DOSE -RESPONSE CURVES

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Foundation II MODULE

Pharmacology

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Objectives

- Determine quantitative aspects of drug receptor binding.
- Recognize concentration binding curves.
- Identify dose response curves and the therapeutic utility of these curves.

Concentration-Binding Curve

Relate concentration [C] of Drug used (x- axis) to the binding capacity at receptors (y-axis)

❖ **Bmax** (the binding capacity)**:-**

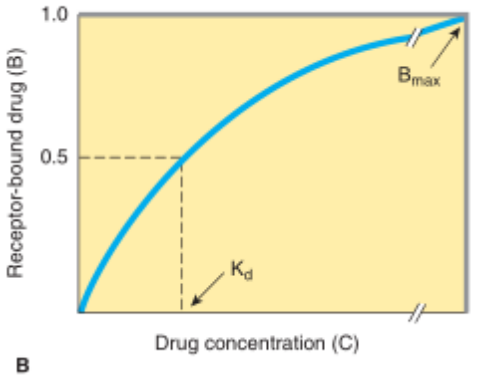
is the total density of receptors in the tissues.

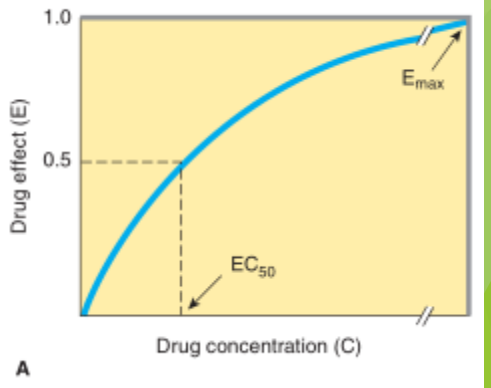
❖ **Kd50:-** K d (the equilibrium dissociation constant)

is the concentration of drug required to occupy 50% of receptors at equilibrium.

❖**The affinity of drug for receptor:-**

The higher the affinity of D for receptor the lower is the Kd i.e. inverse relation (Binding Potential= Bmax/Kd).





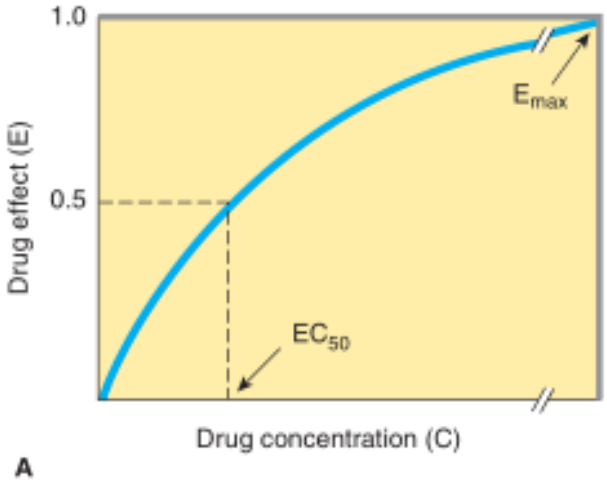
Dose Response Curve

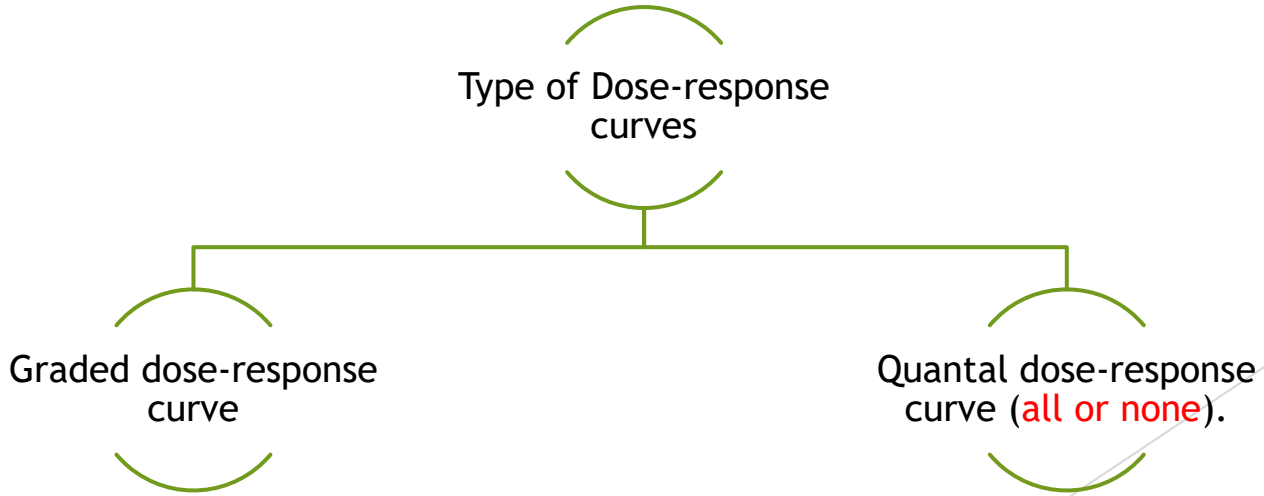
- Used to study how response varies with the concentration or dose.
- Is a correlation between

  drug concentration [C] used (x- axis) and

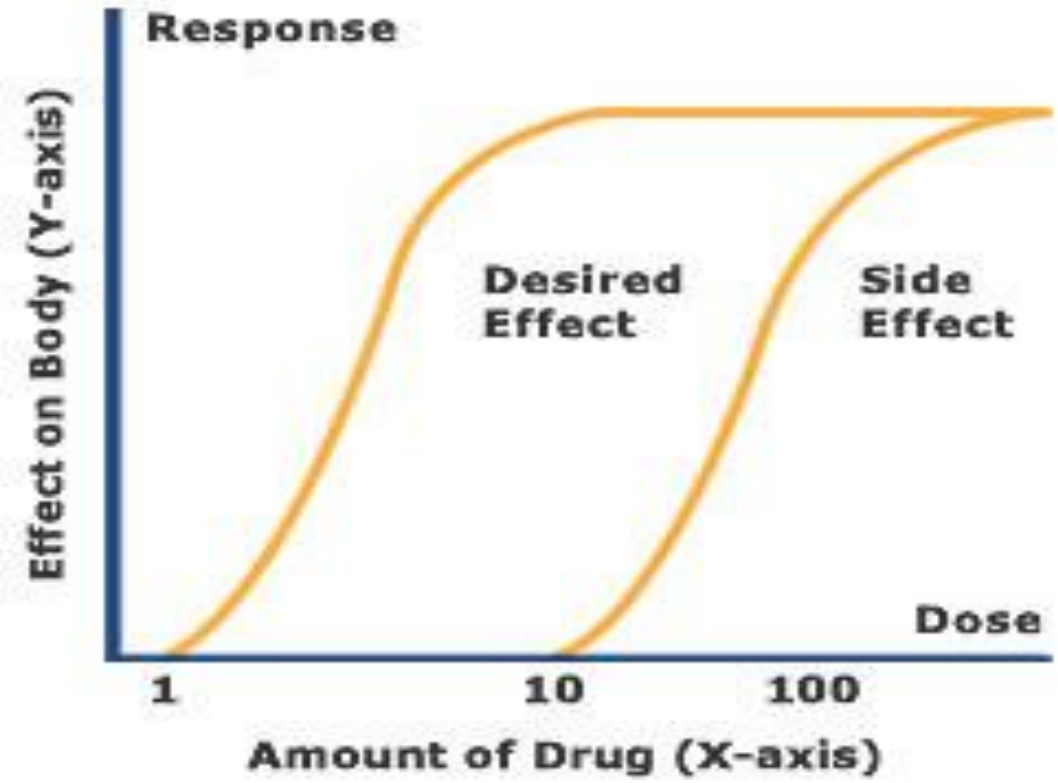
  drug effect [E] (y-axis)

