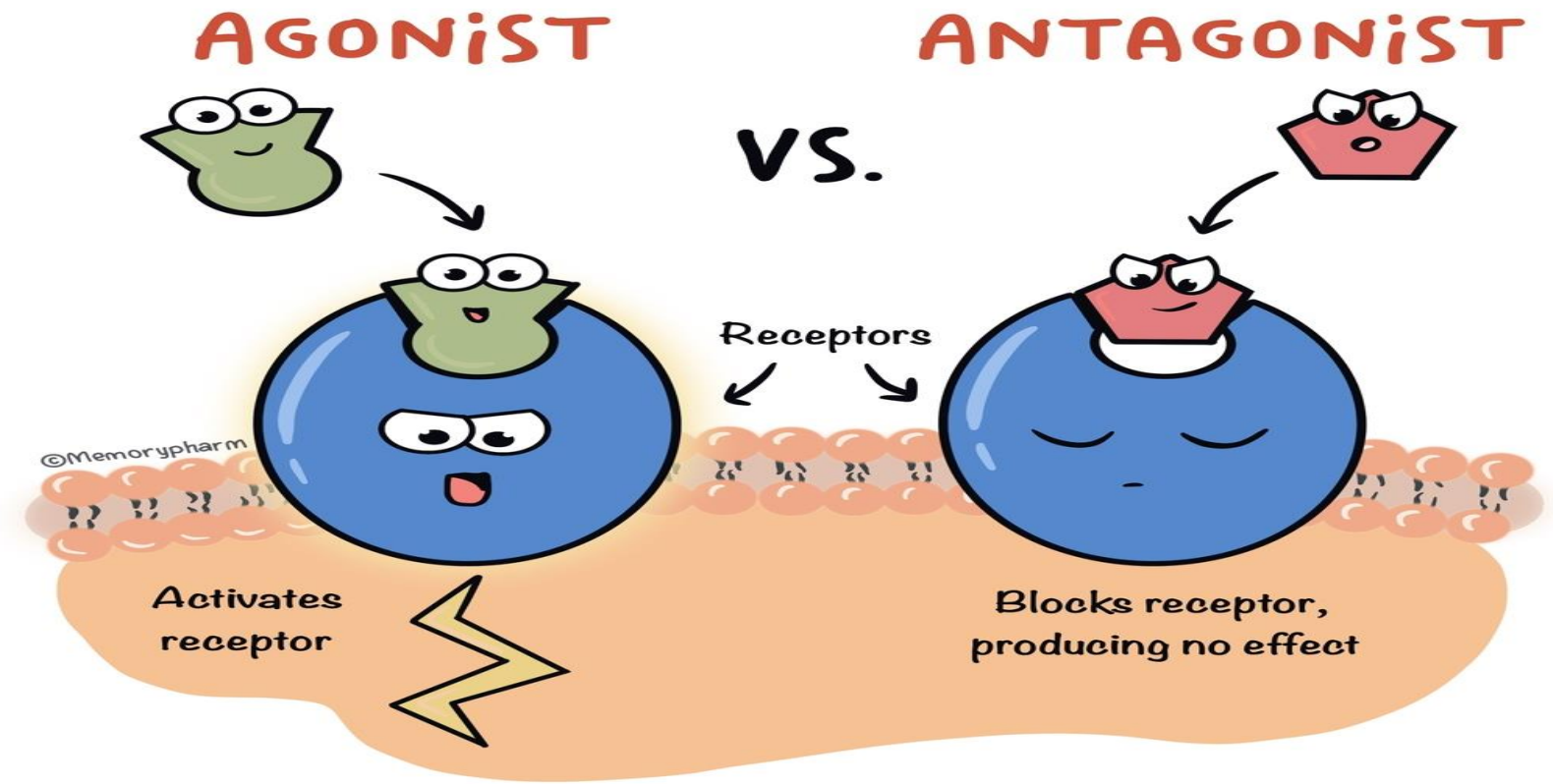
Agonist and antagonist



Intrinsic Activity

an agonist binds to a receptor and produces a biologic response based on the

1-concentration of the agonist

2-, its affinity for the receptor and

3- the fraction of occupied receptors.

However, the intrinsic activity of a drug further determines its ability to **fully or partially** activate the receptors.

Drugs may be categorized
according to their intrinsic activity and resulting Ema**x** values
([Emax] = the maximal effect of the drug.

