Pharmacodynamics I

PHC 721

Winter 2022

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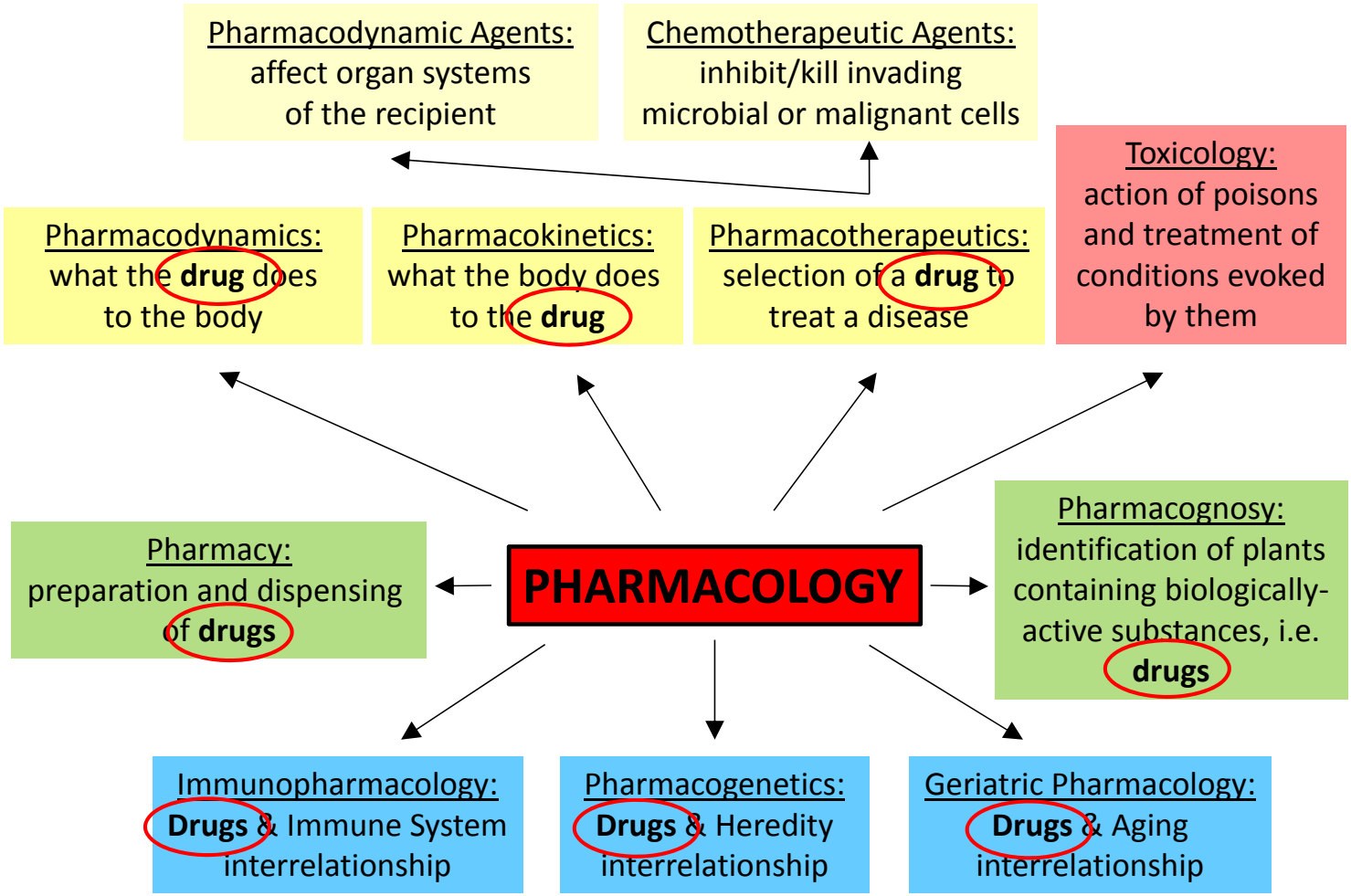