  .i.e. relation between concentration & Response





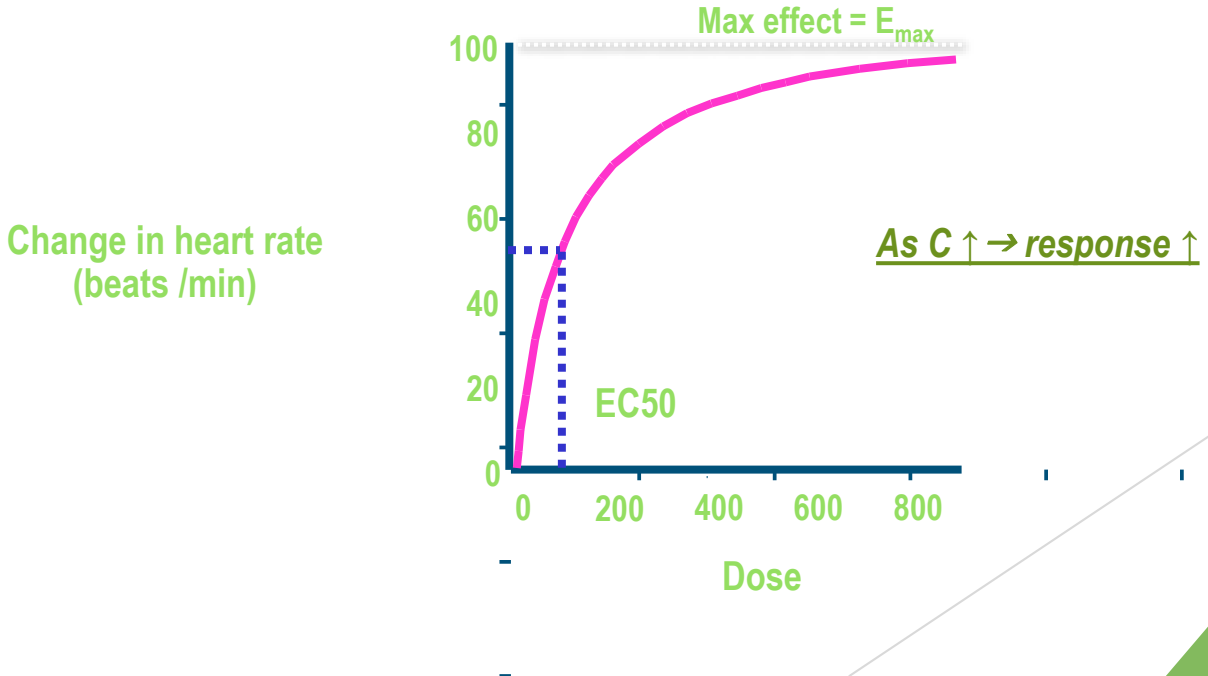
Dose-response curves determine how much of a drug (X-axis) causes a particular effect, or a side effect, in the body (Y-axis).