- Agonist: an agent that can bind to a receptor and produce a biologic response

- Agonists usually mimic the actions of the original endogenous ligand on the receptor

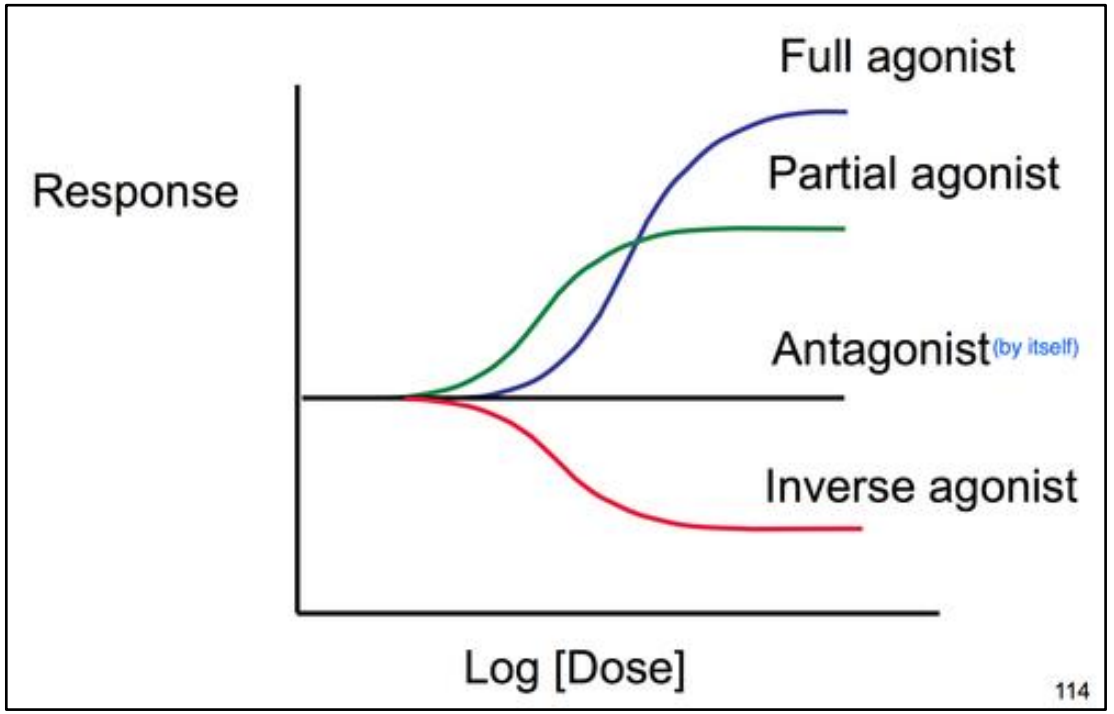
(e.g. Norepinephrine on β1 receptor of the heart)

- Agonists stabilize the receptors in their active state

- The magnitude of the drug effect depends on:
  - The concentration of the drug at the receptor site which depends on:
    - The dose of the drug administered
    - The rate of the drug's ADME

Agonists

- Full agonist
- Partial agonists
- Inverse Agonists



Agonist: any substance which has the affinity to combine with the receptors and causes receptors stimulation and pharmacological action. Example is acetylcholine which combines to muscarinic receptors and adrenaline which combines to the adrenergic receptors

Full agonists

- Full agonist: A drug that binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand

