UNIVERSITY OF PUTHISASTRA

PRINCIPALE OF PHARMACODYNAMIC

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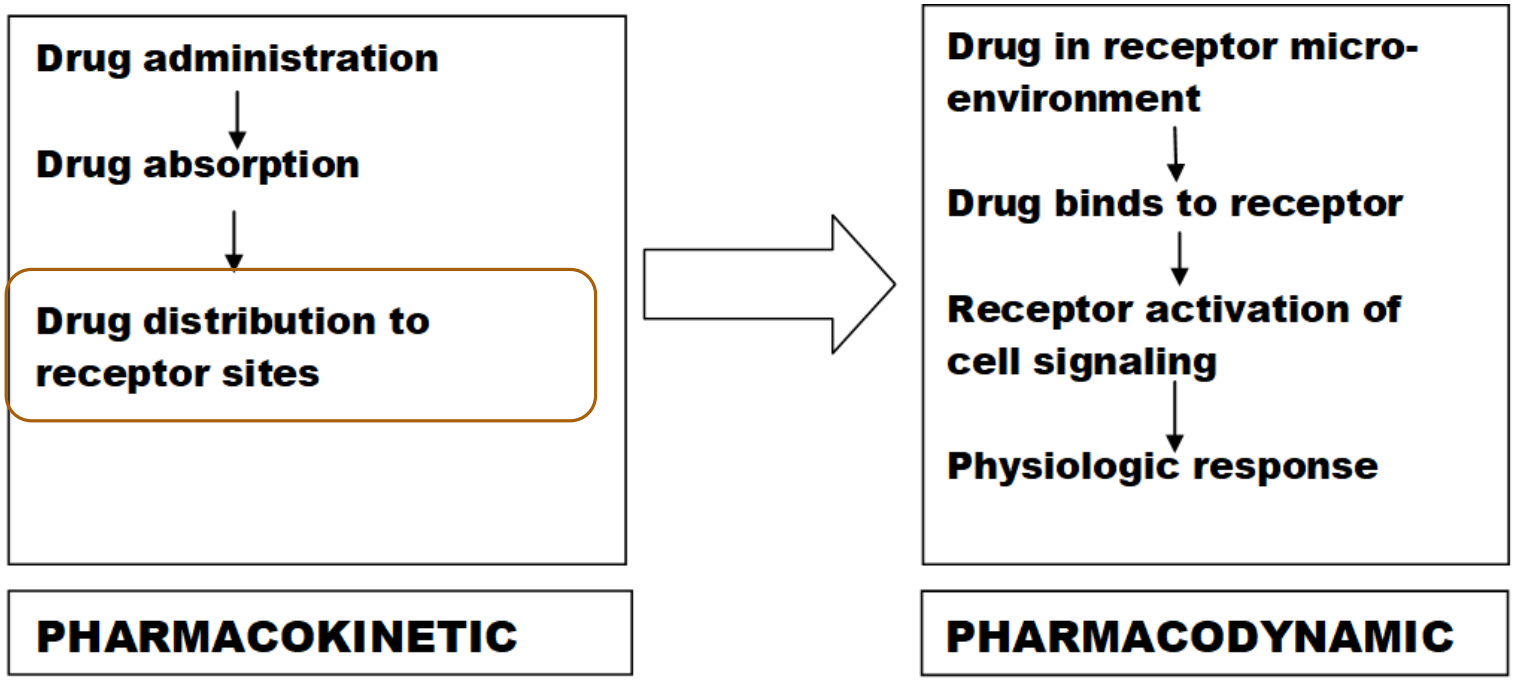
Learning Objectives

After completion of this section, students will be able to:

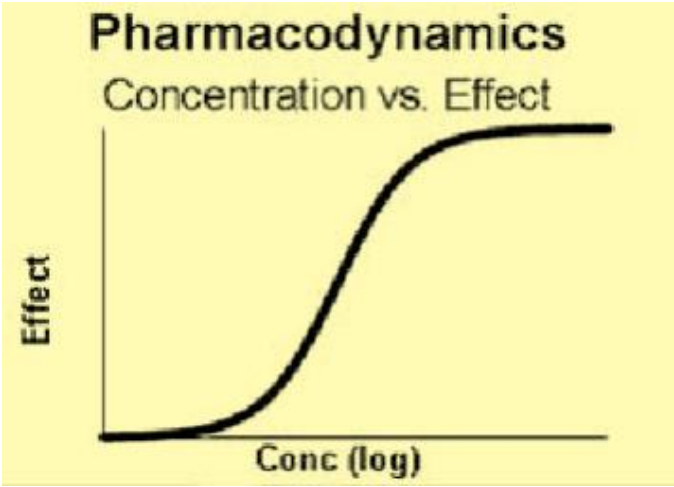
- The different types of receptors at which drugs can act
- The concept of affinity and those factors that cause a drug to bind to a receptor
- The difference between full and partial agonists
- The definitions of potency and efficacy
- The definition of ED50
- How it differs from an irreversible receptor agonist
- The definition of LD50
- The concept of a therapeutic index and how it is calculated

Pharmacodynamics and Drug Receptors (how drugs work on the body)



Pharmacodynamics and Drug Receptors (how drugs work on the body)

The action of a drug on the body, including receptor interactions, dose-response phenomena, and mechanisms of therapeutic and toxic action.



Pharmacodynamics and Drug Receptors (how drugs work on the body)

- **Many drugs inhibit *enzymes:***

- Enzymes control a number of metabolic processes
- A very common mode of action of many drugs
  - in the patient (ACE inhibitors)
  - in microbes (sulfas, penicillins)
  - in cancer cells (5-FU, 6-MP)