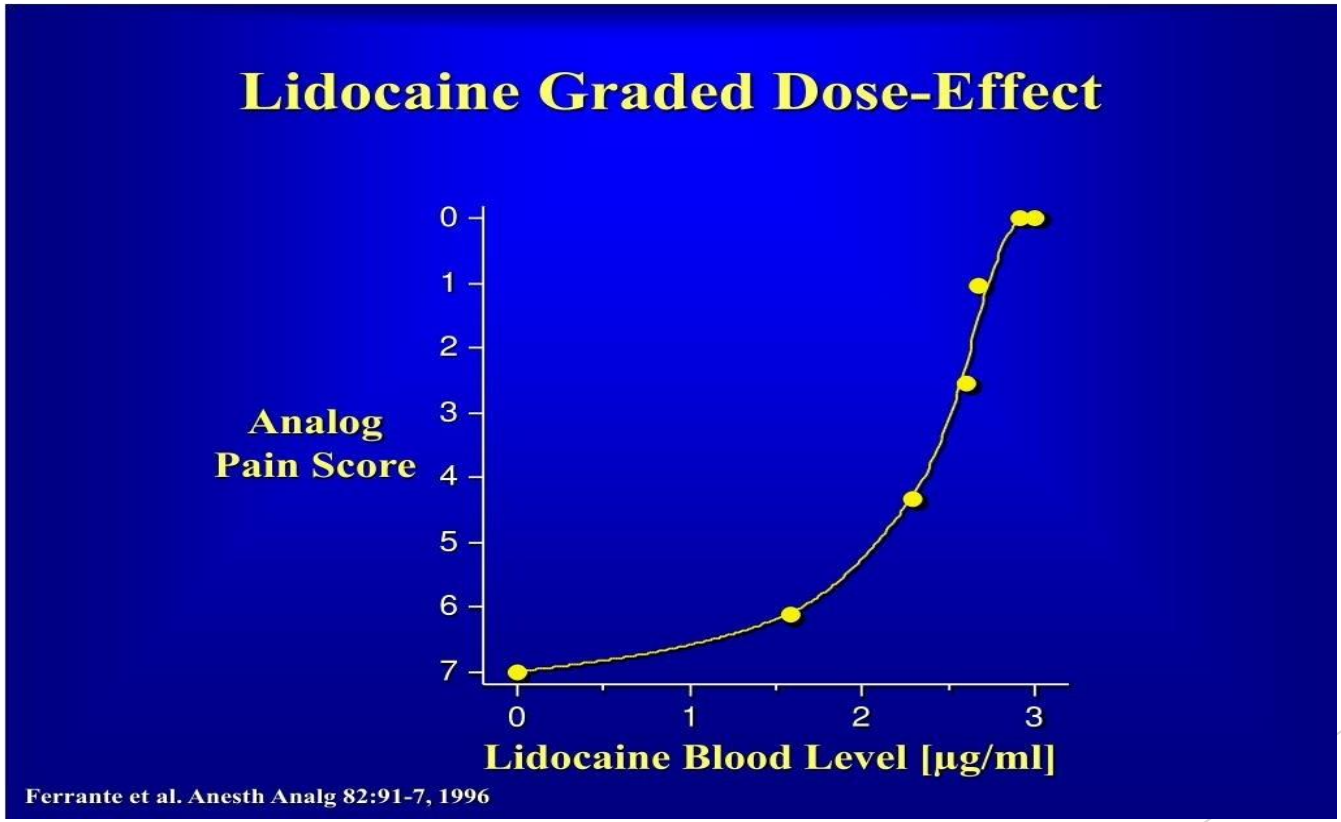
Graded dose response curve

Graded dose-response curve

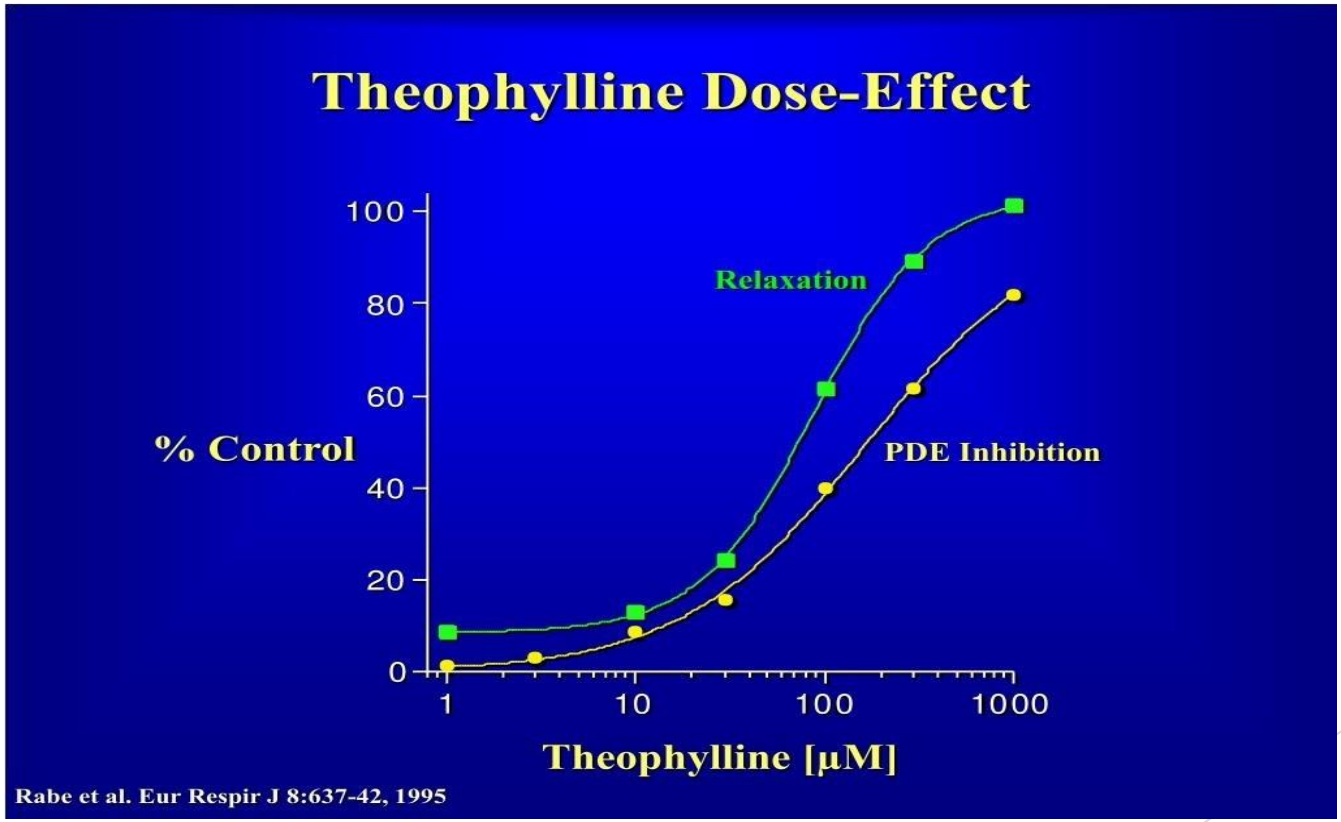
- Response is gradual.
- Gradual increase in response by increasing the dose (continuous response)
- Curve is usually sigmoid in shape.
- e.g. ↓blood pressure, heart rate, blood glucose level, cholesterol,…



Example of graded-dose response curve



Example


Theophylline Dose-Effect
100
80
60
40
20
0
% Control
Relaxation
PDE Inhibition
1
10
100
1000
Theophylline [µM]
Rabe et al. Eur Respir J 8:637-42, 1995

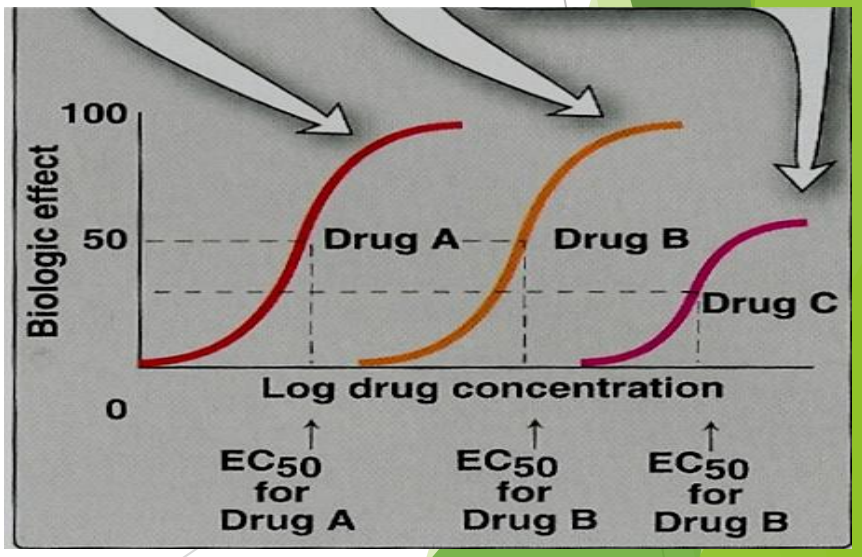
Graded dose-response curves are used to calculate

- Efficacy: --often called maximal efficacy(Emax).
- **Emax:** is the maximal biological response produced by a drug at highest tolerated drug level.
- **EC50:** The dose of the drug required to produce half the maximal effect
- **Potency:** the concentration of drug required to produce a specified response (EC50 is the international parameter)

Potency is inversely proportional to EC50.

(lower concentration → higher potency.

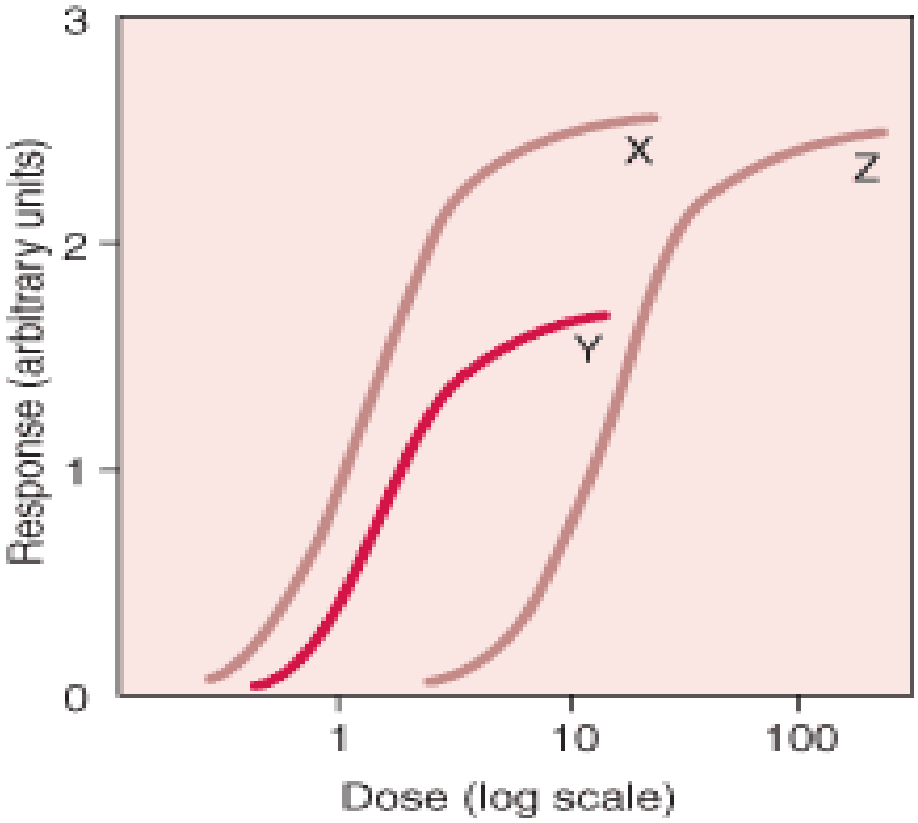
higher concentration → lower potency).



The potency of drug A is more than drug B & C.
The efficacy of drug A & B are the same and they are more efficacy than drug C.