- A full agonist has a strong affinity to the receptor and good efficacy

Full agonists

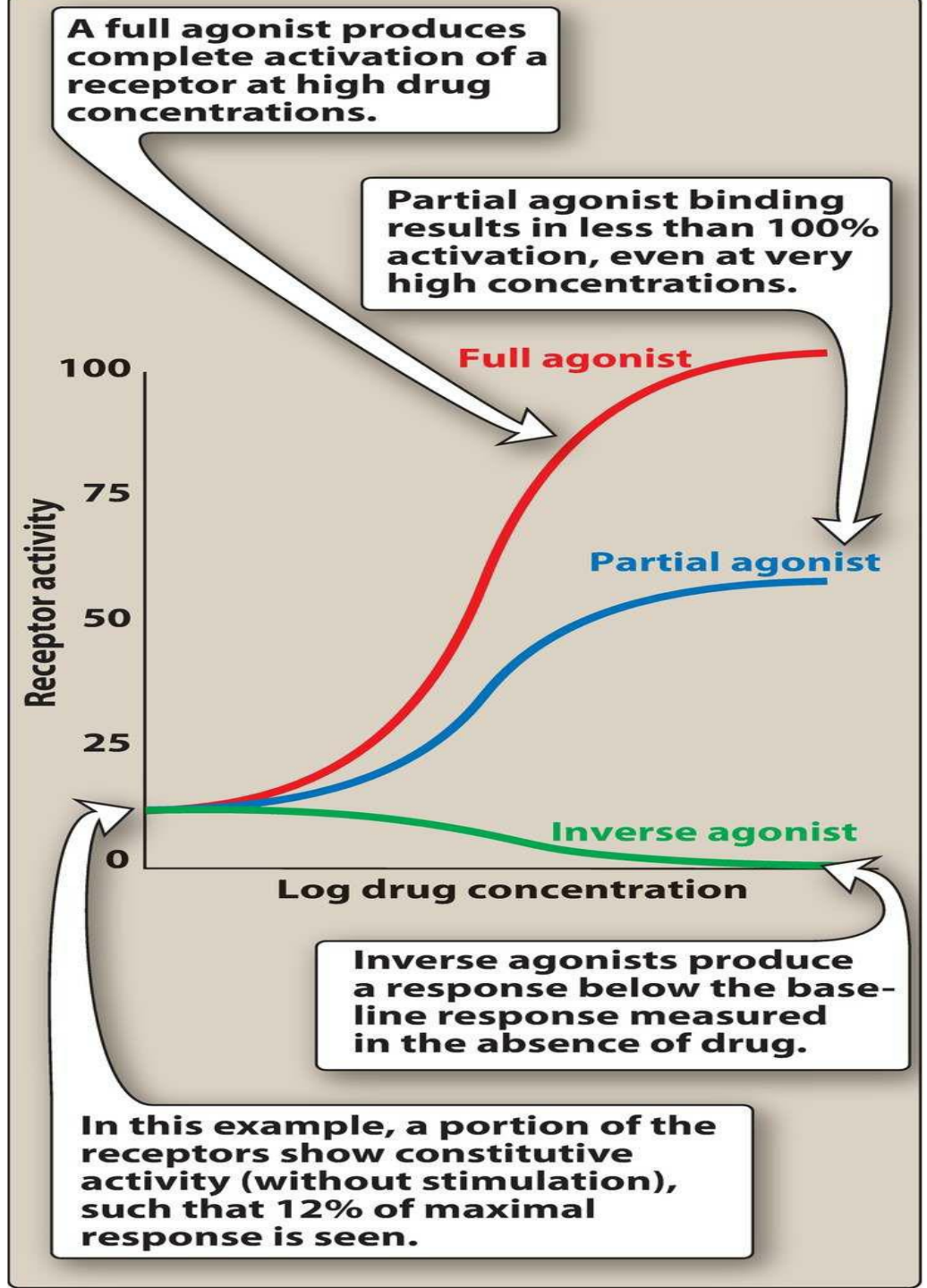
If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is a full agonist).

Full agonists bind to a receptor, stabilizing the receptor in its active state and are said to have an intrinsic activity of one.

All full agonists for a receptor population should produce the same Emax.
For example, *phenylephrine* is a full agonist at α1-adrenoceptors, because it produces the same Emax as the endogenous ligand, norepinephrine.

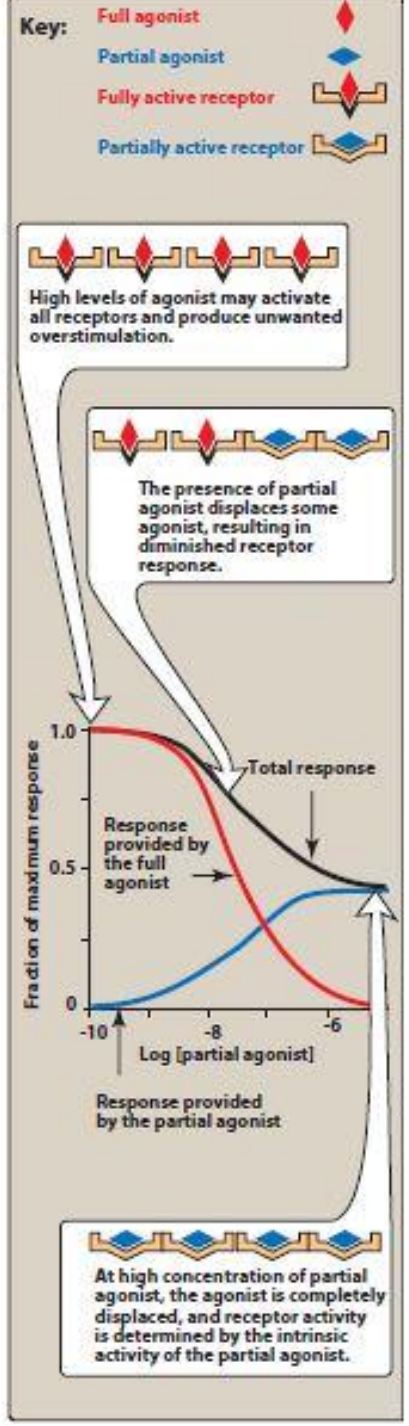
Upon binding to α1-adrenoceptors on vascular smooth muscle, both norepinephrine and *phenylephrine* stabilize the receptor in its active state,.

For full agonists, the dose–response curves for receptor binding and each of the biological responses should be comparable.