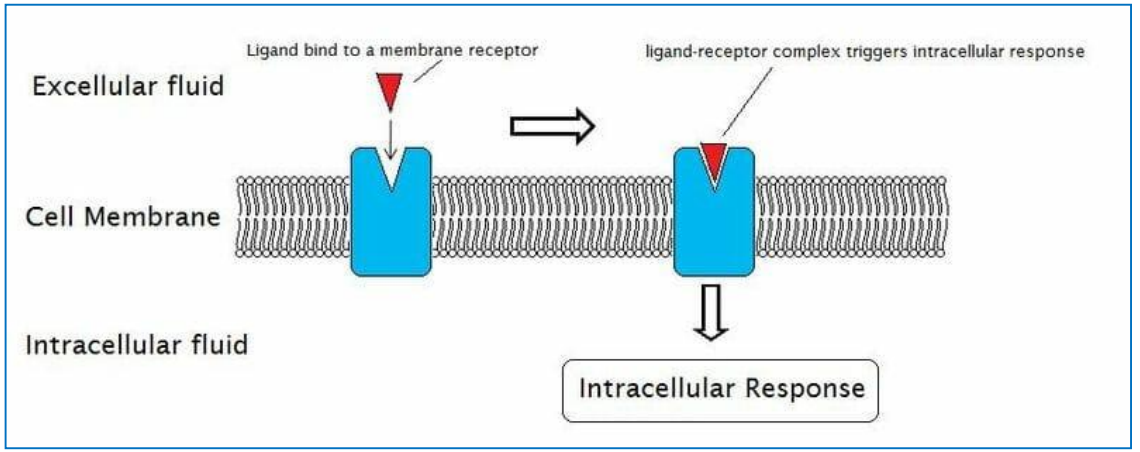
- **Some drugs bind to:**
  - proteins (in patient, or microbes)
  - the genome (cyclophosphamide)
  - microtubules (vincristine)

Pharmacodynamics and Drug Receptors (how drugs work on the body)

- **Most drugs act (bind) on *receptors***
  - in or on cells
  - form tight bonds with the *ligand*
  - exacting requirements (size, shape, stereospecificity)
  - can be *agonists* (salbutamol), or *antagonists* (propranolol)
- **Receptors have *signal transduction methods***

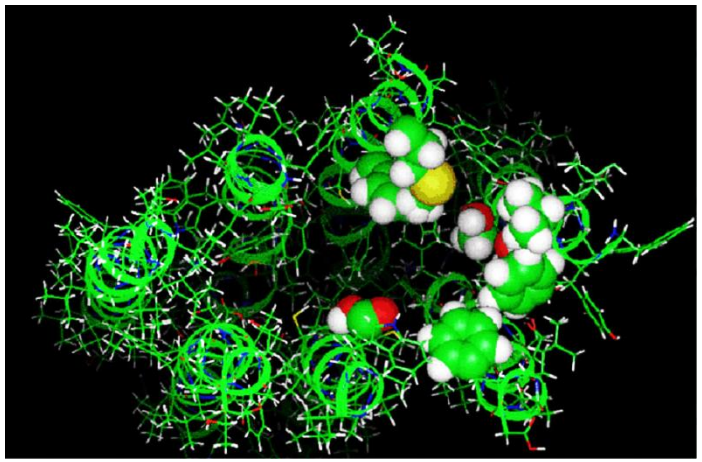
Drug Receptor

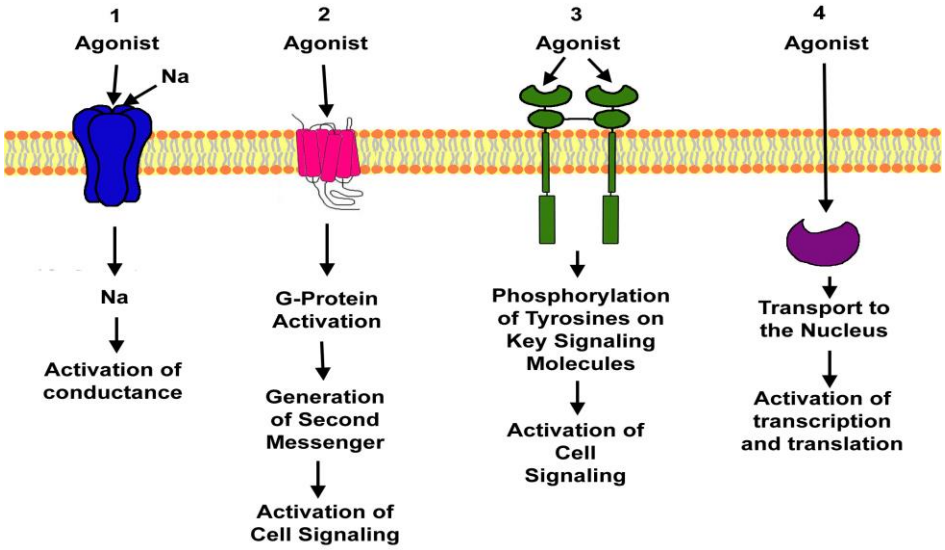
- Any cellular macromolecule to which a neurotransmitter or drug binds to initiate its effects.
- The endogenous function of a receptor is to participate in neurotransmission or physiologic regulation.
- Usually a protein.



Types of Protein Receptors

1. Regulatory – change the activity of cellular enzymes
2. Enzymes – may be inhibited or activated
3. Transport – e.g. Na^+/K^+ ATP'ase
4. Structural – these form cell parts





Factors Governing Drug Actions

- **Affinity** is a measure of the tightness with which a drug binds to the receptor.

$$D + R \underset{\text{Affinity}}{\rightleftharpoons} DR\ Complex$$

- **Intrinsic activity (Efficacy)** is a measure of the ability of an agonist that is bound to the receptor to generate an activating stimulus and produce a change in cellular activity.

Understanding the Concept on Intrinsic Activity

1) Both agonists and antagonists can bind to a receptor. However, only agonist molecules can activate the receptor.

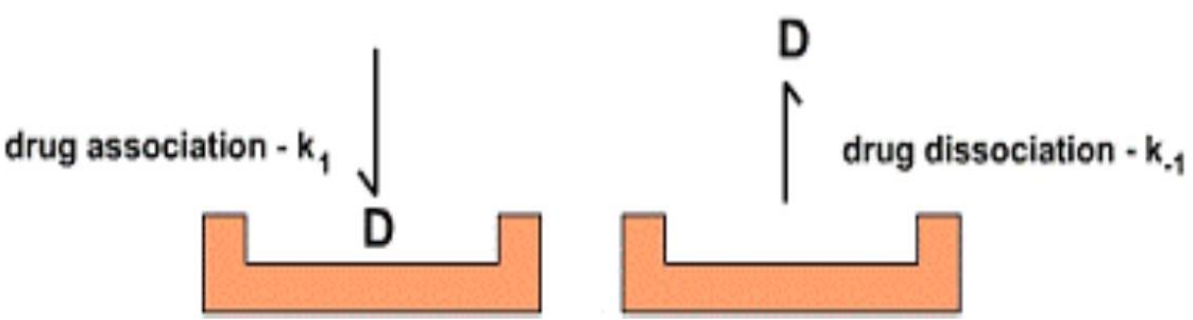
2) Using the symbol e to represent intrinsic activity the physiologic response of a drug can be described by the equation below:

Physiologic response =(**e**) X (the # of receptors occupied) or = $\frac{\mathbf{e}\,[D]}{[D] + Kd}$

Understanding the Concept on Affinity

1) **Affinity** describes the strength of binding to receptors.