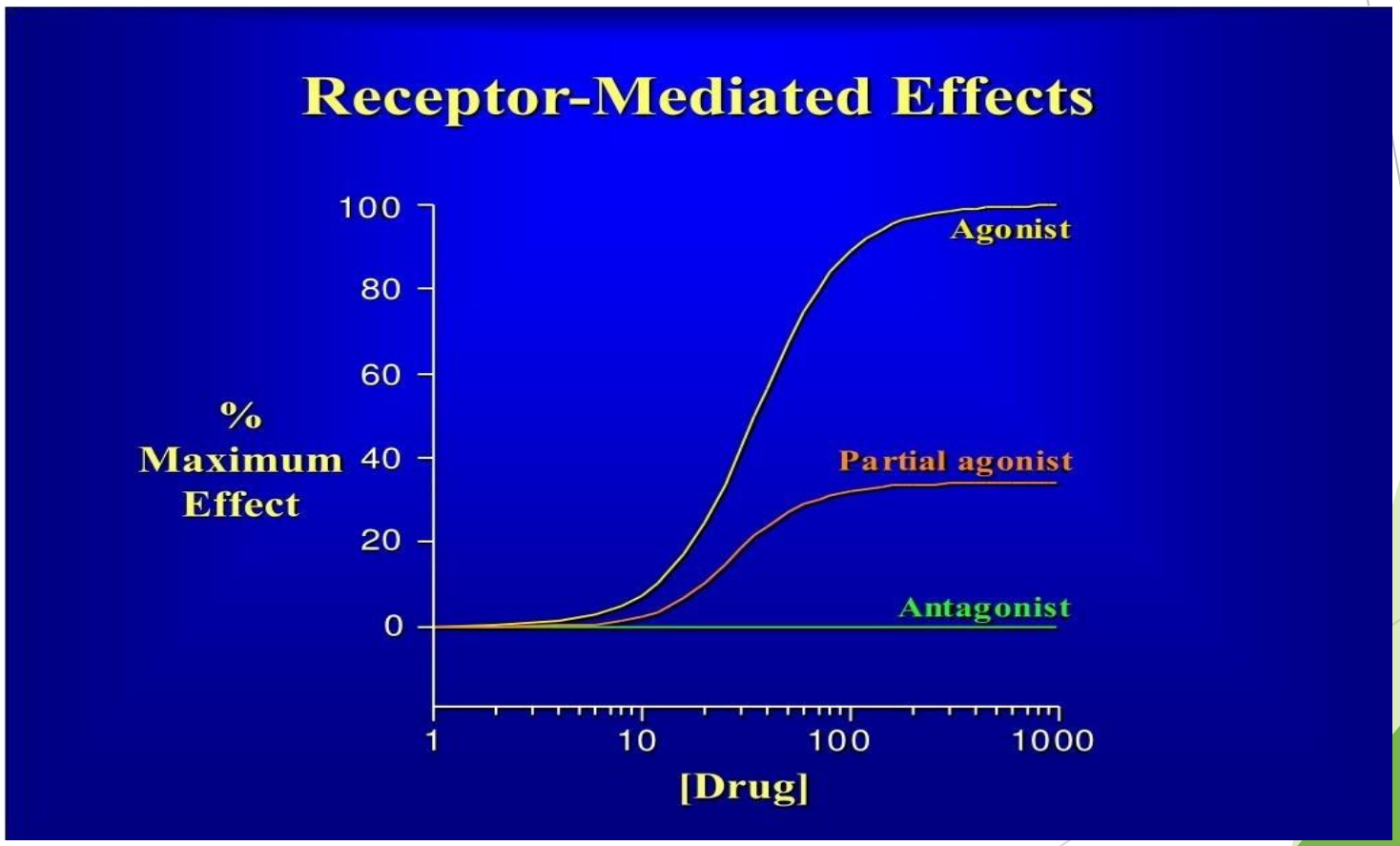
Graded dose response curve significance summary

- Along with assessing efficacy and potency of drug this curve also
- Identify therapeutic dose/concentration
- Classify drug effect by drug receptor ineration (agonist, antagonist)
- Compare relative efficacy and potency of difrrent drug with same effect
- Assess mechanism of drug interation

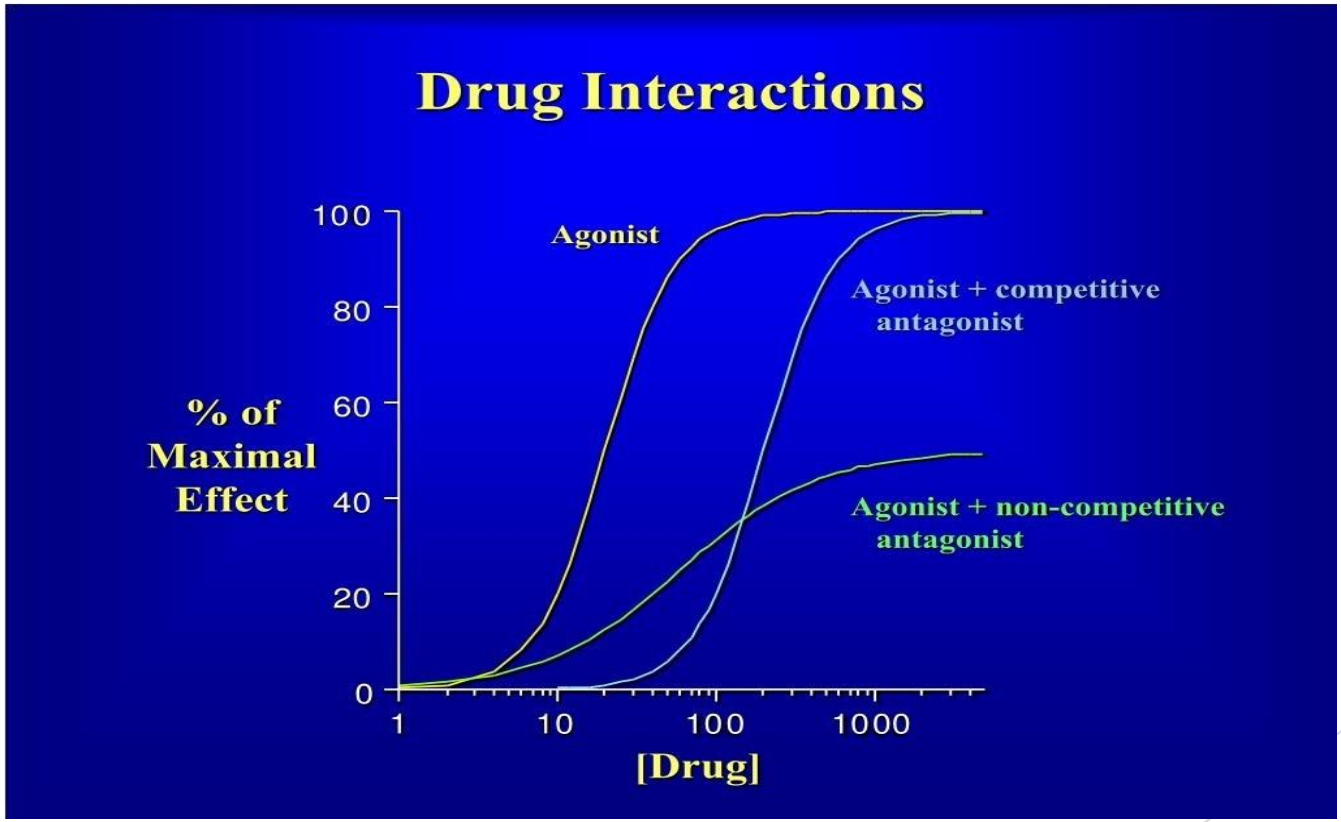


Drug X has greater biologic activity per dosing equivalent and is thus more potent than drug Y or Z. Drugs X and Z have equal efficacy, indicated by their maximal attainable response (ceiling effect). Drug Y is more potent than drug Z, but its maximal efficacy is lower.