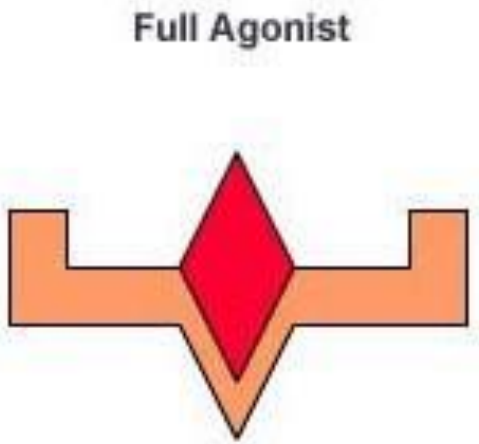

A full agonist produces complete activation of a receptor at high drug concentrations.
Partial agonist binding results in less than 100% activation, even at very high concentrations.
Full agonist
Partial agonist
Inverse agonist
100
75
50
25
0
Receptor activity
Log drug concentration
Inverse agonists produce a response below the base-line response measured in the absence of drug.
In this example, a portion of the receptors show constitutive activity (without stimulation), such that 12% of maximal response is seen.

Partial agonists

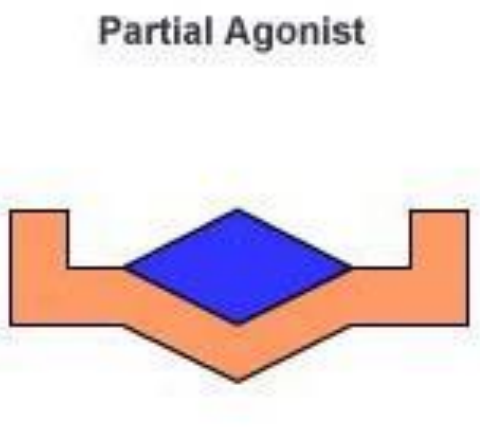
- Partial agonists have efficacies greater than zero but less than that of a full agonist
- A partial agonist can not produce an Emax of as great a magnitude as a full agonist
- The affinity of a partial agonist might be greater than, less than or equal to a full agonist
- A partial agonist may act as an antagonist of a full agonist



Partial agonist: is a drug which has affinity and some efficacy to the receptors and it does not produce maximum effect even when all the receptors are occupied and it may antagonize the action of other agonists that have a greater efficacy.



The full agonist can induce a conformational change in the receptor leading to a maximal effect. The ability to induce changes in the receptor conformation leading to activation is a measure of the intrinsic activity.



Partial agonists can induce some degree of receptor activation but not of sufficient magnitude for a maximal response

Partial agonists

As the number of receptors occupied by the partial agonist increases, the number of receptors that can be occupied by the full agonist decreases and therefore Emax would decrease until it reached the Emax of the partial agonist.

This potential of partial agonists to act as both an agonist and antagonist may have therapeutic utility.

For example, *aripiprazole*, an atypical antipsychotic, is a partial agonist at selected dopamine receptors. Overactive dopaminergic pathways tend to be inhibited by *aripiprazole*, whereas underactive pathways are stimulated. This might explain the ability of *aripiprazole* to improve symptoms of schizophrenia, with a small risk of causing extrapyramidal adverse effects.

Inverse agonists

Typically, unbound receptors are inactive and require interaction with an agonist to assume an active conformation.

However, some receptors show a spontaneous conversion from R to R* in the absence of an agonist. Inverse
agonists, unlike full agonists, stabilize the inactive R form and cause R* to convert to R.

This decreases the number of activated receptors to below that observed in the absence of drug

.Thus, inverse agonists have an intrinsic activity less than zero, reverse the activation state of receptors, and exert the opposite pharmacological effect of agonists.

Inverse Agonists

- Stabilize the inactive receptor state
- This decreases the number of activated receptors below that in the absence of the drug
- Inverse agonists reverse the activity of receptors and produce the opposite pharmacological effects of a full agonist

Antagonists

- Antagonist: An agent (drug) that decreases or opposes the actions of another drug or endogenous ligand

- An antagonist binds to a receptor and blocks its physiologic response
  (e.g. Antihistamine, used for allergy)

- 2 types of antagonists
  - Competitive antagonists
  - Irreversible antagonists

Antagonists bind to a receptor with high affinity but possess zero intrinsic activity. An antagonist has no effect on biological function in the absence of an agonist, but can decrease the effect of an agonist when present.
Antagonism either
blocking the drug's ability to bind to the receptor or by blocking its ability to activatethe receptor.

Competitive antagonist

- An antagonist that binds to the same site on the receptor as the agonist
- Prevents an agonist from binding to its receptor and maintains the receptor in its inactive state
- The effect can be overcome by adding more agonist
- Increase EC_{50}

EC_{50} = drug dose that shows 50% of maximal response.