Pharmacodynamic Agents:
affect organ systems of the recipient
Chemotherapeutic Agents:
inhibit/kill invading microbial or malignant cells
Toxicology:
action of poisons and treatment of conditions evoked by them
Pharmacodynamics:
what the drug does to the body
Pharmacokinetics:
what the body does to the drug
Pharmacotherapeutics:
selection of a drug to treat a disease
Pharmacognosy:
identification of plants containing biologically-active substances, i.e. drugs
Pharmacy:
preparation and dispensing of drugs
PHARMACOLOGY
Immunopharmacology:
Drugs & Immune System interrelationship
Pharmacogenetics:
Drugs & Heredity interrelationship
Geriatric Pharmacology:
Drugs & Aging interrelationship

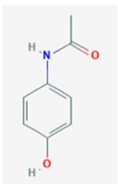
DRUG:

Any chemical agent that has an effect on biological processes.

By law, Chlorine (water), Fluoride (water), Iodides (table salt), Tobacco & Alcohol are considered 'non-drugs' (no oversight by the U.S. Food and Drug Administration)

Chemical Name:
describes molecular structure

* 4-Acetamidophenol $HOC_6H_4NHCOCH_3$



Nonproprietary (Generic) Name:
abbreviation of the chemical name

* Acetaminophen Paracetamol

↘ name in other countries continent

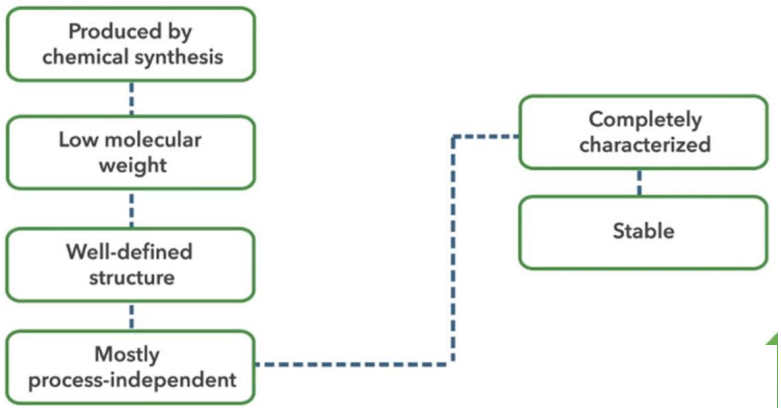
Proprietary (a.k.a., Trade, Brand) Name:
established by the company selling the product and protected by copyright (®, ™).

Pharmacologic / Therapeutic Class (Family):
shares a similar mechanism of action (e.g., COX inhibitors)
and/*or physiologic effect (e.g., Analgesic)*
on pain

* Analgesic

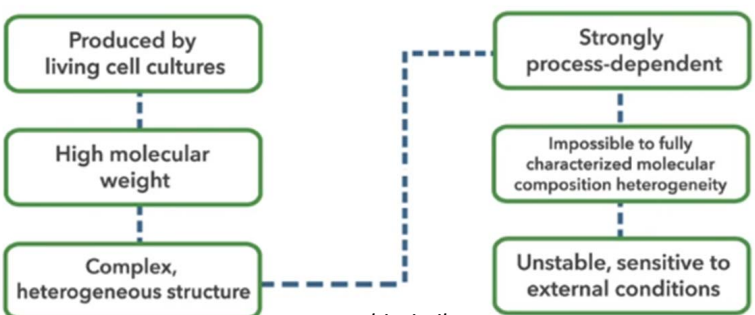
Small Molecule Drugs *vs.* Biologics

Chemical/Small Molecule



Biological/Biologic

not small
produce by biological process



www.tevabiosimilars.com

* Biological Products ("Biologics"): A diverse category of products, mostly large, complex molecules, e.g. Vaccines, Monoclonal Antibodies, Recombinant Therapeutic Proteins

Examples: anti-SARS-CoV-2; Infliximab, Adalimumab (Humira; monoclonal antibodies for autoimmune disorders, such as Rheumatoid Arthritis); Insulin Glargine (Lantus; recombinant human insulin analog).