2) **k_1** describes the rate at which a drug associates with the receptor while k_{-1} describes the ease at which a drug dissociates from its receptor.



Understanding the Concept on Affinity

$$[D] + [R] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [DR] \longrightarrow \text{effect}$$

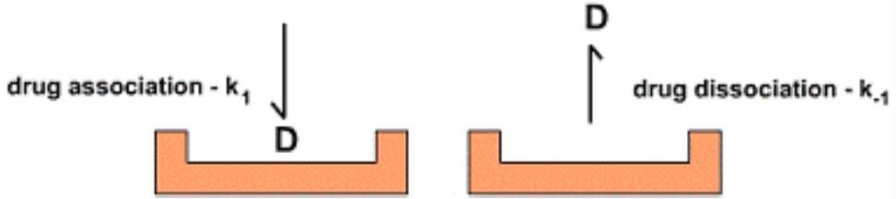
$$[D]\,[R]\,k_1 = [DR]k_{-1}$$

$$K_D = k_{-1}/k_1$$

k_1/k_{-1} = affinity const.

k_{-1}/k_1 = dissociation const.(k_d)

$$\text{Amount of bound to receptor} = \frac{[D]}{[D] + K_D}$$



The *lower* the $\mathbf{k_d}$ the more *potent* the drug

Understanding the Concept on Affinity

Amount bound to receptor = $\frac{[D]}{[D]+KD}$

Terazosin has an equilibrium dissociation constant of **1.0 nM.**

Calculate the percentage of receptors occupied at each Terazosin concentration

Terazosin	**% Receptors Occupied**
0.5 nM	**?**
1.0 nM	**?**
4.0 nM	**?**
10.0 nM	**?**

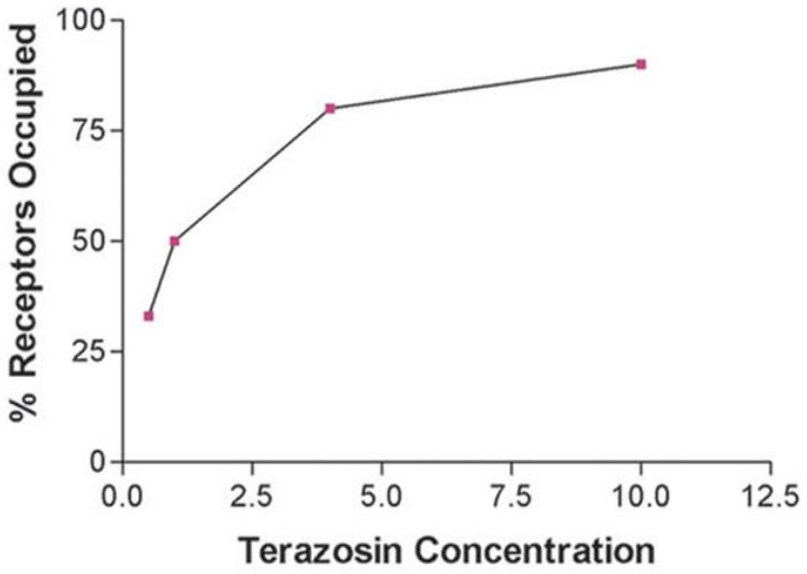
Understanding the Concept on Affinity

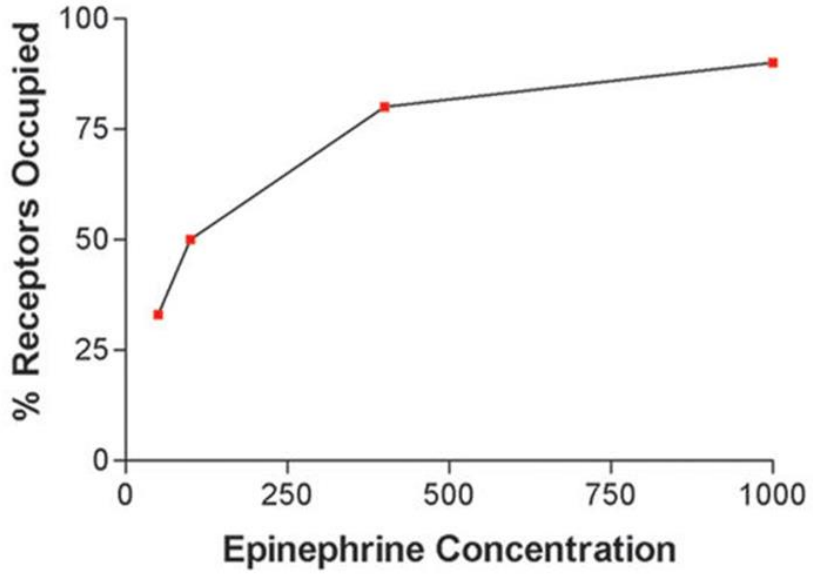
Amount bound to receptor = $\frac{[D]}{[D]+KD}$

Terazosin at:	**% Receptors Occupied**
0.5 nM	33 %
1.0 nM	50 %
4.0 nM	80 %
10.0 nM	90 %

50% OF RECEPTORS WILL BE OCCUPIED WHEN A DRUG IS GIVEN AT A CONCENTRATION EQUAL TO ITS KD

Understanding the Concept on Affinity



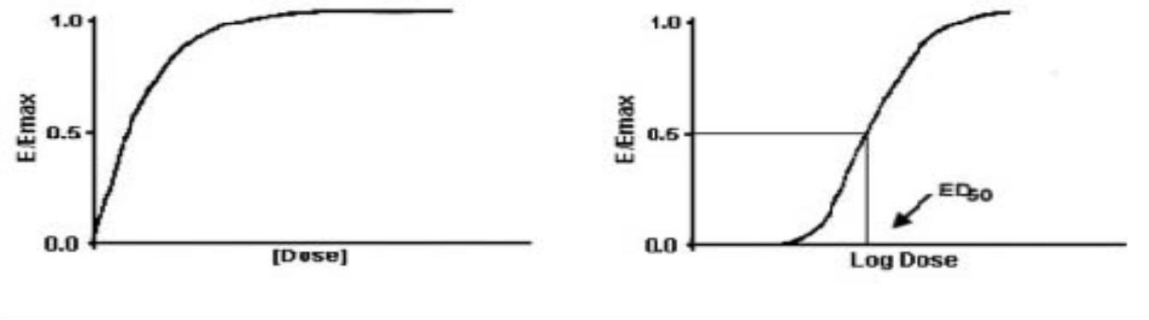


50% OF RECEPTORS WILL BE OCCUPIED WHEN A DRUG IS GIVEN AT A CONCENTRATION EQUAL TO ITS KD

Dose-Response Curve

1) Dose-response relationships are a common way to portray data in both basic and clinical science.