For example, the antihypertensive drug terazosin competes with the endogenous ligand norepinephrine at α1-adrenoceptors, thus decreasing vascular smooth muscle tone and reducing blood pressure.
However, increasing the concentration of agonist relative to antagonist can overcome this inhibition. Thus, competitive antagonists characteristically shift the agonist doseresponse
curve to the right (increased EC50) without affecting Emax.

Irreversible antagonists

- Non-competitive
- Cannot be overcome by adding more agonists
- Mechanism:
  - The antagonist binds covalently or with high affinity to the active site of the receptor reducing the amount of the receptor available to the agonist
  - The antagonist binds to a site (allosteric site) preventing the receptor from being activated even when the agonist binds to the active site

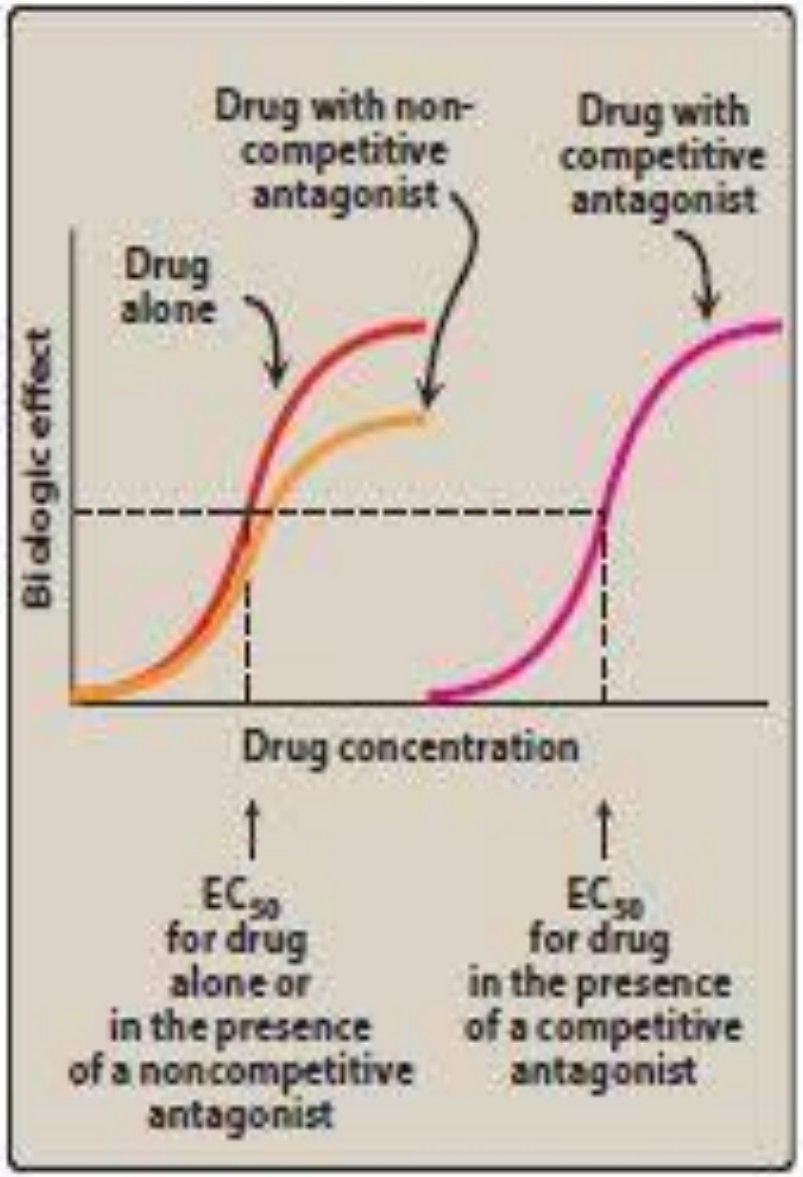
Competitive vs non-competitive antagonism

For example, the antihypertensive drug *terazosin* competes with the endogenous ligand norepinephrine at α1-adrenoceptors,

