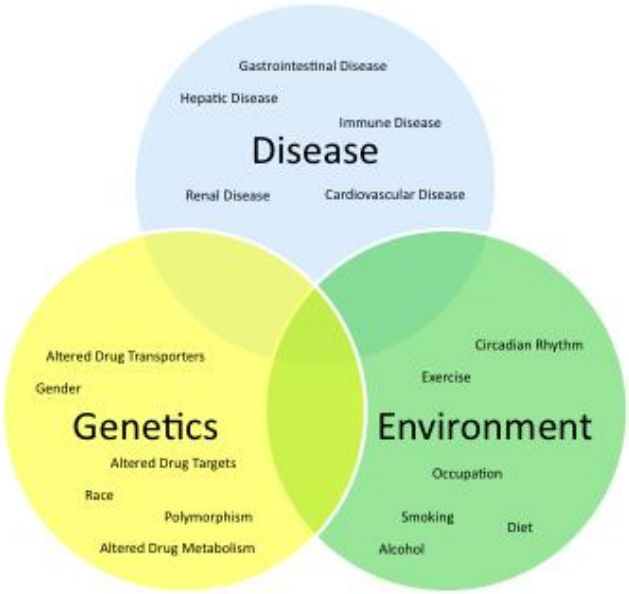
PHARMACODYNAMICS: THERAPEUTIC INDEX

9.1 Interpatient Variability in Response

- In an ideal world the response to medications would be the same for every patient.
- Unfortunately in reality, response to medications is quite variable between patients.
- Because response to medications is variable, every patient's response must be evaluated to ensure an adequate therapeutic response.
- The response to medication is influenced by genetics, disease state, and the environment.



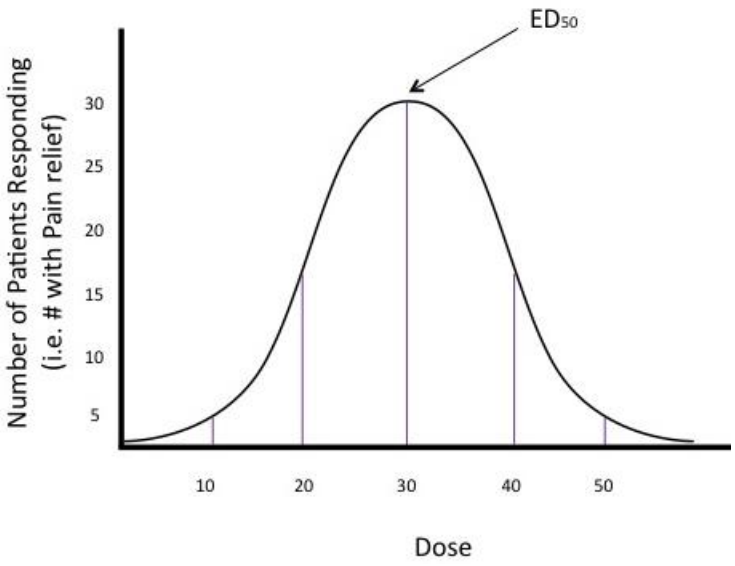
Determining Interpatient Variability

Clinical trials are an important first step in determining interpatient variability to drug response

Phase 1	•20 -100 health volunteers, •evaluation of pharmacokinetics and pharmacodynamics •Animal studies guide dosing
Phase 2	•In 300-500 patients with the disorder, •Short term trial to determine efficacy and side effects. •Dose-response is determined.
Phase 3	•500 -5000 patients with the target disorder. •Efficacy verified and long term side effects evaluated.
Phase 4	•Post-marketing surveillance

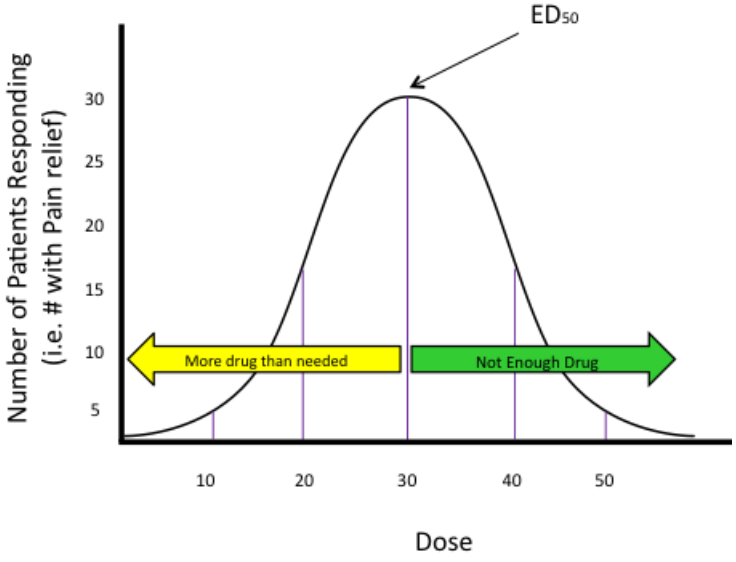
- Phase II clinical trials establish dose response information over a range of doses.
- To determine interpatient variability in response to medications, we first set an endpoint. For example, if we were talking about an analgesic drug, the endpoint would be pain relief.

