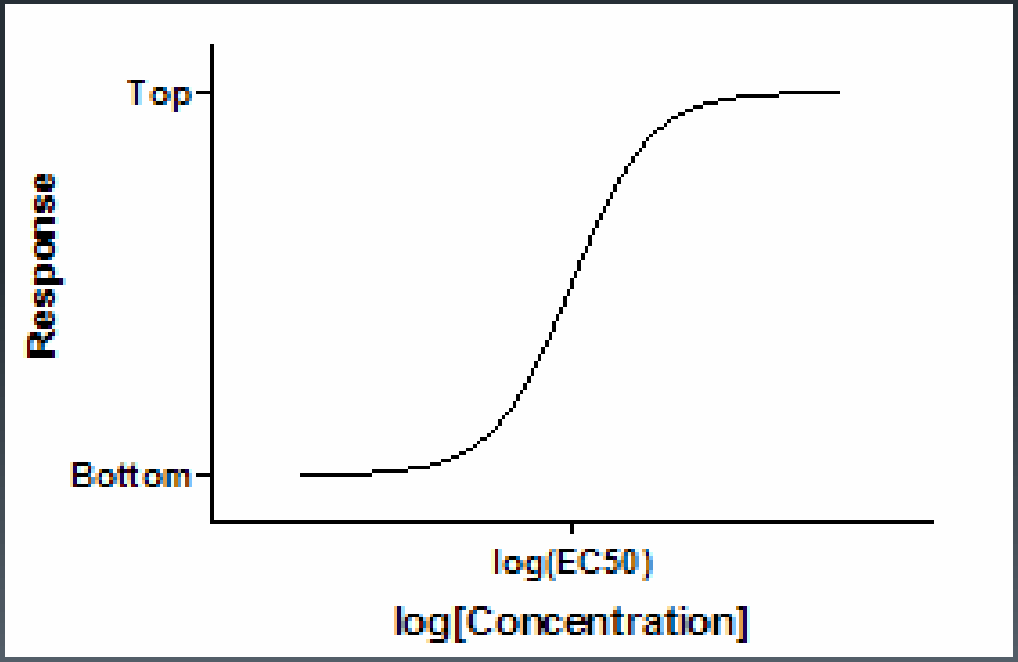
Doses & Therapeutic Index

Learning Objectives

- Dose & its significance
- Dose response curves
- E_{max} Efficacy
- Minimal Dose
- EC_{50} or ED_{50} Potency
- LD_{50} Lethal dose
- TD_{50} Toxic dose
- Therapeutic Window
- Therapeutic Index
- Maintenance Dose
- Loading Dose
- Sub therapeutic Dose
- Fatal Dose
- Booster Dose

Dose-Response curve

- Dose-Response curve shows the relationship between the dose of a drug administered and its pharmacological effect