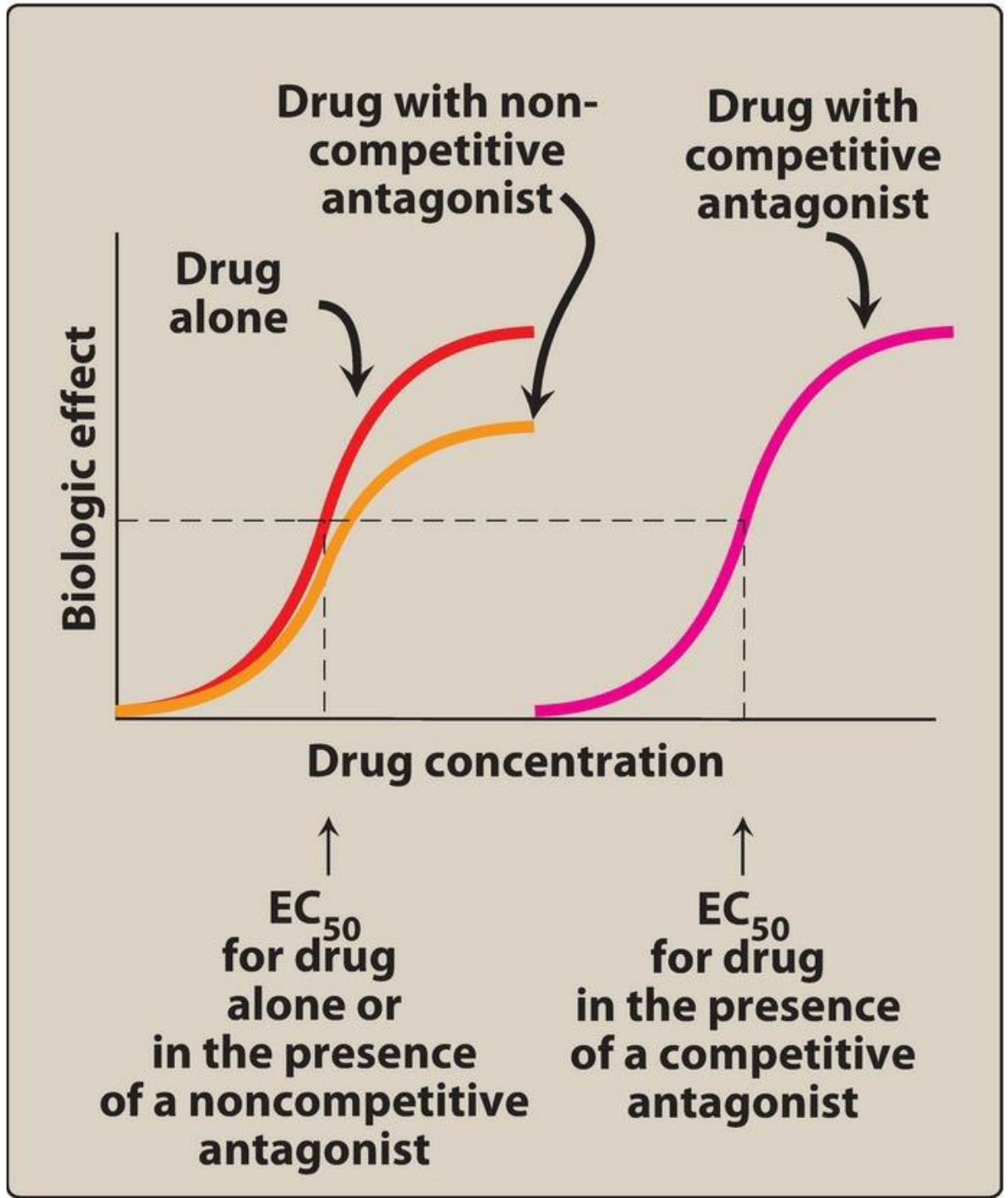
thus decreasing vascular smooth muscle tone and reducing blood pressure.

However, increasing the concentration of agonist relative to antagonist can overcome this inhibition.

Thus, competitive antagonists characteristically shift the agonist dose–response curve to the right (increased EC50) without affecting Emax



Effects of drug antagonists. EC_{50} = drug dose that shows 50% of maximal response.



Effects of drug antagonists. EC_{50} = drug dose that shows 50% of maximal response.

3. Allosteric antagonists

binds to a site (allosteric site) other than the agonist-binding site and prevents receptor activation by the agonist.

It causes a downward shift of the Emax of an agonist, with no change in the EC50 value.
example of an allosteric agonist is picrotoxin, which binds to the inside of the GABA controlled chloride channel. When picrotoxin binds inside the channel, no chloride can pass through the channel, even when GABA fully occupies the receptor.

4. Functional antagonism

An antagonist may act at a completely separate receptor, initiating effects that are functionally opposite those of the agonist.
example is the functional antagonism by epinephrine to histamine-induced bronchoconstriction.
Histamine binds to H1 histamine receptors on bronchial smooth muscle, causing bronchoconstriction of the bronchial tree. Epinephrine is an agonist at β2-adrenoceptors on bronchial smooth muscle, which causes the muscles to relax.
This functional antagonism is also known as “physiologic antagonism.”

Quantal Dose–Response Relationships

Quantal-dose response (dose percent effect): for determination of drug response in the population, it is used for all or none effect as prevention of convulsion, cardiac arrhythmias and in acute toxicity studies.

Another important dose–response relationship is that between the dose of the drug and the proportion of apopulation of patients that responds to it.

These responses are known as quantal responses, because, for any individual, either the effect occurs or it does not.

