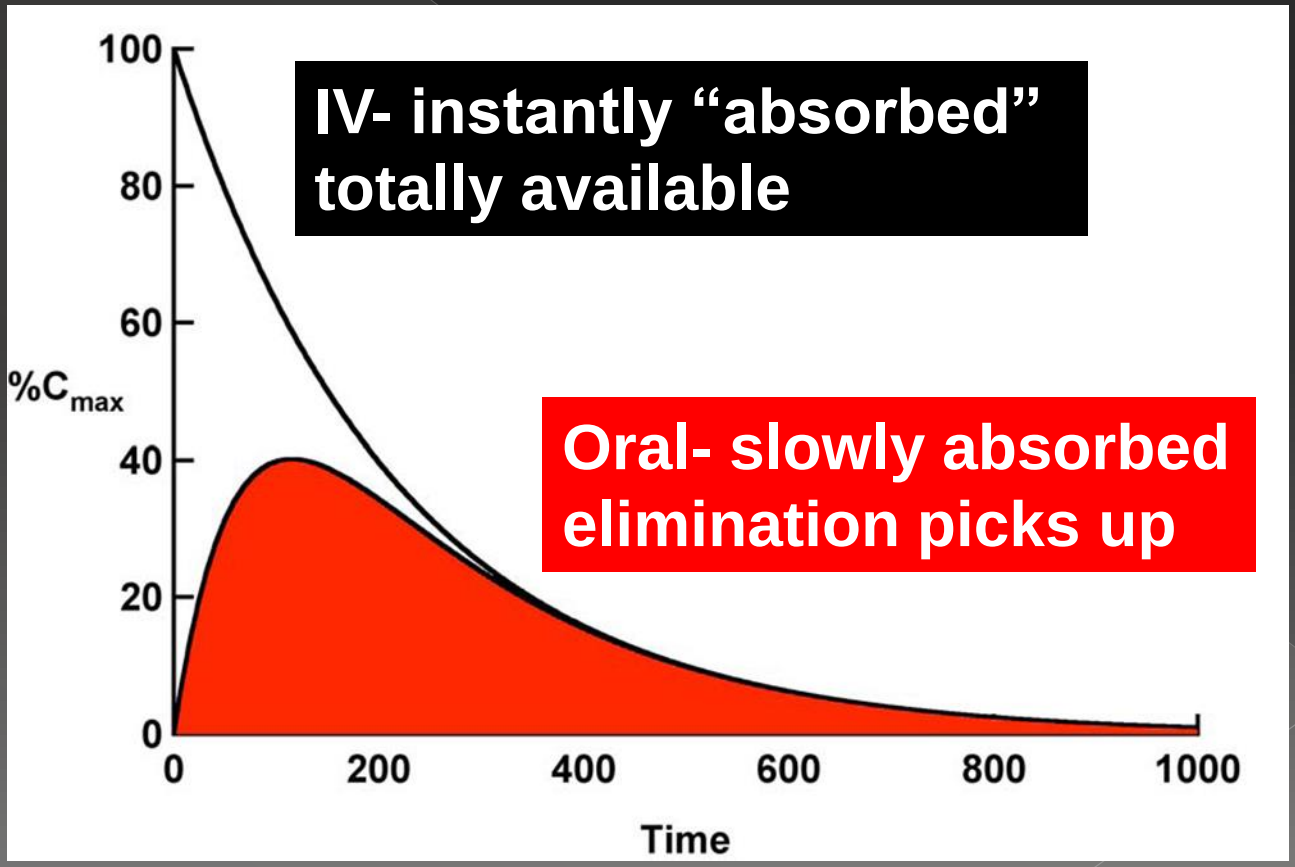
Zero order plot is **not** linear

Reality of Elimination

- Combination of zero→first order elimination
  - Start out high, go to low

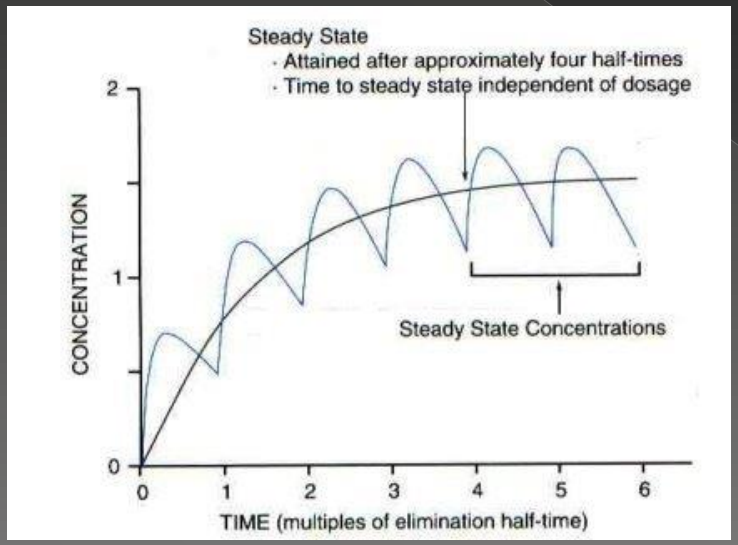


The Full Picture



What is the goal?

- Steady state kinetics
  - Rate in = rate out
    - Usually take 4-7 half-lives
    - Not actually steady, but it bounces between 2 points