Assess effect of drug



Assess mechanism of drug interation



Quantal dose response curve

Quantal Dose-Response Curves

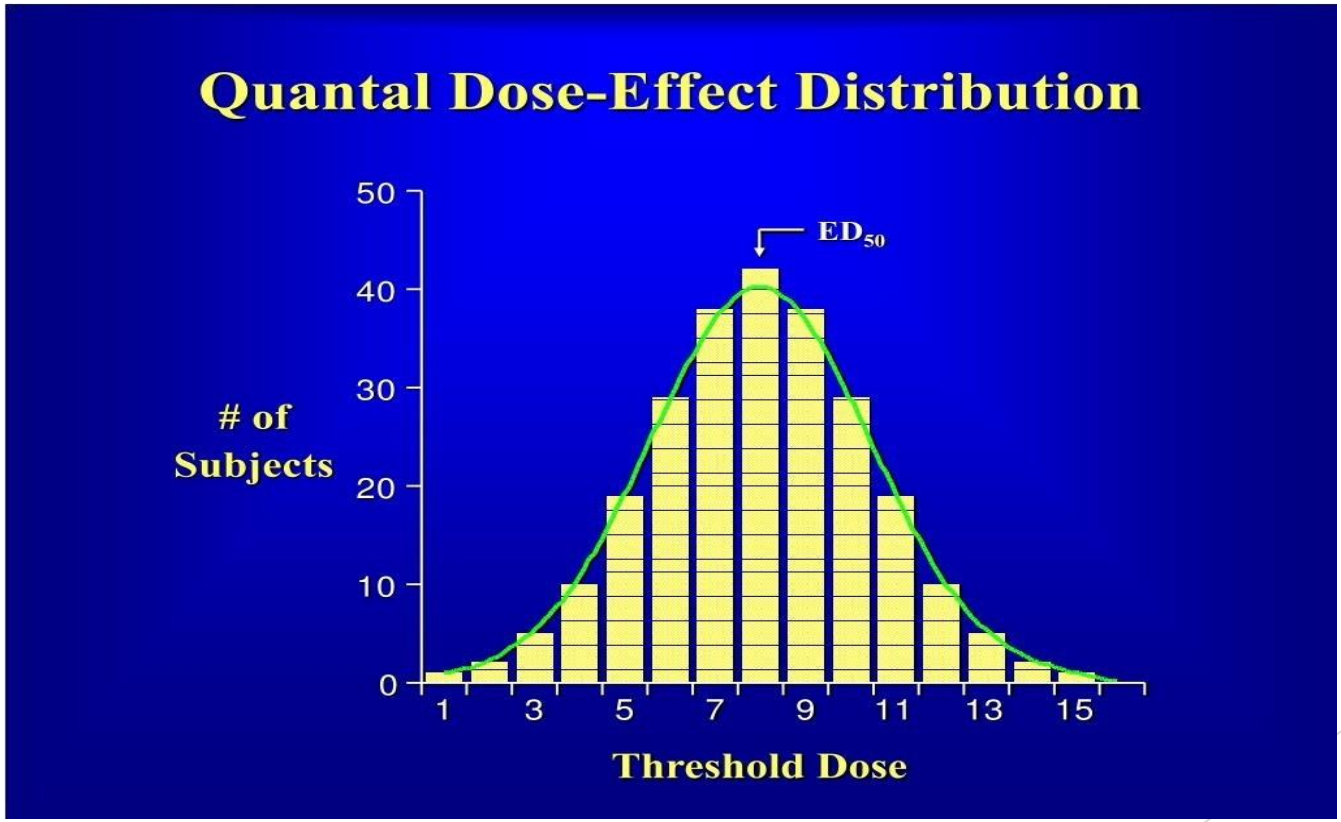
- Relates drug concentration to % percentage of patients responding

(all or none response).

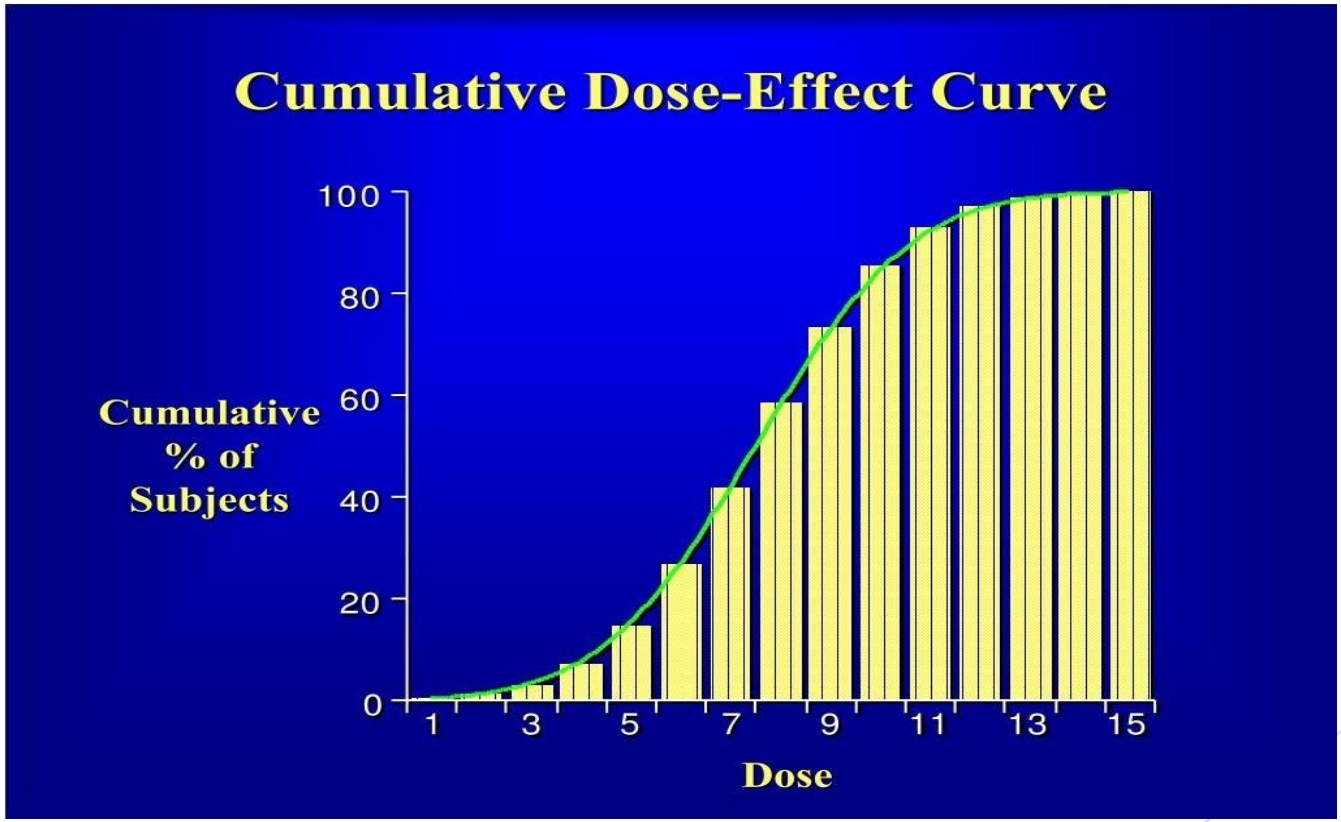
- Population studies
- The response may be

  therapeutic response, adverse effect or lethal effect.