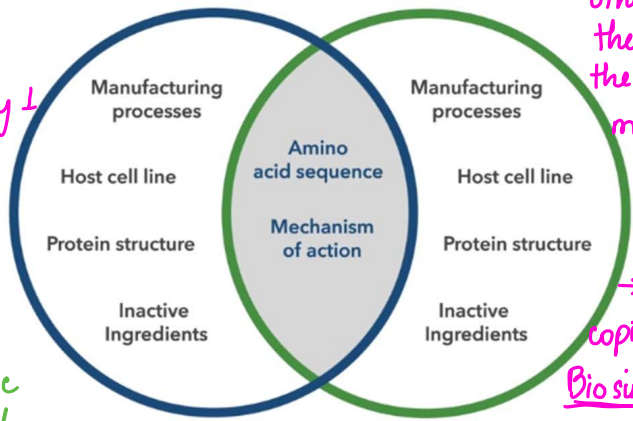
Biologics are isolated from human, animal or microorganism sources, or may be produced using biotechnology.

Understand these terms

Biologics *vs.* Biosimilars *vs.* Generics

a product originally develop by 1 pharmaceutical company

Reference Biologic



other companies attemp to make the same biologics → it's NEVER the same b/c the substance is made in a biological system, so that Biosimilar differences are just differences b/w organisms that made → This is why biologics that made as copies of original biologics are called Biosimilar, not Bioidentical

www.tevabiosimilars.com

There is posibility of difference but not clinically meaningful

A **Biosimilar** is a biological product that is highly similar to, and has no clinically meaningful differences from, an existing FDA-approved reference **Biologic**.

www.fda.gov

An **Interchangeable Biosimilar** meets additional requirements (e.g., expected to produce the same clinical result as the reference product in any given patient) and may be substituted at the pharmacy, much like **Generic drugs** are routinely substituted for **Brand-Name drugs**.

Compared to the **Brand-Name drugs**, **Generic drugs**: Easy for the pharmacist to substitute one for another.

- Contain the same active/key ingredient;
- Have the same strength;
- Use the same dosage form (e.g., a tablet) and
- Use the same route of administration (e.g., oral, topical, injection)

All generic drugs approved by FDA have the same high quality, strength, purity and stability as brand-name (or innovator) drugs.

www.fda.gov

The role of the pharmacist to make a decision whether they can substitute one product for another. When it comes to biosimilar, the pharmacist can only substitute when the new product has the classification of being interchangeable biosimilar