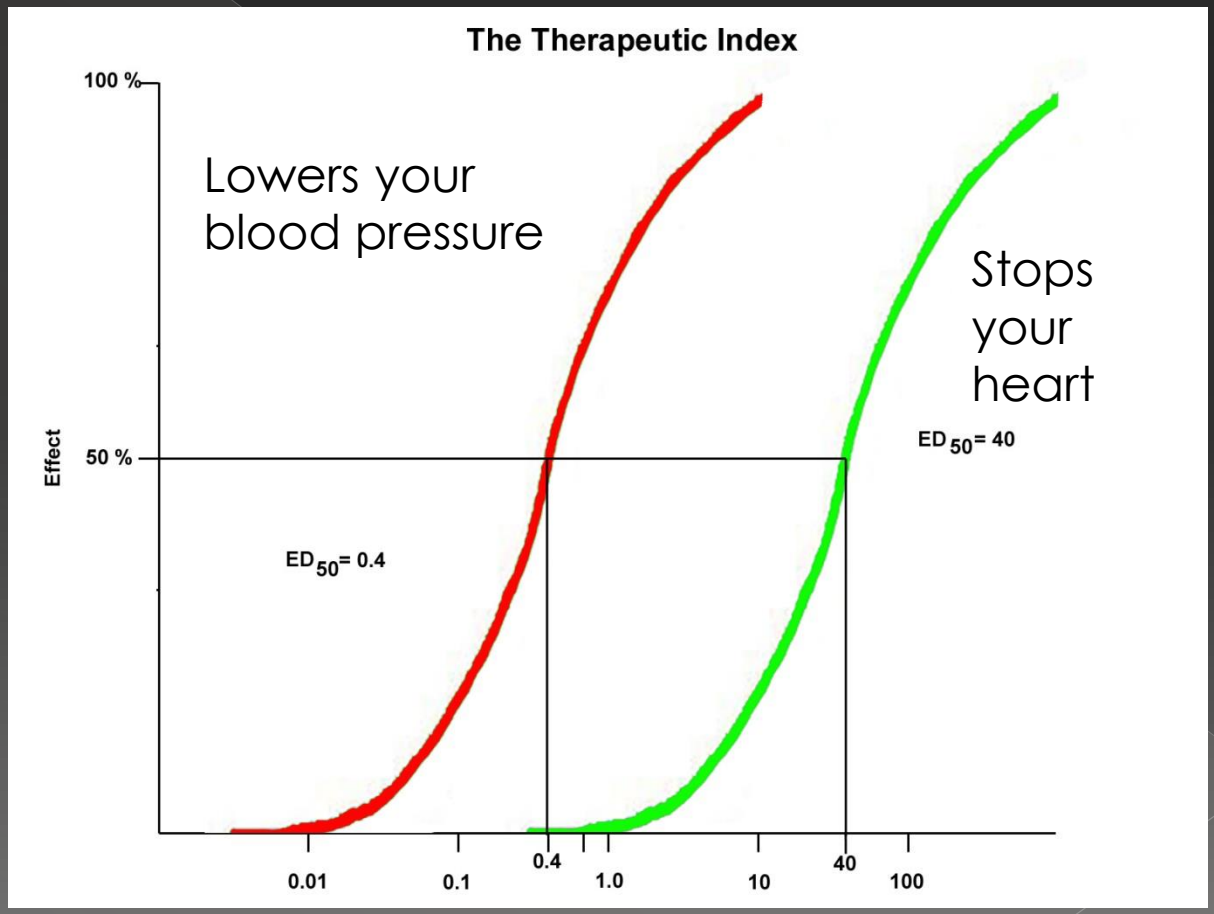


Therapeutic Drugs

- Why do TDM?
  - ID non-compliance
  - Prevent OD/UD
  - Maximize therapeutic effect
    - Unpredictable dose/response relationship
    - Very toxic drug
  - Optimize dose regimen, control for physiological differences
    - Protein binding
    - Renal function
    - Hepatic function

Therapeutic Drugs

- Therapeutic Drug Ranges
  - Aka Therapeutic index
  - Ratio between toxic dose and therapeutic dose
  - Therapeutic Range= $\frac{TD\ 50}{ED_{50}}$


The Therapeutic Index
100 %
50 %
Effect
Lowers your blood pressure
Stops your heart
ED 50= 0.4
ED 50= 40
0.01
0.1
0.4
1.0
10
40
100

Therapeutic Drugs

- Digoxin
  - Cardiac glycoside derived from digitalis
    - Increases strength of cardiac contraction
    - Treats CHF
    - Measure 8-10 hours after dose for peak
      - Most drugs are 2-3 hours
      - Digoxin sequesters inside myocytes
    - Digibind
      - Antidote: Ovine Anti-Digoxin