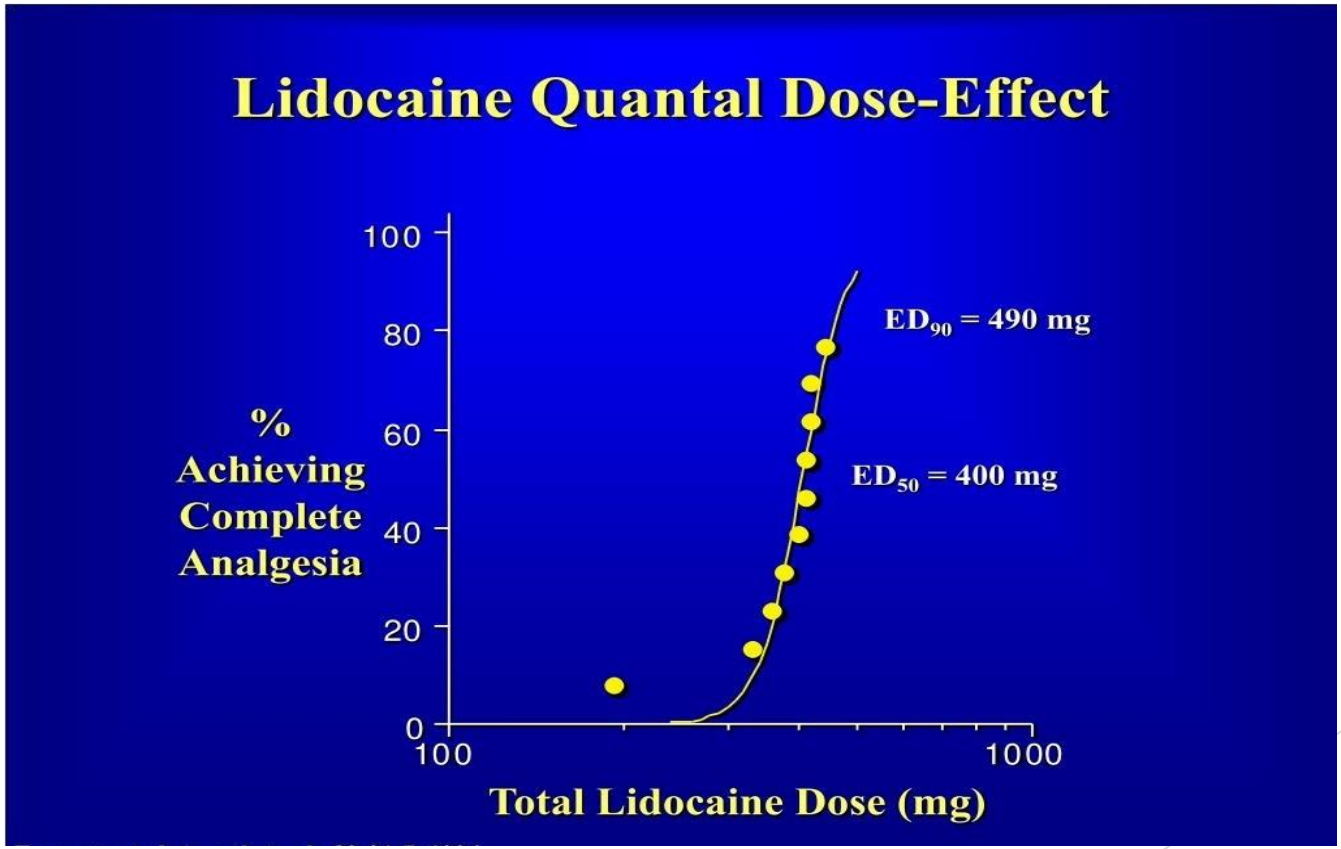
Quantal dose response curve



Hyperbolic curve



Example quantal dose response curve



Quantal Dose-Response Curves

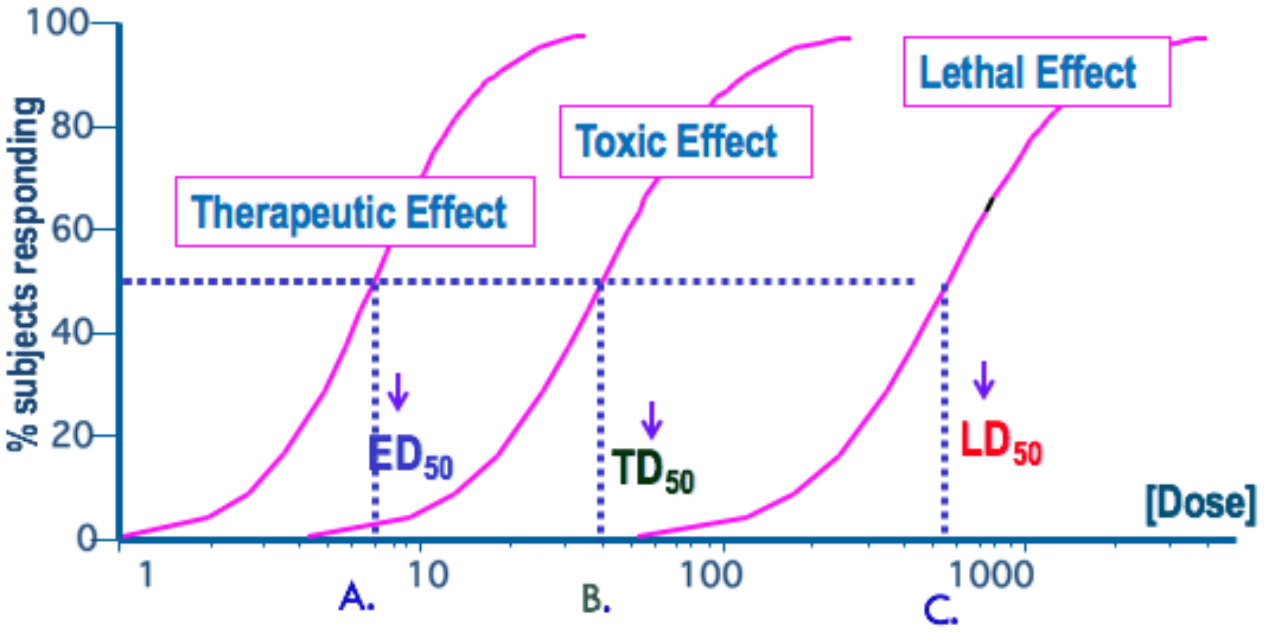
Used to determine:

- ED_{50}: the dose of drug Required to exhibit a therapeutic effect in 50% of patients.
- TD_{50}: the dose of drug required to exhibit a toxic effects in 50% of patients.
- LD_{50}: the dose of drug required to exhibit death in 50% of patients.

- Therapeutic index (T.I):

  It is a measure of safety profile.

$$\textbf{\textit{Therapeutic Index}} = \frac{TD_{50}}{ED_{50}} \textit{ or } \frac{LD_{50}}{ED_{50}}$$