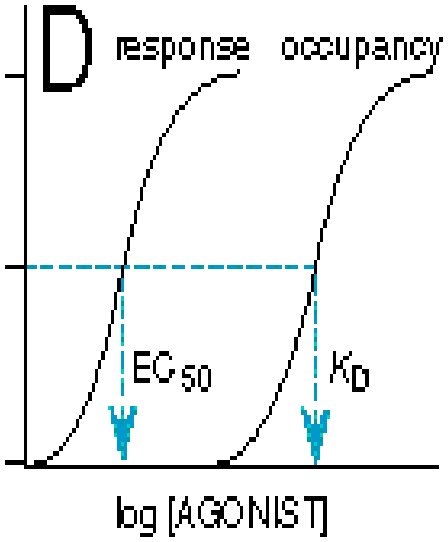
2) To present the data, the concentration of the drug is plotted on the x-axis and the effect would be presented on the y-axis. A plot of drug concentration ([D]) versus effect (E/Emax in the graphs) is a rectangular hyperbola.



The dose at which 50% of the maximal effect is observed is referred to as the **ED50**

Spare Receptors

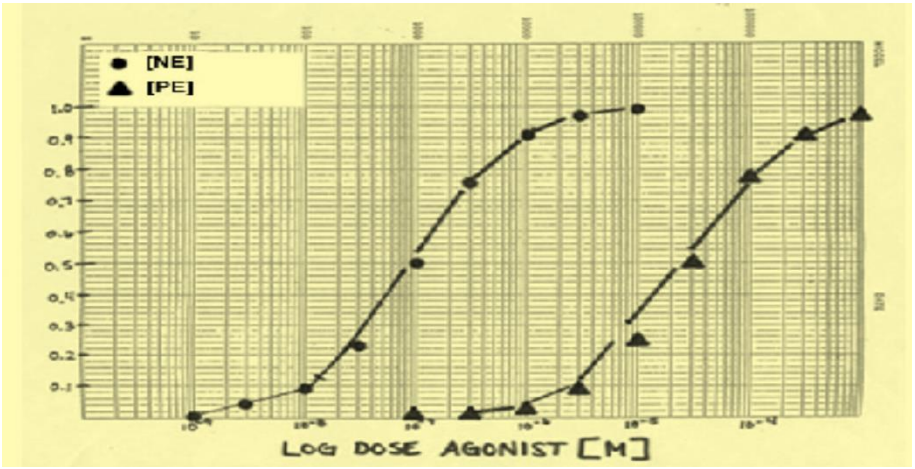
- **allow maximal response without total receptor occupancy – increase sensitivity of the system.**
- **spare receptors can bind (and *internalize*) extra ligand preventing an exaggerated response if too much ligand is present.**



The receptor theory assumes that all receptors should be occupied to produce a maximal response. In that case at half maximal effect EC50=kd. Sometimes, full effect is seen at a fractional receptor occupation.

Potency

- **Potency** refers to the concentration of a drug required to produce a given physiologic effect. Drugs with high receptor affinity will exhibit greater potency than those with lower affinity



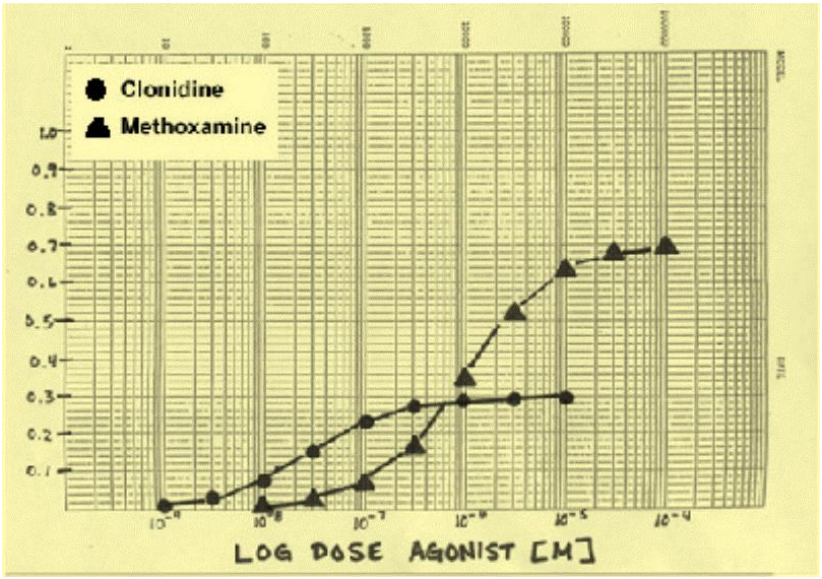
Norepinephrine (NE) has a higher affinity for a receptor than does phenylephrine(PE).

The ED50 for norepinephrine is 100 nM while the ED50 for phenylephrine is 35,000 nM.

Norepinephrine would be said to have greater **potency** than phenylephine.

Efficacy

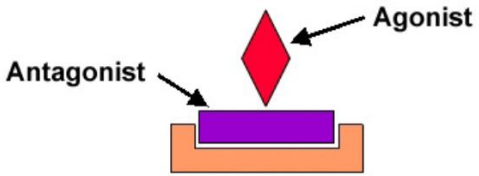
- **Efficacy** is often used to describe the maximal level of response a drug can produce.



Norepinephrine would have a greater efficacy than methoxamine which in turn would have a greater efficacy than **Clonidine**.