For example, a quantal dose–response relationship can be determined in a population for the antihypertensive drug *atenolol*.
A positive response is defined as a fall of at least 5 mm Hg in diastolic blood pressure.
Quantal dose– response curves are useful for determining doses to which most of the population responds.

Therapeutic index

- **Therapeutic index** of a drug: the ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in 50% of the population

- $$\text{Therapeutic index} = \frac{TD_{50}}{ED_{50}}$$

TD_{50}: the drug dose the produces a toxic effect in 50% of the population

ED_{50}: the drug dose the produces a therapeutic effect in 50% of the population

Therapeutic index is the ratio of toxic dose to the effective dose

Therapeutic index = toxic dose / effective dose

Therapeutic index is a measure of the drug safety, the larger the index, the safer is the drug.

Lethal dose (LD50): it is the dose that kills 50% of the experimental animals; it is also useful in finding the therapeutic dose in the early experimental studies of drug discovery. It can also be used to measure the therapeutic index a follow:

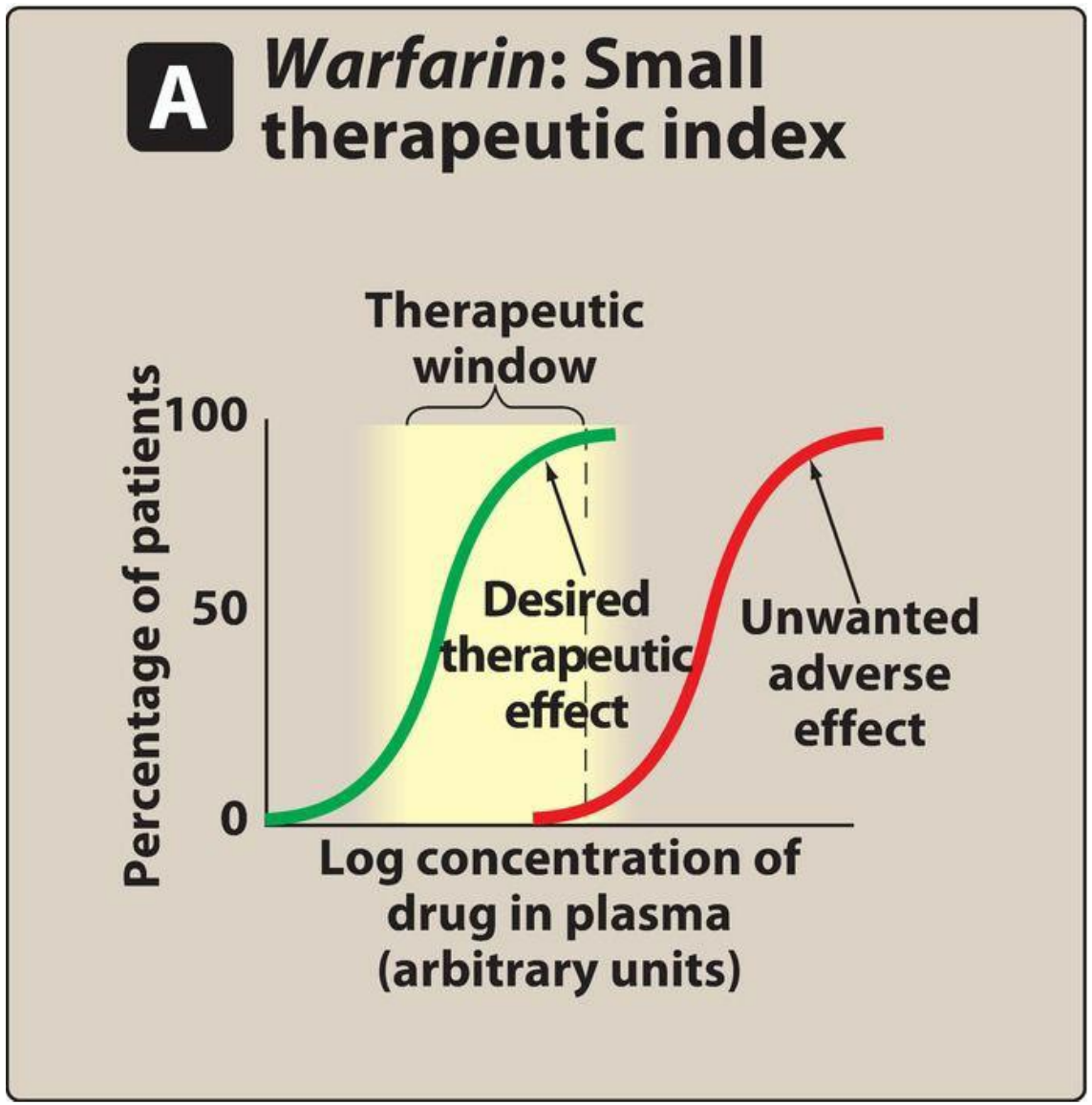
Therapeutic index = LD50/ ED50

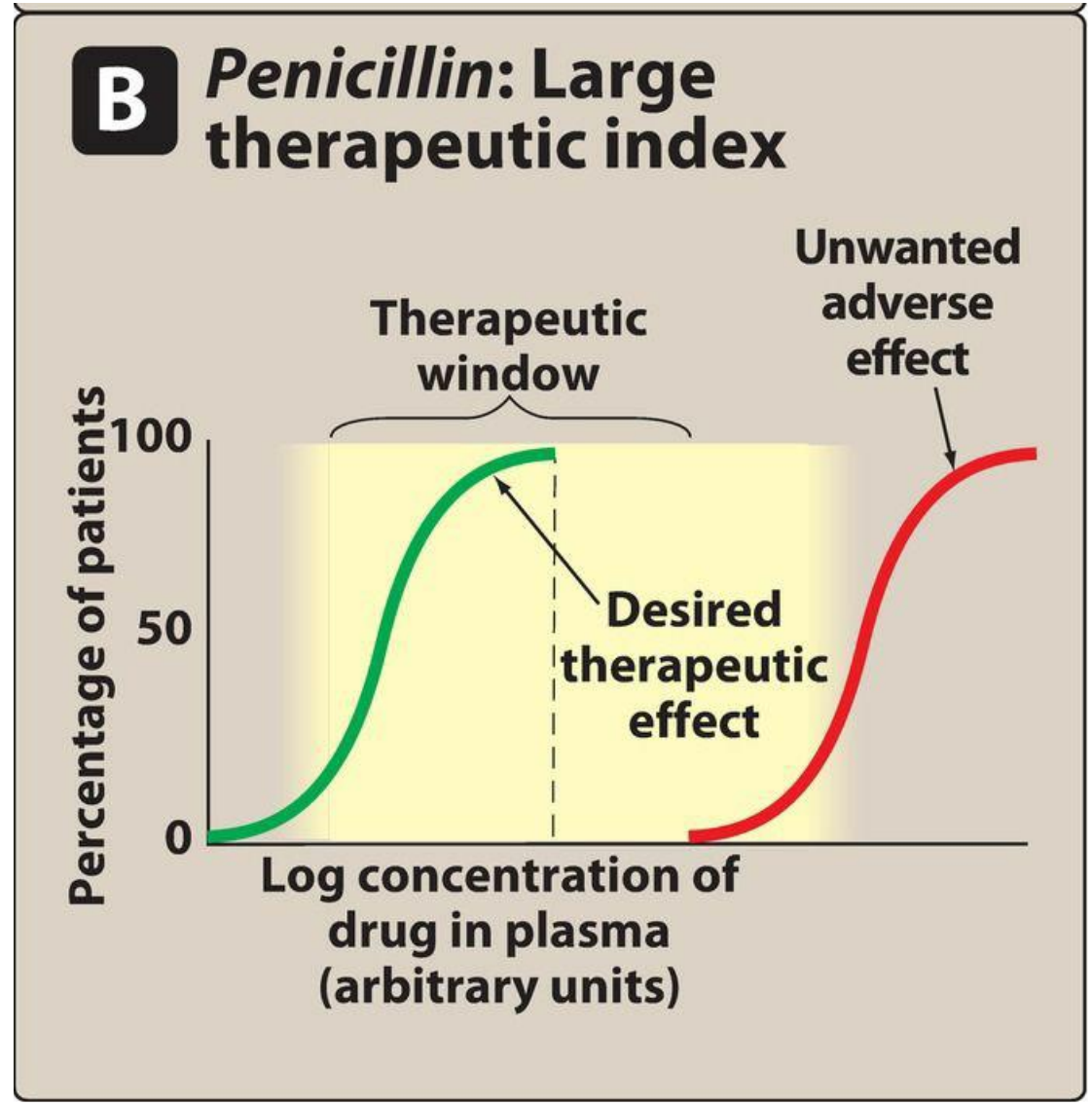
Clinical usefulness of the therapeutic index

Although high TI values are required for most drugs, some drugs with low therapeutic indices are routinely used to treat serious diseases.

In these cases,

the risk of experiencing adverse effects is not as great as the risk of leaving the disease untreated. e. g. the responses to *warfarin*, an oral anticoagulant with a low TI, and *penicillin*, an antimicrobial drug with a large TI


A
Warfarin: Small therapeutic index
Therapeutic window
Percentage of patients
100
50
0
Desired therapeutic effect
Unwanted adverse effect
Log concentration of drug in plasma (arbitrary units)


B
Penicillin: Large therapeutic index
Unwanted adverse effect
Therapeutic window
Percentage of patients
100
50
0
Desired therapeutic effect
Log concentration of drug in plasma (arbitrary units)


Thank
you