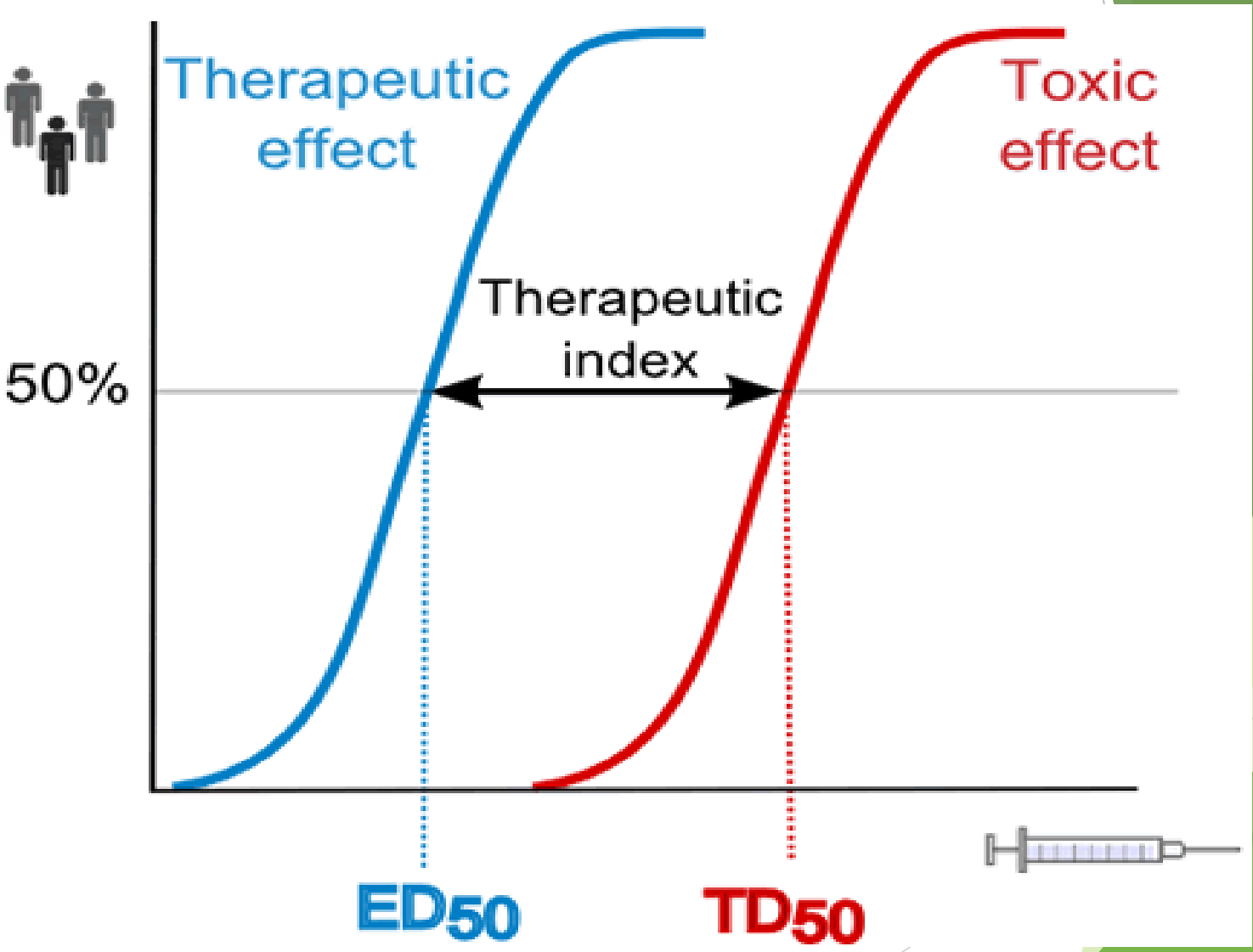


A. 50% of individuals exhibit the specified therapeutic response

B. " " " toxic effects

C. " " " death

Predict the safety profile

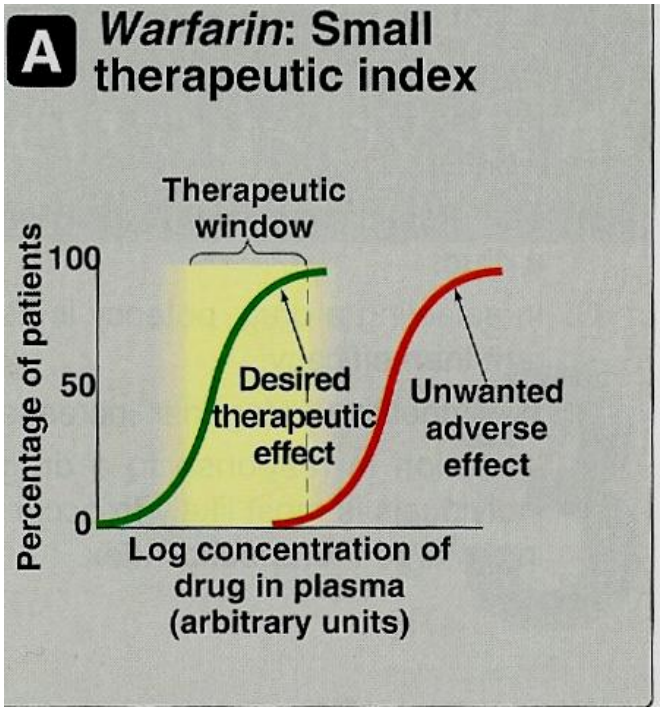

Therapeutic effect
Toxic effect
Therapeutic index
50%
ED50
TD50

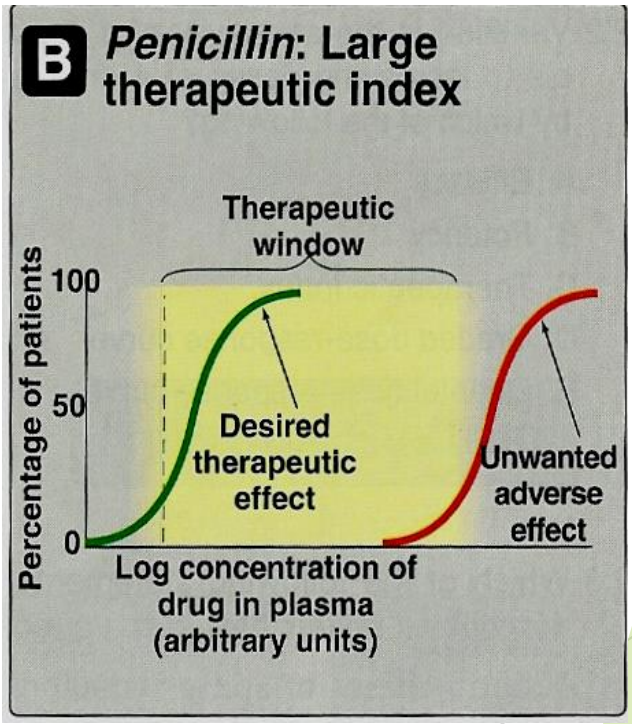
Quantal Dose-Response Curves uses

Theraupeutic index

Large value = drug has wide margin of safety e.g. diazepam

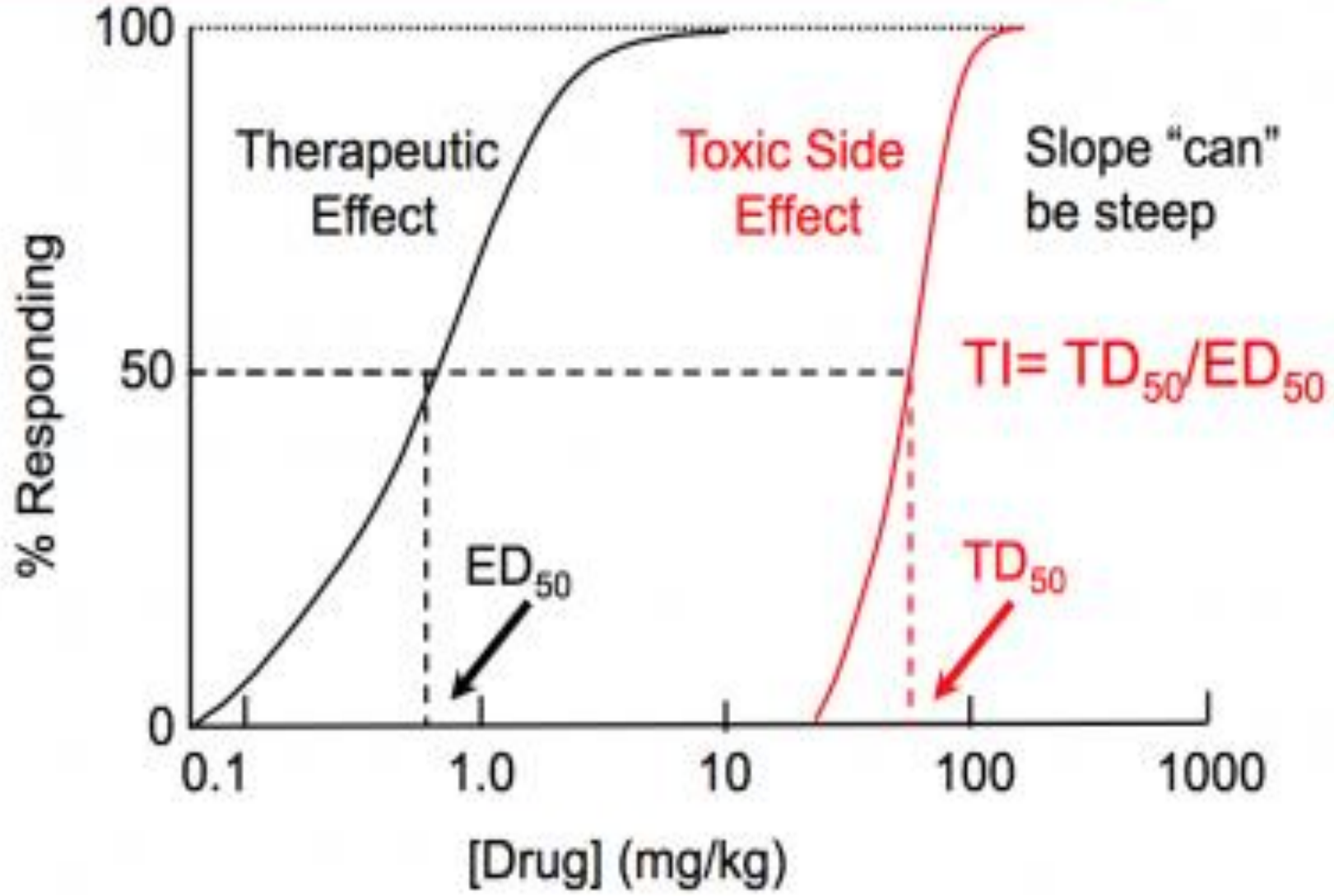
Small value = a narrow margin of safety e.g. digoxin