Pharmacodynamics: what the drug does **to the body**

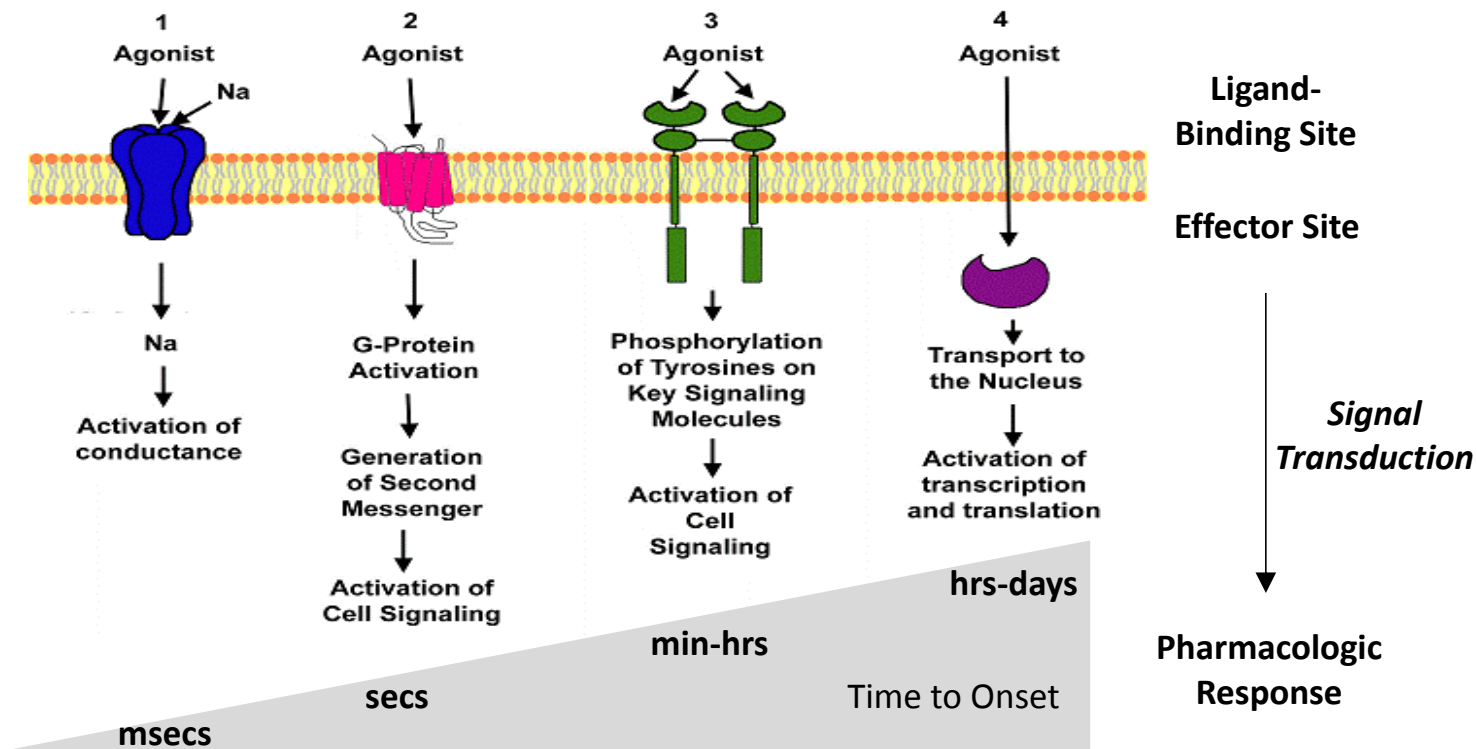
Dynamis (Greek) - Power

Most drugs bind to, and act through, **RECEPTORS**:

Ion channel-, **G protein**-, **Enzyme**-linked & **Intracellular** (cytosolic proteins, nucleic acids)

*Drugs do not create de novo effects, but **modify** existing physiological processes.*

(except 'drug receptors', e.g. benzodiazepine receptor, sulfonylurea receptor)



Majority of drugs does create new effects. They basically either inhibit or enhance the existing biological process. They modify the physiological functions. There are few exceptions, but imo those exceptions are only temporary. Specifically, the exceptions are drugs receptors.
The receptors in the body tell us that these receptors don't have any physiological functions. We haven't been able (so far) to identify endogenous ligand photos receptors, so we call them "drug receptors".

One of those is actually very IMPORTANT for you guys bc they have benzodiazepines receptors. You will be using benzodiazepines to calm the patients, so that's agonist hypnotic drug. Benzodiazepines receptors are receptor binding side for those drugs on GABA receptors.

Another example here is sulfonylurea. They bind to sulfonylurea receptors, which are receptors on potassium rectify channel that regulate glucose levels. These are oral antidiabetics or hypoglycemic drugs.