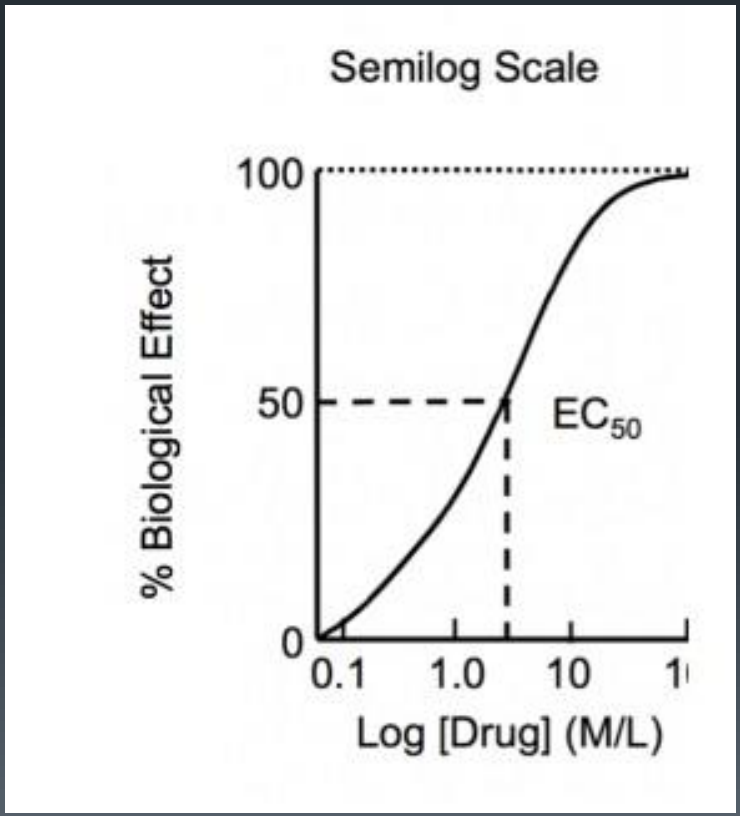


Types of dose response curve

- Graded dose response curve
- Quantal dose response curve

Graded dose response curve

- The graph of increasing response to increasing drug concentration.

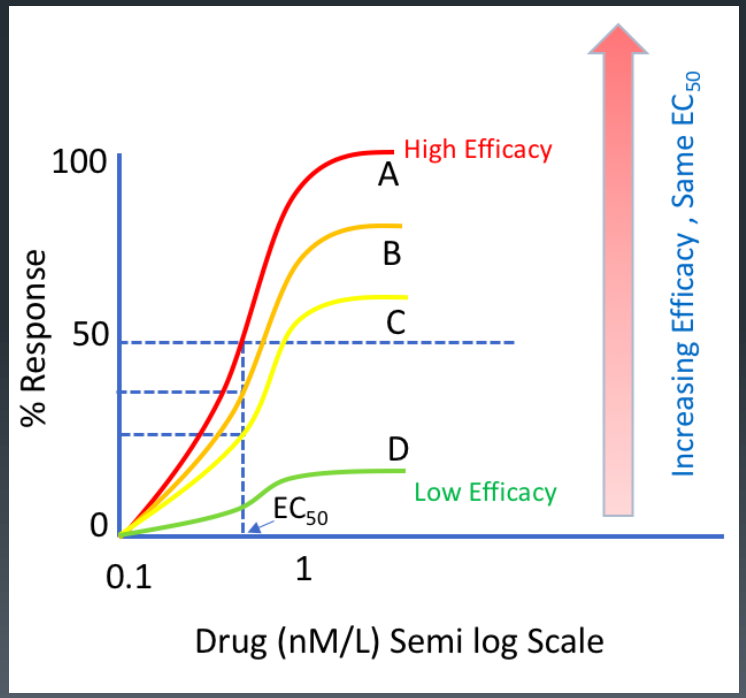


Information we get from graded dose response curve

- Efficacy
- Potency

Efficacy Emax

- The maximal effect that can be achieved by a drug.

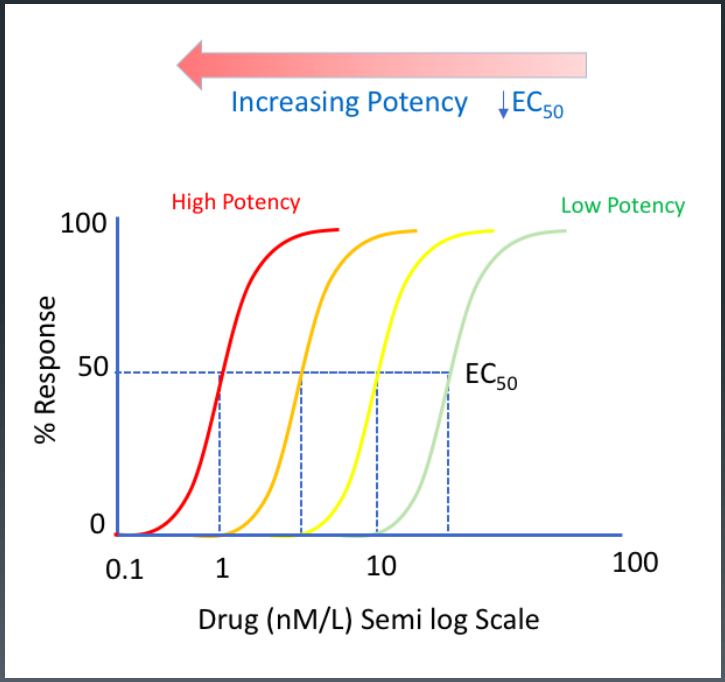


Minimal Dose

- It is the smallest amount of drug which can just produce an observable pharmacological change.