        - Only free-digoxin should be ordered

Therapeutic Drugs

- Quinidine (antiarrhythmic)
  - Sulfate = immediate 2 hrs
  - Gluconate = slow release 4-5hrs
    - Cause nausea, vomiting, abdominal discomfort
    - Usually only need to make sure it is *at least* therapeutic

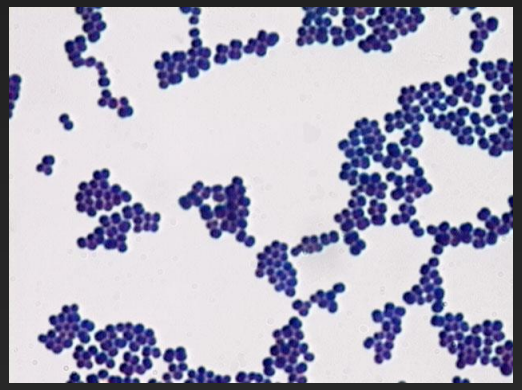
Therapeutic Drugs

- Procainamide (antiarrhythmic)
  - Rapidly absorbed ~1 hr
  - *N*-acetylprocainamide
    - Hepatic metabolite, still antiarrhythmic
    - Must take into account this metabolite
- Disopyramide(antiarrhythmic)
  - Used when adverse effects found to quinidine
  - Patients with low GFR will be extra slow to clear

Therapeutic Drugs

- Aminoglycosides (gram – antibiotic)
  - Next level antibiotics (bring out the big guns)
    - Gentamicin, tobramycin, amikacin, kanamycin
  - Nephrotoxic, ototoxic
    - Some irreversible
  - Not well absorbed from GI tract
    - IV and IM administration
  - Peaks *AND* trough measured