But those are really exceptions. **For the majority of pharmacology drugs, they either ACTIVATE or INHIBIT the existing process.** This is why pharmacology is so close to physiology. When you know physiology well, it's very easy to increase or decrease existing physiological process. This is an overview (step 1-4)

Now specifically, there is a ligand-binding site of the membrane. **Ligand** is where the drugs bind to. The **effector site** meaning the information is now being processed by the receptors, some changes are now activate or inhibit that pathway. In this example, it is agonist, so it will be activating the system. But those could be also antagonist, they will block the informational transfer system. **Signal transduction** is physiology, cellular physiology. **Pharmacologic response** in the end.

Those different receptors have one characteristic difference among them is that **TIMING of their action = time to onset.**

- The fastest is ion channel (msecs trend). Then G-coupling receptors, those response to the drugs that within secs.
- Then, we have agonist…those activate enzymes such as phosphorylation of tyrosines kinases within min-hours. Those pause could be activation such as protein synthesis and so on. This will be time-scale of minutes to hours.
- The longest delay we get with those that act intercellarly, e.g. hormones physiology. These are hours to days to take action.
- One clinical important that is missing from the picture is **TRANSPORTERS** group. We talk about transporters when we talk about antidepressant drugs because that will be a time transporters. Also, in diabetic, we have transporters in the kidney that are targeted by varies diabetic drugs. So that will be one of the major categories.
- Also, drugs that are power (as we talk about pharmacodynamics) invade physiological properties. They don't bind to any receptors. One example in the diuretic category, it monitor and change osmotic pressure. It doesn't bind to any receptors, but purely physiological process. Also, acid…drugs that change the pH in the stomach. These drugs are biologically active, but don't bind to any receptors.

Drug 'Dose – Response' Relationship

The Occupation Concept of Drug Action (Clark, 1937):
Drug **(D)** and receptor **(R)** interact according to the law of mass action.
The magnitude of a **pharmacologic response** (effect, **E**) elicited by a **drug** is **directly proportional** to the number (fraction) of **receptors occupied** by the drug.

IMPORTANT

$$D + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} DR \longrightarrow E$$

Rate Constants: $\frac{k_2}{k_1} = k_d$, **Dissociation Constant,** a measure of drug affinity for the receptor:

$k_d \uparrow \Rightarrow$ affinity $\downarrow$

Occupation of receptors is essential, but **not sufficient** to elicit a response. Two factors to consider:

1. **Affinity** – the ability to **bind** with the receptor
2. **Efficacy** – the ability to **activate** a receptor (induce a **functional change**).

Ligand	= **Affinity** + Any Efficacy
Agonist (Full Agonist)	= **Affinity** + **Maximal Efficacy** (e.g. Morphine)
Partial Agonist	= **Affinity** + **Submaximal Efficacy** (e.g. Acetaminophen)
Competitive Antagonist	= **Affinity** / No Efficacy (e.g. Naloxone)
Non-Competitive Antagonist	= No Affinity / No Efficacy

Most drugs bind to receptors and act thru receptors, but we really do NOT know for sure how drugs interact w the receptor to get the response that they involve. The most commonly accepted concept is **the Occupation Concept of Drug Action**

According to this concept, the drug occupies the receptor and they interact according to the law of mass action. So the response is directly proportional to the number of receptors occupied by the drugs. Basically, when you increase the drug dose, you'll have more receptors occupied by the drugs. More receptors will give greater pharmacologic response.

Drug + Receptors —> Drug Receptor complex k1,k2: rate constant

The fact that we have rate constant means binding is NOT permanent, but there is binding & unbinding of the drugs from the receptors. So you have 2 rxn going on in both directions. At the end, we have the Effect, which comes from the occupation of receptors bind the drugs.