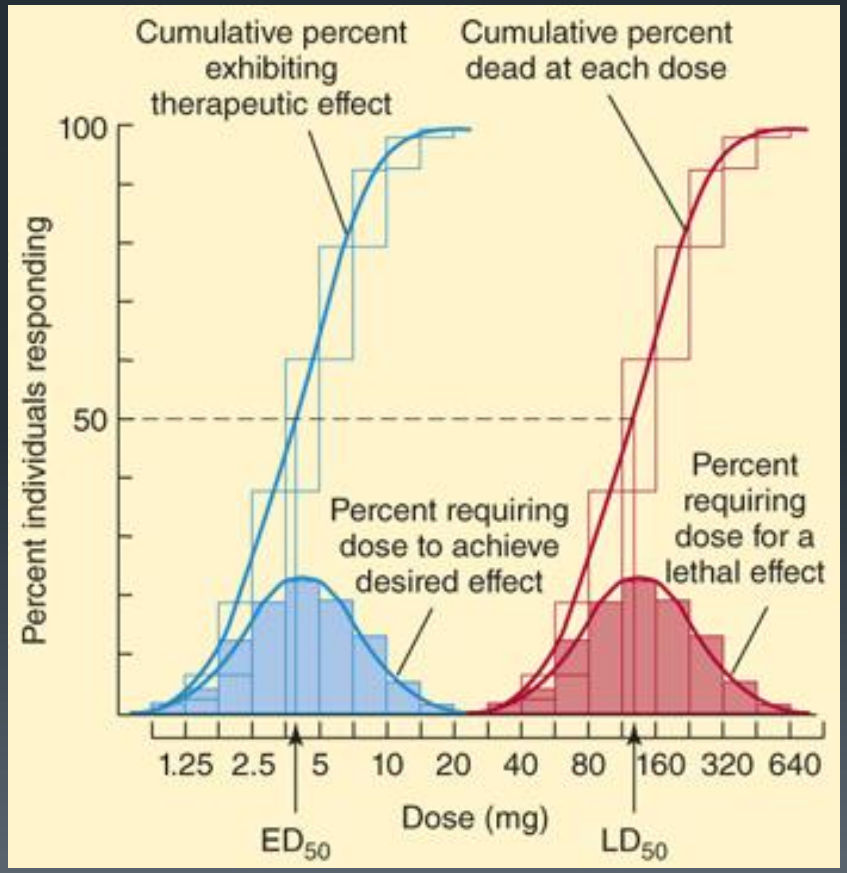
Potency EC_{50} or ED_{50}

- Potency refers to the concentration (EC_{50}) or dose (ED_{50}) of a drug required to produce 50% of the maximal effect.



Quantal Dose response curve

- It is a graph of specified response to the concentration or dose of a drug in a fraction of a population.