Therapeutic Drugs



- Vancomycin (gram + antibiotic)
  - Glycopeptide (GPC and bacilli)
  - Poor GI absorption, IV administration
  - Some toxic effects occur in therapeutic range!
    - Red Man Syndrome
      - Mast cell degranulation (no IgE)
    - Nephrotoxic, ototoxic
      - Usually only trough measured

Therapeutic Drugs

- Phenobarbital (anti-seizure)
  - Slow oral absorption ~ 10 hrs
    - Compromised renal or hepatic patients will be slow to eliminate
    - Only trough levels usually taken
    - Downiness, fatigue, depression, reduced mental capacity
    - Induces MFO system, up dosage after 2 weeks
      - Primidone- Inactive prodrug, you make the phenobarbital

Therapeutic Drugs

- Phenytoin (anti-seizure) Dilantin
  - Variable GI absorption
    - Variable protein binding capacity too
      - Easily displaced by other drugs
  - Odd side-effects
    - Hirsutism, gingival hyperplasia, Vit D & folate def.
  - MFO inducer

Therapeutic Drugs

- Valproic acid (anti-seizure) Depakote
  - Rapid and complete absorption
    - Many drug-drug interactions
    - Nausea, lethargy, and weight gain
      - Pancreatitis, hallucination, hyperammonemia with further increased levels
- Carbamazepine (anti-seizure) Tegretol
  - Induces own metabolism
    - Diverse Side effects (leukopenia, vertigo, rash)

Therapeutic Drugs

- Gabapentin (anti-seizure)
  - Bioavailability decreases with antacid use
- Levetiracetam (anti-seizure)
  - Not usually monitored unless pregnant
- Oxcarbazepine (anti-seizure)
  - Prodrug metabolized to licarbazepine

Therapeutic Drugs

- Lithium (anti-mania)
  - Ingested as salt (carbonate) Li_2CO_3
  - Distributes throughout all water-based compartments
  - May cause lethargy, speech difficulty, weakness
    - With more, rigidity, seizures, coma
  - ISE, flame emission photometry, AAS

Therapeutic Drugs

- Tricyclic Antidepressants (guess)
  - Original anti-depressants
    - Amitriptyline, doxepin, imipramine most important
      - Imipramine → Desipramine (also active)
      - Amitriptyline → Nortriptyline (also active)
    - Effects not seen for 2-4 weeks
      - Drowsiness, constipation, blurred vision
      - Seizure, arrhythmia, unconsciousness at higher dose
    - Polyclonal antibodies will detect many TCAs
      - Total TCAs

Therapeutic Drugs

- Clozapine (antipsychotic)
  - Treatment-refractory schizophrenia
    - Check for compliance, altered pharmacokinetics
- Olanzapine (antipsychotic)
  - Schizophrenia, acute mania
    - Men and smokers tend to metabolize faster

Therapeutic Drugs

- Cyclosporine (immunosuppressant)
  - Absorption of cyclosporine between5-50%
    - TDM important to establish dose
  - Cyclosporine is sequestered into RBCs
    - This is done in temperature dependent manner
      - Instead of trying to make sure we keep it a certain temp, we just test whole blood
  - Heart, liver, pancreas Tx require highest levels

Therapeutic Drugs

- Tacrolimus (FK-506)
  - Discovered in fungus from Japan
    - Thought to have low toxicity
      - Whoops…
    - Nephrotoxicity similar to cyclosporine
      - Metabolic products eliminated into bile

Therapeutic Drugs

- Sirolimus (immune suppressant) rapamycin
  - Discovered on Rapa Nui
  - Largely variable both intra&inter-individual
- Mycophenolic acid (immune suppressant)
  - Lymphocyte proliferation inhibitor
    - Supplement for renal transplant

Therapeutic Drugs

- Methotrexate (antineoplastic)
  - Leucovorin used to rescue patients
  - MTX inhibits DNA synthesis
    - Leucovorin reverses actions of MTX, if not done cytotoxicity will affect all cells