- From phase II clinical trial data we can evaluate the number of patients that experience pain relief from each dose of the drug.
- This data is plotted on a frequency distribution curve.
- The average effective dose (ED50) is at the peak of the frequency distribution curve. The ED50 is the dose required to produce a response in 50% of the population.
- The ED50 is often used as the initial dose for therapy.



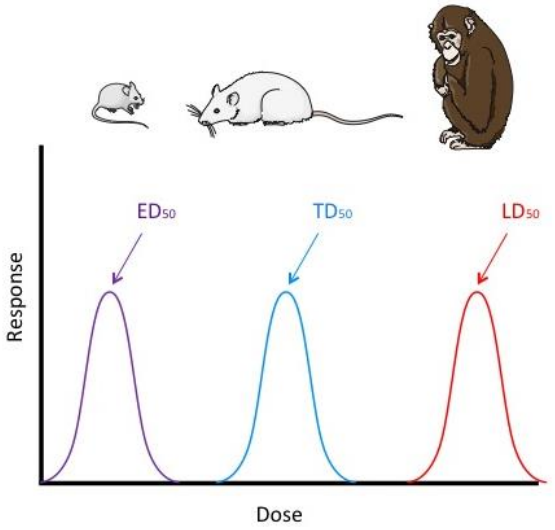
Dosing Implications

- If all patients are given the ED50 as a starting dose, some patients will have more drug than they need and others will not have enough as seen in the graph below.
- The initial dose of a drug is a starting point, however many patients will require dose adjustments to optimize efficacy and minimize adverse events.
- When is it okay to use the ED50 as a starting dose? When the drug has a wide therapeutic range. If the drug has a wide therapeutic range there will be a decreased risk of adverse events.
- How do we dose drugs that have a narrow therapeutic range? Drugs with a narrow therapeutic range should have their dose titrated (start low and increase slowly until the desired response is achieved).
- Most importantly, responses to medication can be quite variable. It is more important to adjust dosing based on the patient's response rather than simply using a dosing reference.



Toxic and Lethal Doses

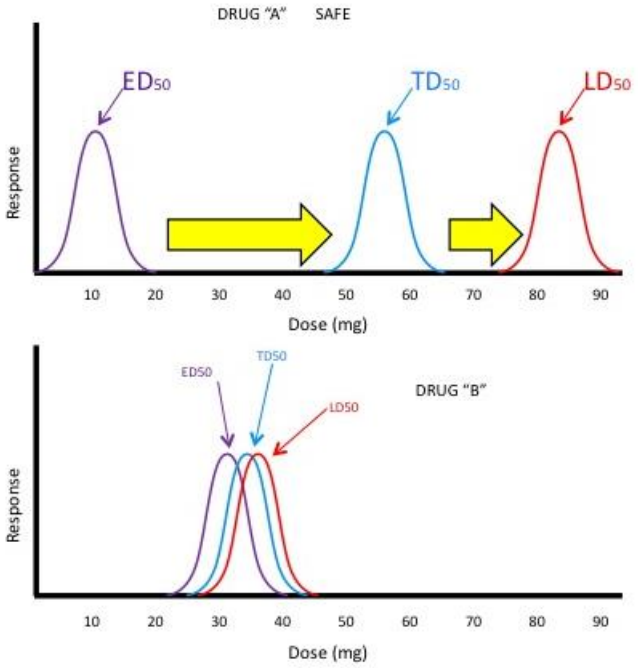
- Up until now we have always looked at a response as a measure of efficacy (i.e. pain relief).
- Responses can also include toxicity or even death due to drug treatment.
- We obviously do not want to test for toxic or lethal responses in humans. For this reason, these tests are carried out in experimental animals.
- Acute (short term) and chronic (6 month – 2 year) animal testing is carried out to determine the doses that produce toxicity or death in multiple animal species.
- The average toxic dose (TD50) is the dose in which 50% of animals experience drug toxicity.
- The average lethal dose (LD50) is the dose in which 50% of animals die.
- TD50 and LD50 are typically expressed in mg drug/kg body weight.