Information we get from quantal dose response curve

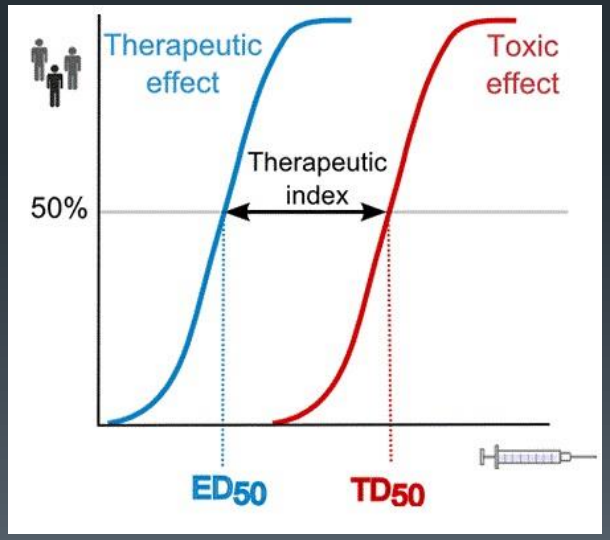
- It gives information about variation in sensitivity to a drug in a given population.
- Median effective dose (ED50),
- Median toxic dose (TD50)
- Median lethal dose (LD50) can be derived.

Median Effective dose ED_{50}

- It is the dose at which 50% of individuals exhibit specified response.