Agonist and Antagonist

- Agonist has affinity plus intrinsic activity
- Antagonist has affinity but no intrinsic activity
- Partial agonist has affinity and *less* intrinsic activity
- Competitive antagonists can be overcome

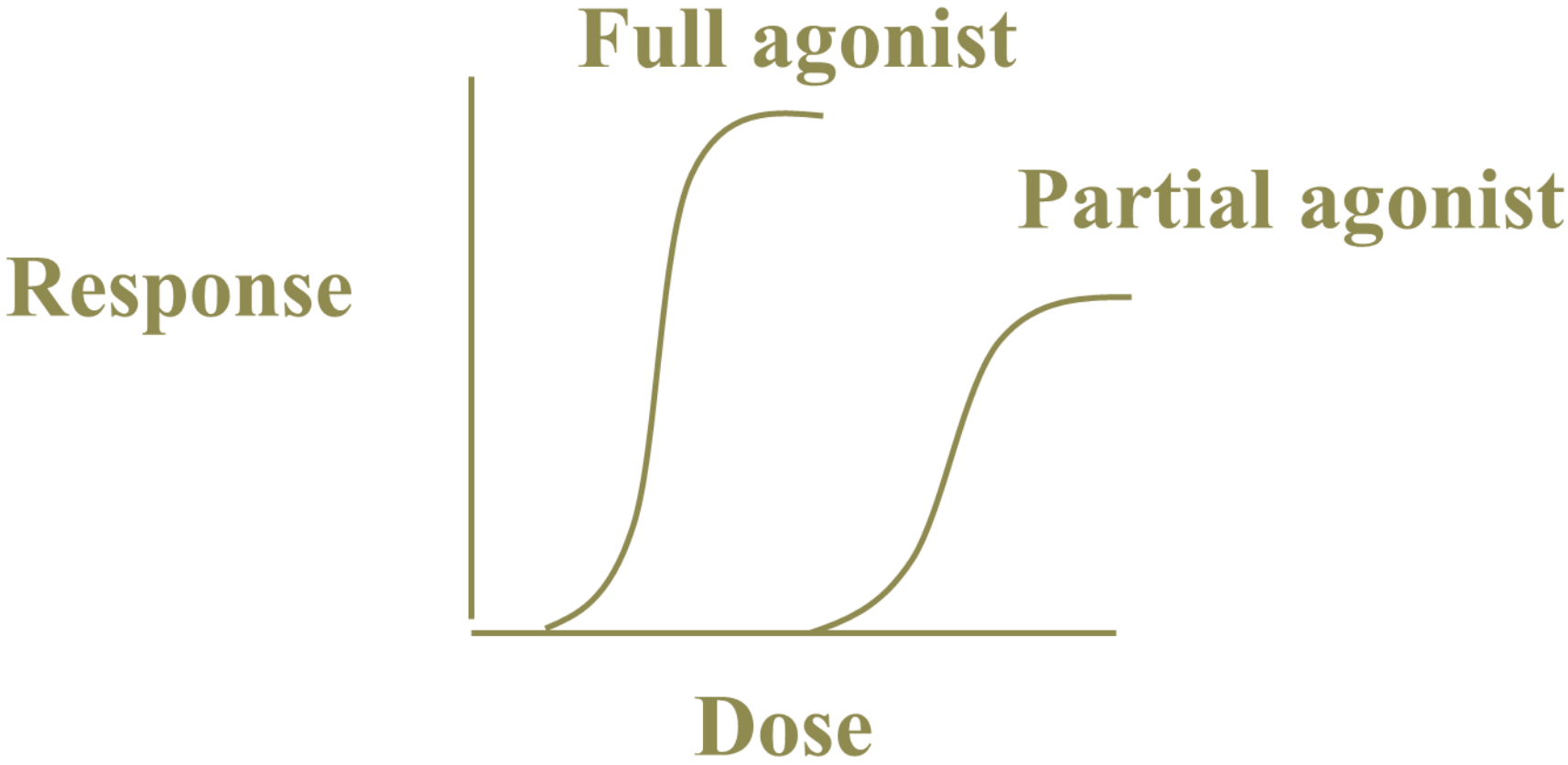


Antagonists bind to receptors but do not lead to receptor activation

Agonist Drugs

- **Agonist:** Drugs that interact with and activate receptors; they possess both affinity and efficacy.
- **Two types:**
  - **Full agonist:** an agonist with maximal efficacy
  - **Partial agonist:** an agonist with less then maximal efficacy

Agonist Dose Response Curves

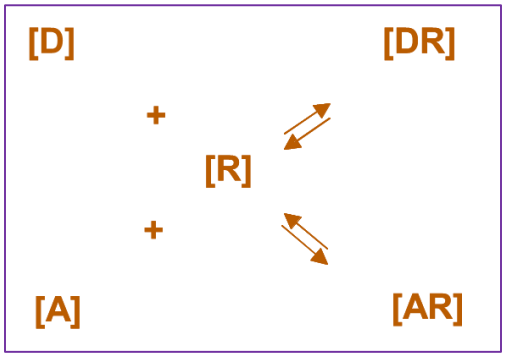


Antagonist Drug

- **Antagonists** interact with the receptor but do **NOT** change the receptor.
- They have affinity but NO efficacy
- **Two types:**
  - Competitive
  - Noncompetitive

Antagonist Drug

- The antagonist [A] and agonist [D] are competing for the same limited number of receptors [R].



- Amount of agonist bound to the receptor in the presence of an antagonist $= \frac{[D]}{[D]+Kd(1+[A]/Ka)}$

Antagonist Drug

Examine the effect of Terazosin (Ka= 1.0 nM) on the occupancy of the alpha1-adrenergic receptor by epinephrine (= K_D 100 nM).

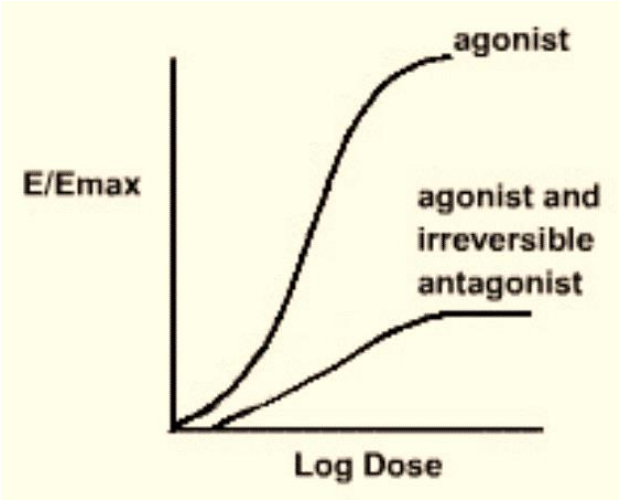
Epinephrine	% Receptors Occupied **(Teraz = 0)**	%Receptors Occupied **(Teraz = 1nM)**	% Receptors Occupied **(Teraz = 10 nM)**
50.0 nM	?	?	?
100.0 nM	?	?	?
400.0 nM	?	?	?
1000.0 nM	?	?	?