9.2 Therapeutic Index

- Therapeutic index is an indicator of a drug's safety.
- The therapeutic index is calculated by determining the ratio of the TD50 or LD50 to the ED50.

  TI = TD50/ED50
  or
  TI = LD50/ED50



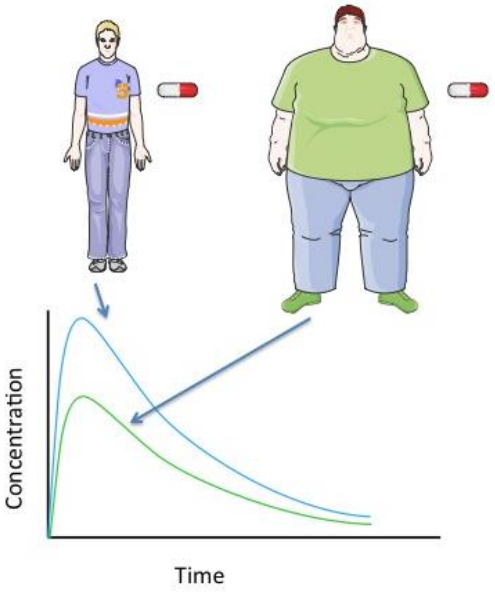
- Drugs with a high therapeutic index are considered safe whereas those with a low therapeutic index are considered unsafe.
- Drugs that are safe have a large space in between the dose that produces a therapeutic response and the dose that produces a toxic or lethal response.

9.3 Factors Affecting Interpatient Variation in Response

1. **Body Weight and Composition**
2. **Genetics**
3. **Gender**
4. **Race**
5. **Kidney Disease**
6. **Liver Disease**
7. **Environment**

1. <u>Body Weight and Composition</u>

- We know that the response to medications is largely determined by the concentration of the drug in the body, with the higher concentrations giving a greater response.



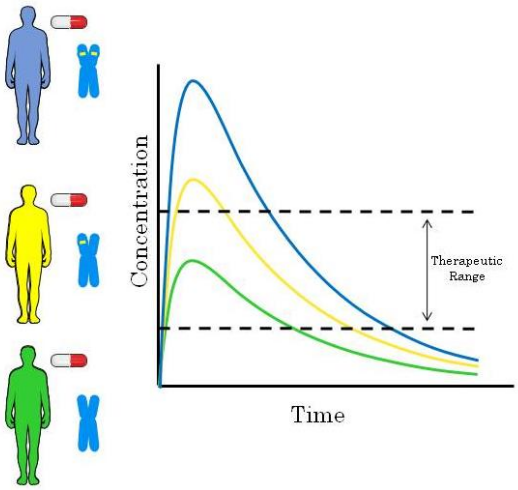
- Let's give the same dose of drug to these two guys. What would you expect in terms of plasma concentration?
- For many drugs, the dose is adjusted for the body weight of the patient (i.e. mg drug/kg body weight) in order to compensate for differences in size.
- Although body weight helps to normalize dose, what happens when two people have the same body weight but different body composition? Percentage body fat can change the distribution of the drug so obese patients may respond differently. Clinicians often adjust the dose of drugs by body surface area (BSA) because this partially accounts for body composition as well.

- Normal BSA for an adult is $1.73m^2$ so some drugs are dosed as $mg/1.73m^2$.

2. Genetics

- Pharmacogenetics is the study of the effect of DNA sequence variation to the clinical response of drugs.
- Single Nucleotide Polymorphism (SNP, pronounced "SNIP") is a change in DNA sequence that involves a single nucleotide (A,T,C or G).
- SNPs can exist in genes that regulate drug metabolism, drug transport or drug receptors, as you have already seen in Module 4.
- Genetic variation such as SNPs can explain some of the intersubject variation in drug response.

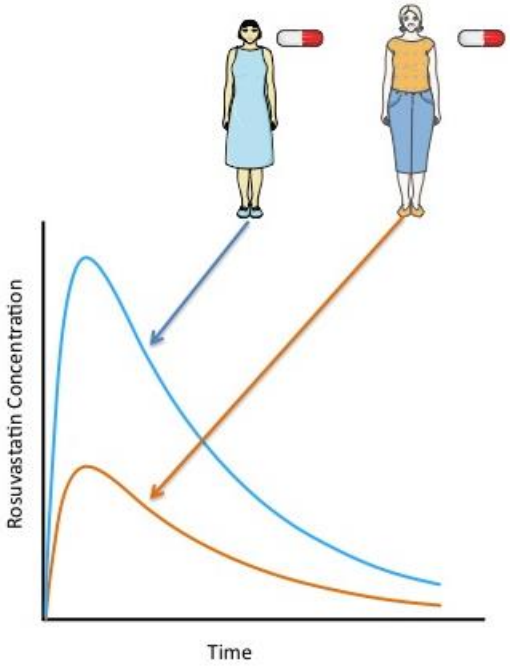
- Doses of some drugs are adjusted based on a patient's genotype (genetic makeup).