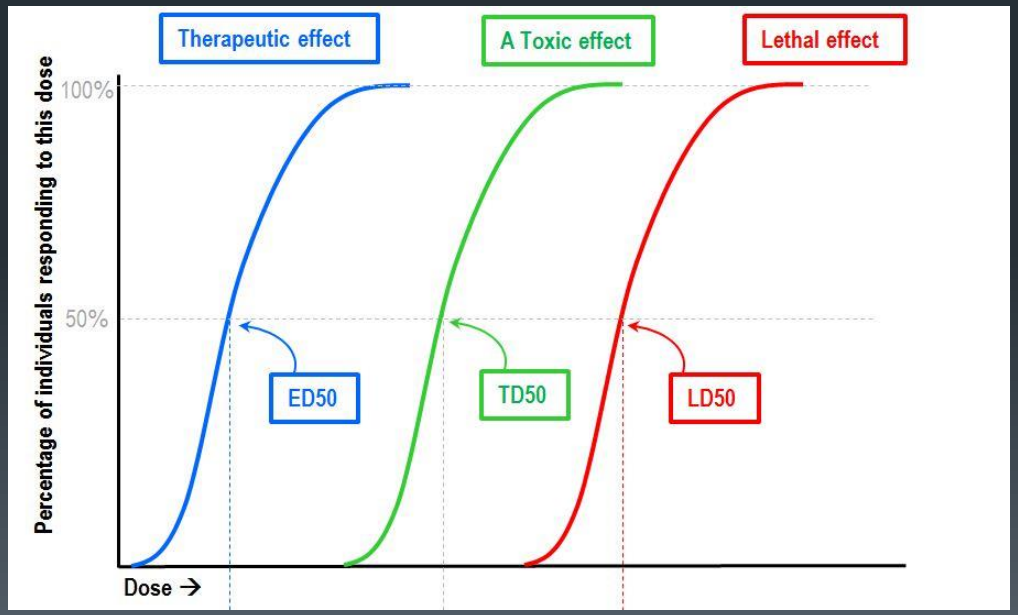
Median Toxic dose TD_{50}

- It is the dose at which 50% of individuals produce toxic effects



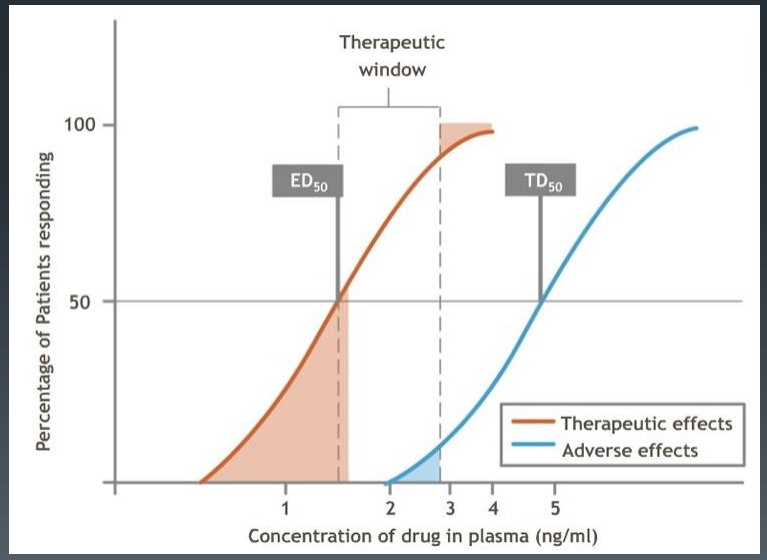
Median Lethal dose LD_{50}

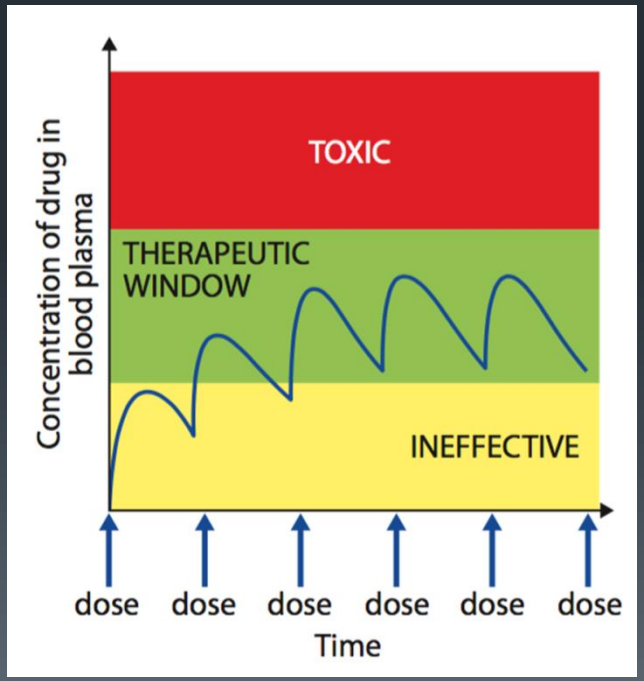
- It is the dose at which 50% of animals die.
- Lethal doses LD_{50} are always used in animal trials



Therapeutic window

- Since the levels of a drug in the bloodstream will not be constant, dosing has to be in acceptable range.
- This target range is known as the therapeutic window.
- Medications with narrow therapeutic windows include digoxin, lithium, and warfarin.



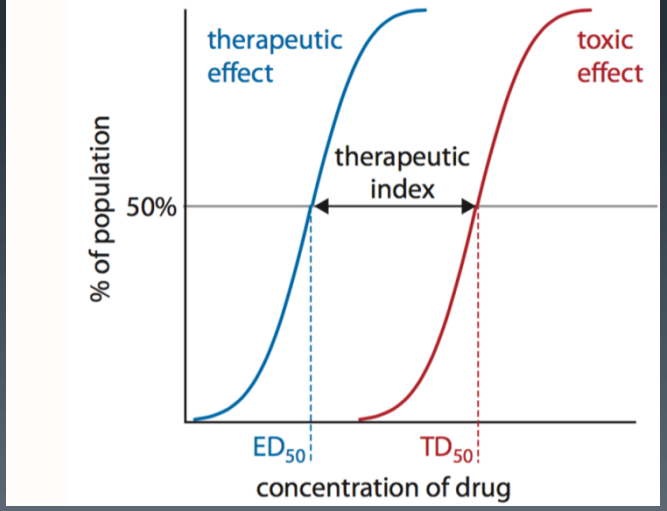


Therapeutic Index

- It is the ratio of the dose that produces toxicity (TD_{50}) to the dose that produces an effective response (ED_{50}) in a population.

- In animal studies, the therapeutic index is the lethal dose of a drug for 50% of the population (LD50) divided by the minimum effective dose for 50% of the population (ED50).
- In humans, the therapeutic index is the toxic dose of a drug for 50% of the population (TD50) divided by the minimum effective dose for 50% of the population (ED50).