K2/k1 = kd —> **dissociation constant** this is IMPORTANT term for you to remember
- K2 rate constant for disassociation of the drugs from the receptors
- Kd increases means the affinity of the drugs for the receptors is LOWER affinity to bind the receptors

important piece is that occupation of receptors is **not sufficient** to elicit a response. So the drugs bind to the receptors, this will be (1) **affinity** the ability to bind w the receptor and (2) **efficacy** the ability to activate a receptor. When you think about blockers of the receptors = antagonist, they have the affinity for the receptors (they can bind to the receptors), but they don't have any efficacy. They don't activate the receptors, they prevent other molecules to binding to the receptors and evoking the response.

1. Ligand has **affinity** because it binds to receptors and **any efficacy** meaning it both agonist or antagonist. All types of molecules that can bind to receptors.
2. Agonist = affinity + max efficacy
3. Partial agonist = affinity + submax efficacy (smaller effect)
4. Competitive Antagonist = affinity / no efficacy
5. Non-competitive antagonist = no affinity means they don't bind to the binding site of the agonist + no efficacy means not involve any effects

‘Drug-Receptor’ Interaction: Terminology

Ligand (Latin: *ligare* - to bind)	Any molecule which **attaches selectively** to particular receptors or sites. It doesn’t tell you whether it activates or blocks the receptors
Agonist (a.k.a. Full Agonist): Maximal effect achievable = Full Agonist	An agent which **attaches selectively** to a particular receptor and **activates** it to produce an effect similar to that of the physiological signaling molecule (endogenous ligand); its **maximal effect is the highest** for any agonist at that receptor.
Partial Agonist: Smaller effect	An agent which **attaches selectively** to a particular receptor and **activates** it to produce **submaximal effect**, but antagonizes the action of a full agonist / endogenous ligand.
Antagonist: Has affinity (Bind to receptor) but they don’t have efficacy	An agent which **prevents the action of an agonist** but does not have any effect of its own.
- Competitive:	**Attaches selectively** (competes with the agonist) and prevents the agonist binding to the receptor. Antagonize the effect of agonist
- Non-competitive:	Allows the agonist binding to the receptor, but prevents receptor activation by the agonist.

Agonist can bind to the receptors, but can not activate the receptors. It doesn’t compete, sometimes bind to different site of the receptors & change the confirmation of the receptors. Now the receptor can not be activated by the agonist. Sometimes, even the non-competive bind to the site of the agonist..

Drug 'Dose – Response' Relationship

E_{max}, Efficacy, K_d, Affinity, EC_{50}

↑ Dose ⇒ ↑ Concentration at Receptor ⇒ ↑Number (%) of Occupied Receptors ⇒ ↑ Response

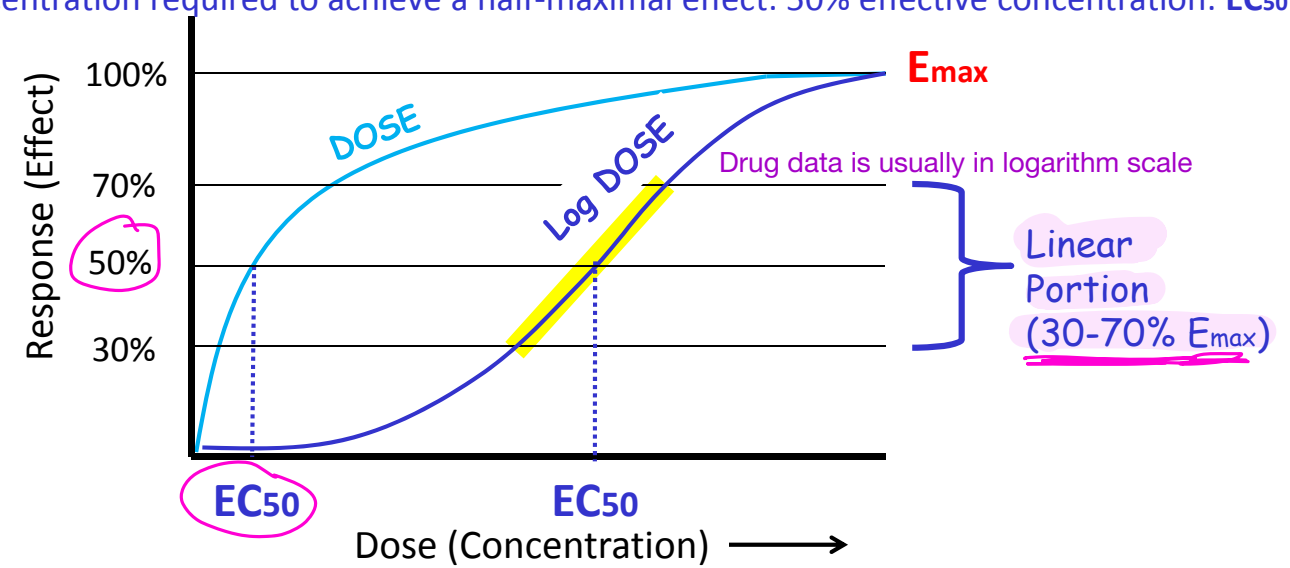
$$E = \frac{E_{max} \times [D]}{K_d + [D]}$$