3. Gender

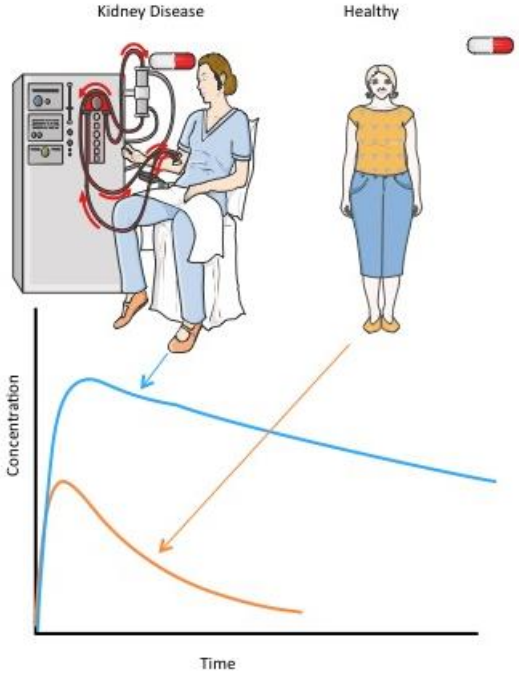
- This may seem like an obvious statement but women and men are different. This is may be true in terms of drug effects as well.
- A drug may be more effective in women than a man or vice versa.
- For many drugs the effect of gender is unknown.
- Why? Until relatively recently, the majority of drug research was conducted in men.
- In 1997 drug regulatory bodies (Health Canada and the US FDA) put pressure on drug companies to include women in trials of new drugs.
- A few differences between women and men that we know of in terms of variation in drug response are:
    - Alcohol metabolism is slower in females.
    - Certain opioids are more effective in women, therefore they require lower doses.
    - Certain drugs used to treat irregular heart beat cause prolongation of the QT interval on the electrocardiogram of women. This means it is more likely for women to have a fatal cardiac dysrhythmia.

4. Race



- The effect of race or ethnicity is difficult to relate to variability of drug response.
- One reason is that race is difficult to define.
- Many people in our society are from an ethnically heterogeneous background so they cannot simply be categorized by a single race.
- There are some instances where generalizations are made by race because of convincing data. For example, concentrations of the cholesterol lowering drug rosuvastatin are 2-3 times higher in Asian compared to Caucasian patients. This can (and has) led to drastic side effects and even death. Therefore doses of rosuvastatin should be decreased in Asian patients.

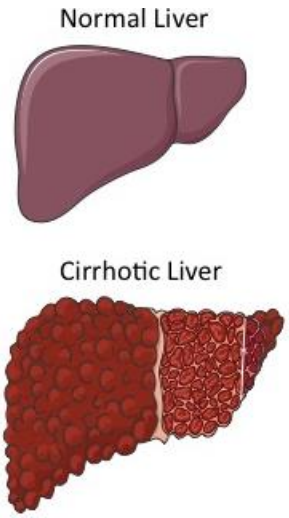
5. Kidney Disease



- The kidney is the primary organ responsible for drug elimination.
- In patients with kidney disease, drug excretion is significantly decreased.
- Decreased drug excretion causes an increase in the half life for drugs that are renally excreted.
- Recent evidence also suggests that hepatic and intestinal drug metabolism is also decreased in renal failure.
- The net effect of renal failure is increased oral bioavailability and decreased excretion.
- Therefore, the dosage of many drugs must be decreased in patients with kidney disease.

6. Liver Disease

- The liver is the primary organ responsible for drug metabolism.
- Patients with liver diseases such as cirrhosis or hepatitis exhibit decreased hepatic drug metabolism.
- For drugs that are extensively metabolized, half life may be significantly increased in patients with liver disease.



7. Environment

- Environmental exposures can significantly change the way patients respond to drugs.
- Environmental exposure can be voluntary (smoking, alcohol, diet, exercise) or involuntary (environmental pesticides).

  Some examples include:

  1. Cigarette smoke induces some drug metabolizing enzymes and can make some drugs less effective.
  2. Alcohol can exacerbate the toxicity of some other drugs.
  3. Exercise improves the actions of insulin.
  4. Some commonly used pesticides can induce CYPs and therefore decrease the response to drugs that are metabolized by CYP enzymes.