- in animals $TI = \frac{LD_{50}}{ED_{50}}$
- in humans $TI = \frac{TD_{50}}{ED_{50}}$



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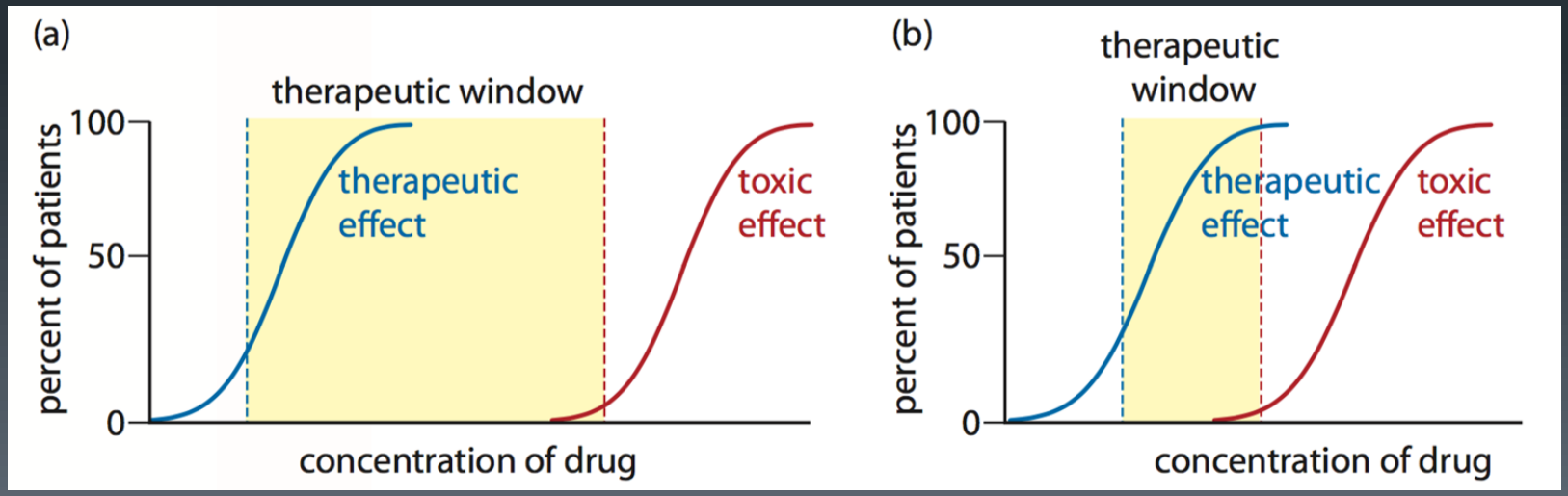
- If a drug has a high (or wide) therapeutic index, this means that there is a large difference between the dose of the drug that causes a therapeutic effect compared with the dose that causes a toxic effect.
- Example:

Penicillin vs. Warfarin



- A high Therapeutic Index (TI) is preferable for a drug to have a favorable safety and efficacy profile. For example :
  - Remifentanil has therapeutic index of 33,000:1.
  - While digoxin, has therapeutic index of approximately 2:1.
- A therapeutic index does not consider drug interactions or synergistic effects. For example:
  - The risk associated with benzodiazepines increases significantly when taken with alcohol, opiates, or stimulants when compared with being taken alone.

Maintenance Dose

- It is amount of drug that maintains steady state concentration of a drug in plasma.
- It can be calculated by

$$\text{Maintenance dose} = \frac{\text{Clearance X Desired plasma concentration}}{\text{Bioavailability}}$$

Loading dose

- It is the amount of drug required to quickly increase the drug plasma concentration.

  or

- It is the dose of drug administered to achieve steady state concentration, it is always first dose & higher in concentration than maintenance dose.

- Loading dose can be calculated by:

$$\text{loading dose} = \frac{\text{volume of distribution X desired plasma concentration}}{\text{Bioavailability}}$$

Sub-theraputic Dose

- Amount of drug which cannot produce desirable therapeutic effect. It is in between minimal and therapeutic dose.

Fatal dose

- The amount of drug capable of causing death.

Booster dose

- It is smaller than initial dose of drug
- Used for induction of immunity.

Thanks