E, the response to / effect of drug concentration **[D]**;

E_{max}, the maximal response (if not exceeded by other drugs, it is known as the 'ceiling effect');
the measure of the **intrinsic activity (efficacy)** of the drug;

No other drugs achieve greater response

K_d, **the dissociation constant** of the 'DR' complex (a measure of drug **affinity** for the receptor: **K_d↓ ⇒ affinity**↑; derived from drug binding data (e.g., radio-ligand binding studies); equal to the concentration required to achieve a half-maximal effect: 50% effective concentration: **EC_{50}**



When we increase the drug dose, we also increase the concentration at receptor, so it increases the number of molecules available to bind the receptors —> increase the number of occupied receptors —> greater response to the drug

Full agonist will have the **Emax** = maximal response that can be achieved
When you increase the drug dose at some points, all the receptors that the drug can occupy are already occupied. So you add more drug, you don't see any increase response. At this point, you achieve the 'ceiling effect' for the given drug. So this term is also used for any drugs, whether it has maximum effect of all drugs or just for its own action.

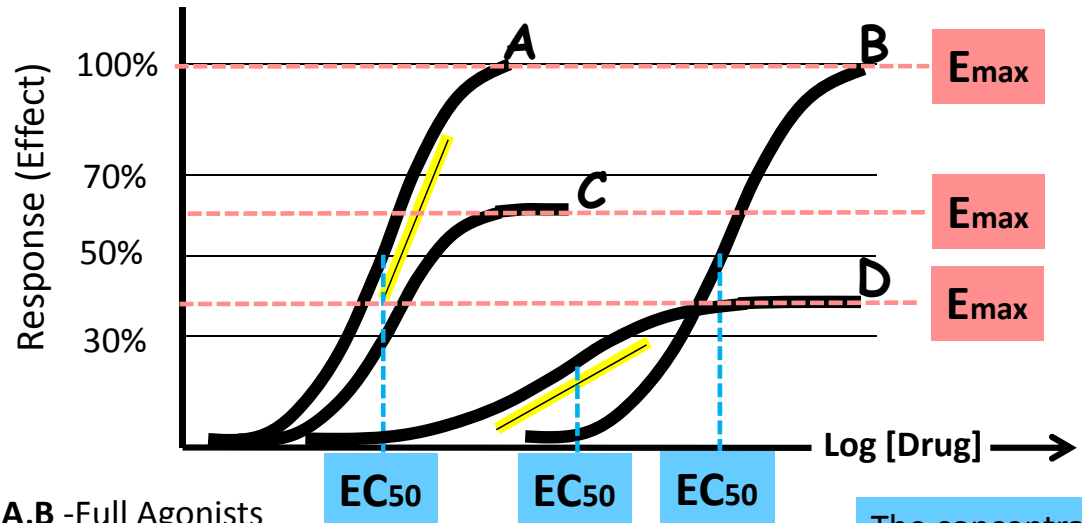
Emax is also called the maximal efficacy & intrinsic activity. Both terms are used interchangeably.