Competitive Antagonist

1) Reversible binding to the receptor.
2) The blockade can be overcome by increasing the agonist concentration.
3) The maximal response of the agonist is not decreased.
4) The agonist dose-response curve in the presence of a competitive antagonist is displaced to the right, parallel to the curve in the absence of agonist.

Non-competitive Antagonist

- Drug binds to receptor and stays bound
- Irreversible – does not let go of receptor
- Produces slight dextral shift in the agonist DR curve in the low concentration range
- This looks like competitive antagonist
- But, as more and more receptors are bound (and essentially destroyed), the agonist drug becomes incapable of eliciting a maximal effect



Therapeutic Index

- The **Therapeutic Index** is the ratio between the dosage of a drug that produce a toxic (or lethal) effect and the dosage that produce a therapeutic effect.
- The dose required to produce death in 50% of a population is referred to as the LD50.

- **ED50** - Median Effective Dose 50; the dose at which 50 percent of the population or sample manifests a given effect; used with quantal DR curves

- **TD50** - Median Toxic Dose 50 - dose at which 50 percent of the population manifests a given toxic effect

- **LD50** - Median Toxic Dose 50 - dose which kills 50 percent of the subjects

Therapeutic Index

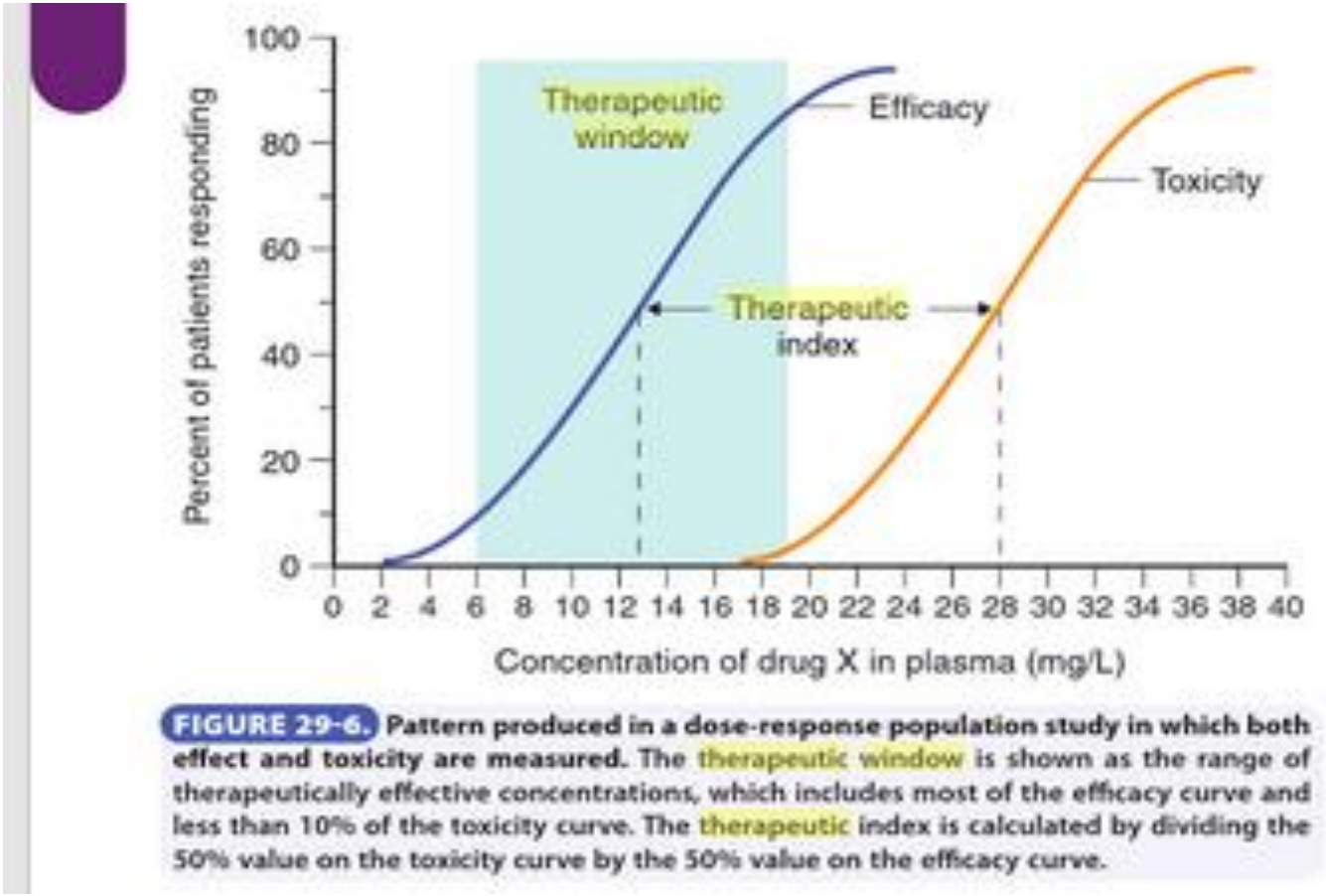


FIGURE 29-6. Pattern produced in a dose-response population study in which both effect and toxicity are measured. The therapeutic window is shown as the range of therapeutically effective concentrations, which includes most of the efficacy curve and less than 10% of the toxicity curve. The therapeutic index is calculated by dividing the 50% value on the toxicity curve by the 50% value on the efficacy curve.