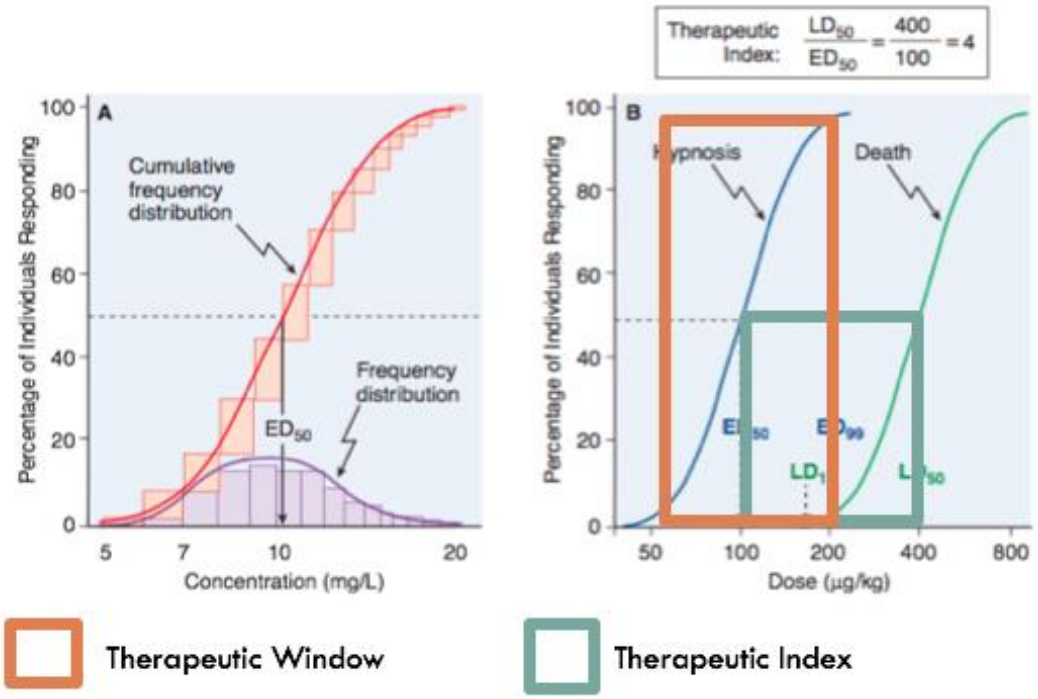
*note the difference in T.I.

Drug Safety - Therapeutic Index



Therapeutic window

- Range of concentration of drug at which it produce desired effect with minimal toxicity



History

- **Hill, a student in Cambridge, explored the concentration-effect curve quantitatively in 1909**
- **A J Clark applied this more generally to concentration-effect curves, in what is now known as classical receptor theory.**
- **Clark assumed that the effect of a drug is directly proportional to the concentration of drug–receptor complex**

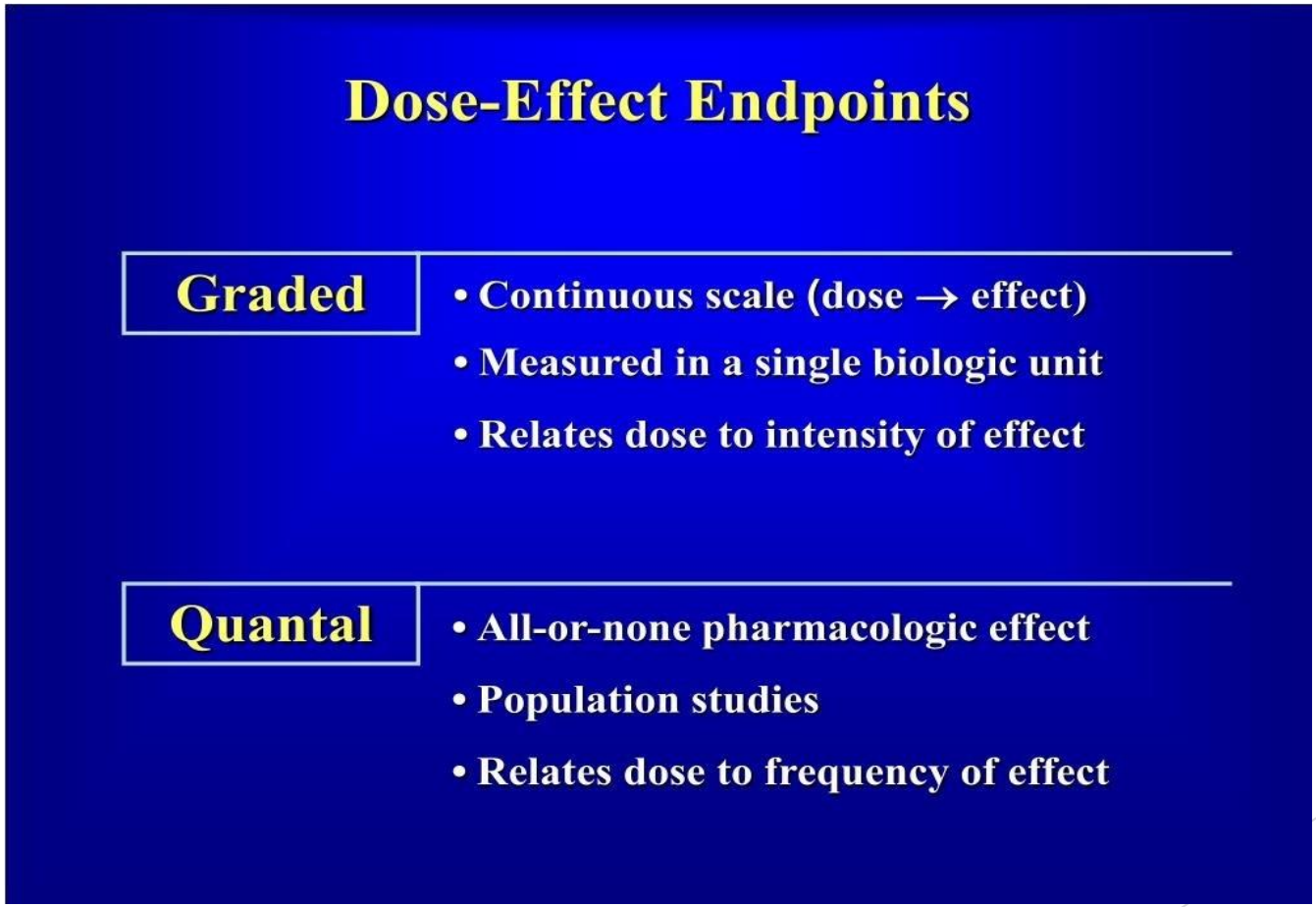
  that the maximum effect occurs when all the receptors are occupied.

- **From this he derived the apparent dissociation constant of the interaction of a drug with its receptor.**

Dose -response studies significance

- Drug development
  - Site of drug action
  - Selection of dose and schedule
  - Potency efficacy safety
  - Drug interations
- Patient management
  - Therapeutic drug monitoring
  - Risk-benefit (theraupeutic indices

Take home mesage




THANK YOU