Kd is the dissociation constant. It tells you the relationship between the drug and the receptors is not permanent. The drugs dissociate from the receptors. Dissociation constant is the ability of the drug to dissociate from the receptors. So **when the dissociation increases, the ability of the drug binding to the receptor decrease**.

Kd is equal to the drug concentration that required to achieve half-maximum response = **EC50**

Drug 'Dose – Response' Relationship

Drug Potency *vs.* Efficacy



Efficacy* Ability to activate a receptor, usually expressed as **Emax**.

A,B -Full Agonists
C -Partial Agonist

Potency* The concentration (or dose) needed to achieve a given level of response, usually expressed as **EC50.**

Characteristic features of the Dose-Response Curve:

- **Upper limit** - index of drug **efficacy**, the maximal response that can be elicited by the drug;
- **Slope:** steep ⇒ a moderate increase in dose markedly increases the response ⇒ high efficacy (high intrinsic activity) ⇒ needs individualized dosing
  flat ⇒ a wide dose range results in similar responses (standard doses for most patients)
- **Position on the dose axis** (leftward ⇒ higher potency; rightward ⇒ lower potency).

* *Compared to Potency,* ***EFFICACY*** *is the* ***more decisive factor in the choice of a drug.***

Efficacy:

- drug A and B achieve the maximum effect 100%, so the upper limit here is the drug efficacy. We can not have more than 100% of effect. There are some measures of the effect of the drug, e.g. drops in B.P, or when pt is in pain, you put in drugs, pt feels less pain —> then another drug, pt feels even less pain —> then some drugs, pt does not feel pain anymore, so this drug is the 100% effect.
    - So **upper limit** is drug **efficacy or max efficacy = Emax**
- Drug C: efficacy is ~60%
- Drug D: efficacy is ~35%

2 types of slope:

- **steep**: drug A and C have steep slope, meaning you have small increase in the dose, you have a large change in the response in the effect. Also, remember the stronger/faster rise of side effect of the drug. For such example of the drug with a steep slope, you **need individualize dosing**…because as you know the dose of the drug might depends on the size of the patient (body weight, fat content, etc.).
- **Flat**: drug D when you change the dose significantly, you don't have much change in the response. So when you talk about the drug that decrease the B.P, the drug that has a very strong effect when you increase the dose significantly, the pt might pass out if the B.P drops too much.

Position on the dose axis: when you have a drug that position leftward, meaning it operates at a lower concentration. The range of concentration that are clinically effective might be similar, but the absolute concentration for drug A is much smaller than for drug B. So drug A has more/higher potency. This usually presents as EC50 meaning the effective concentration 50%…the concentration of the drug that needed to achieve 50% efficacy or 50% of the maximal response.

- EC50 for drug A is same as drug C bc for drug C has a maximum at 60, so its 50% of the effect is 30% on the y-axis. So A and C have the same EC50.
- Drug A and B have the same efficacy but you need much higher concentration of drug B to achieve the maximal effect
- A,B are full agonists for a given effect bc the achieve maximum effect assuming that they act on the same receptor. They act on the same receptors
- C and D will be partial agonist, but D has different shape & slope, so this is prob a different drug that actually different mechanism, so we prob assume different mechanism than A, B, C. So D has to be included in the group of full & partial agonist of a different receptor.

As we discuss, the more important clinically is **efficacy** because for potency, as long as you can deliver the drug safely, then concentration doesn't matter. The concentration could be higher simply bc the drug/molecules has higher molecular weight, so to achieve the given number of the molecules bc it translate to number of receptors occupied… to achieve maximal efficacy, you have to have more receptors occupied, so more drugs.

Why potency of the drug could be lower, but doesn't make the drug less valid for what you want to do/achieve for your pt?