Therapeutic Index

$$\text{Therapeutic Index} = \frac{\text{TD50 or LD50}}{\text{ED50}}$$

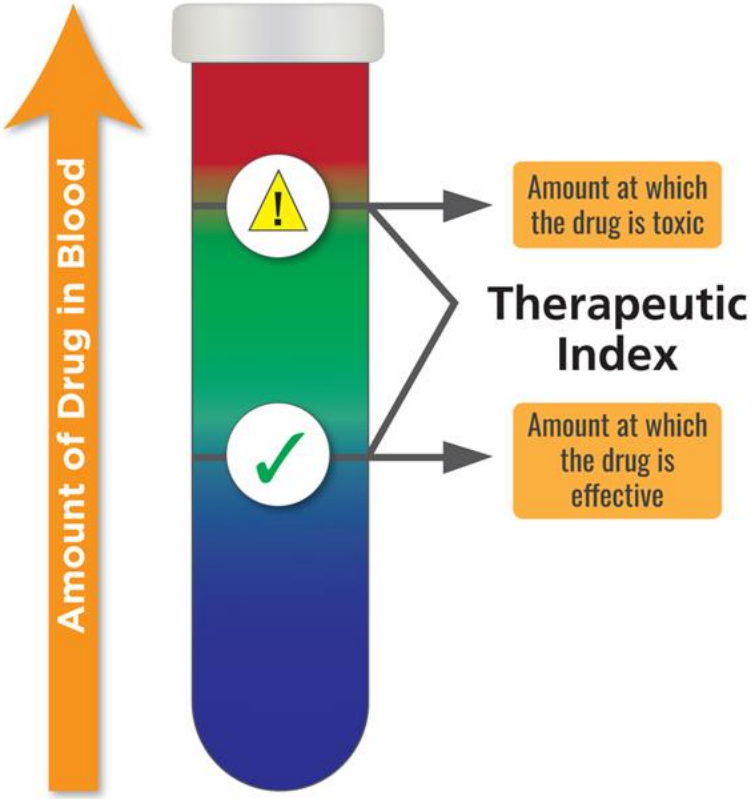
The ED50 for the beneficial effect of blood pressure lowering is 0.4 nM while the LD50 is 40 nM. Therefore, the therapeutic index will be:

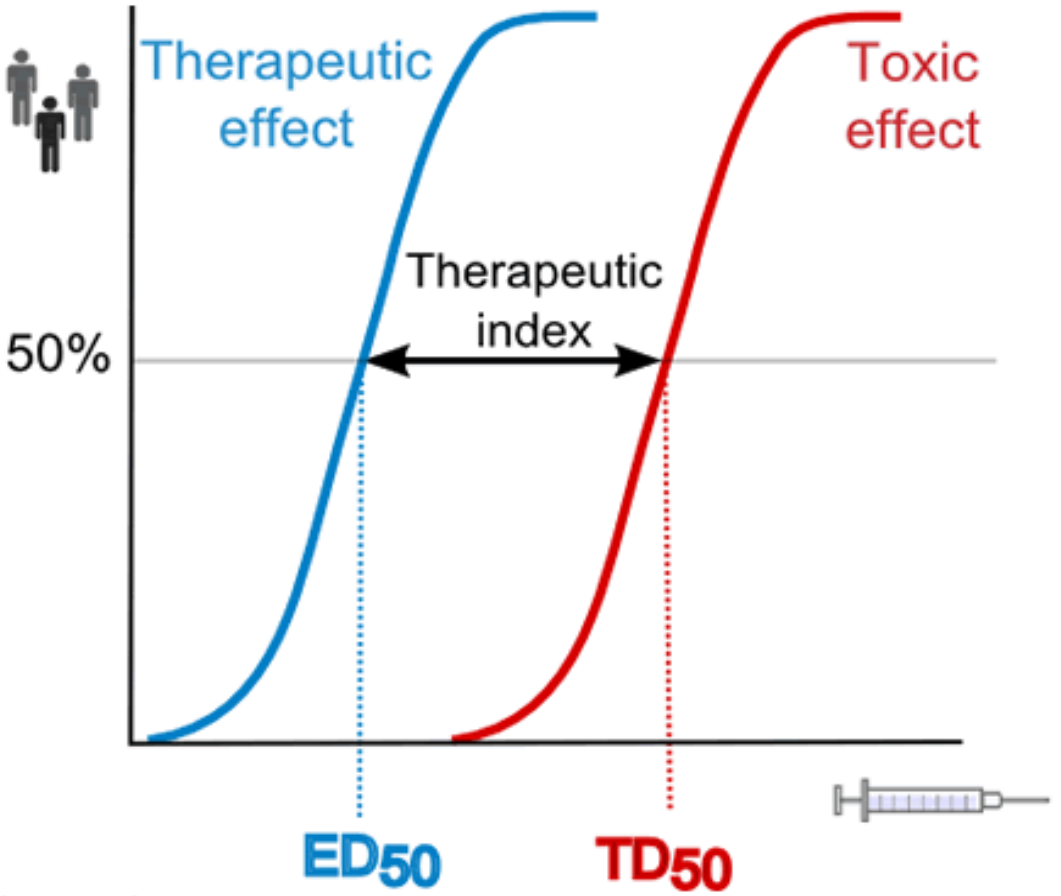
$$TI = \frac{LD50}{ED\ 50}$$

$$TI = \frac{40.0\ nM}{0.4\ nM}$$

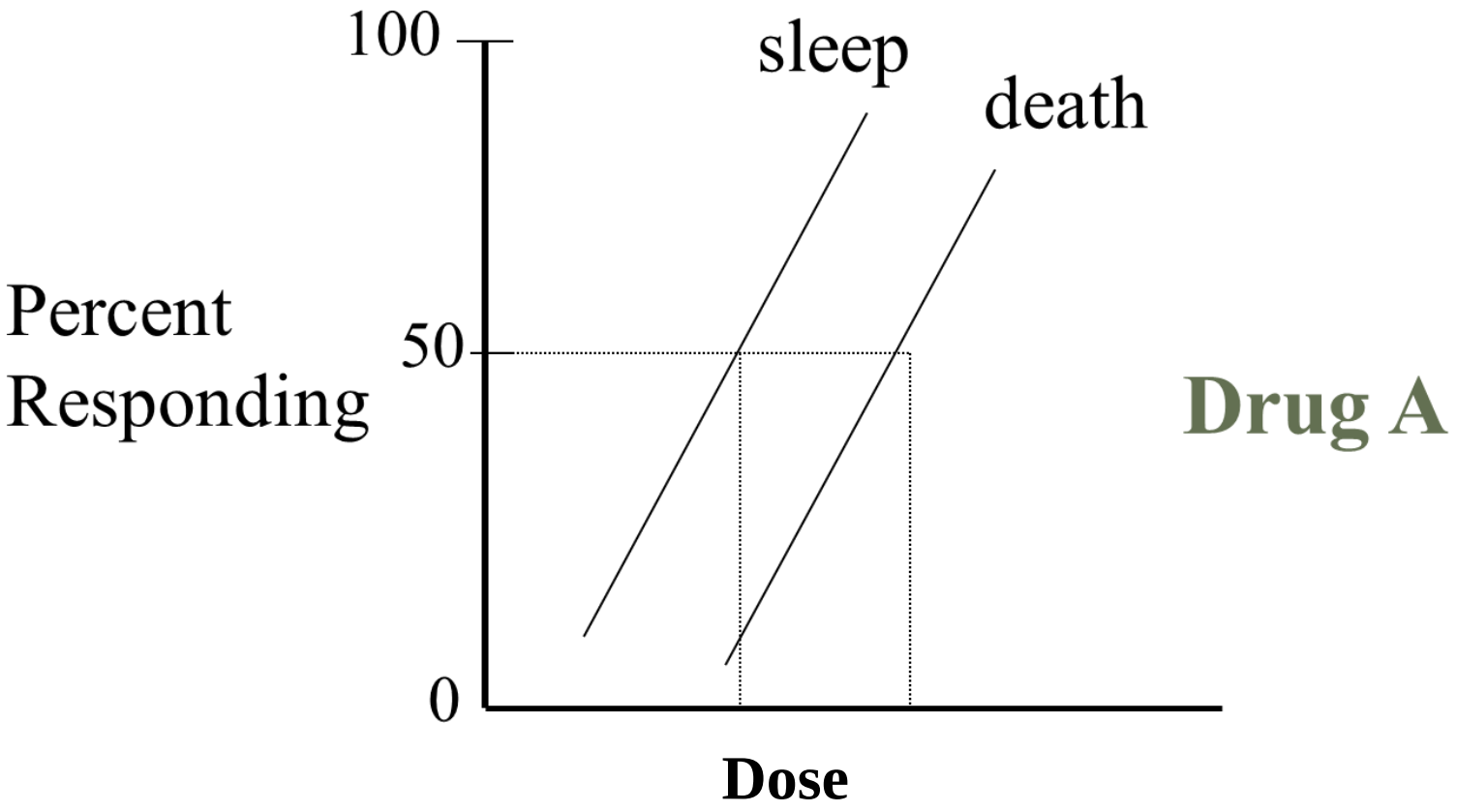
$$TI = 100$$

Therapeutic Index

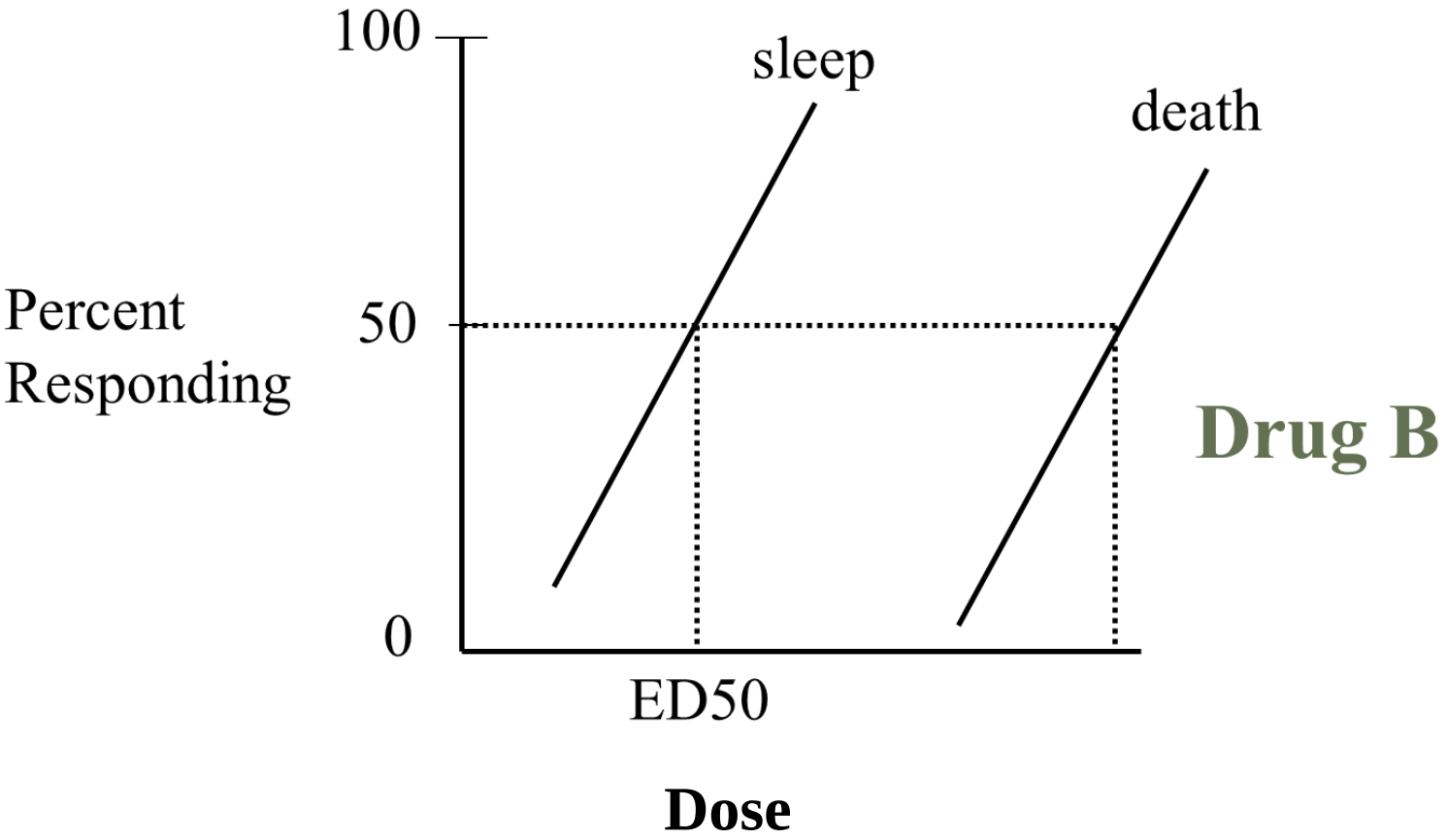




Therapeutic Index



Therapeutic Index



Therapeutic Index

- The higher the **TI** the better efficacy of the drug.

- **TI's** vary from: 1.0 (some cancer drugs)

  to: >1000 (penicillin)

- Drugs acting on the same receptor or enzyme system often have the *same* **TI**: (eg 50 mg of Hydrochlorothiazide about the same as 2.5 mg of Indapamide).

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Pharmacokinetics

Any questions?