Pharmacodynamics part II

I-Pharmacodynamic Characterization of a Drug Candidate

The comprehensive evaluation of a new molecule's pharmacodynamic profile relies on modeling its interaction with its target. These interactions obey the mathematical model of the Law of Mass Action, which governs the kinetic equilibrium between free ligands, free receptors, and the ligand-receptor complex. the Law of Mass Action is formally written in pharmacology like this:

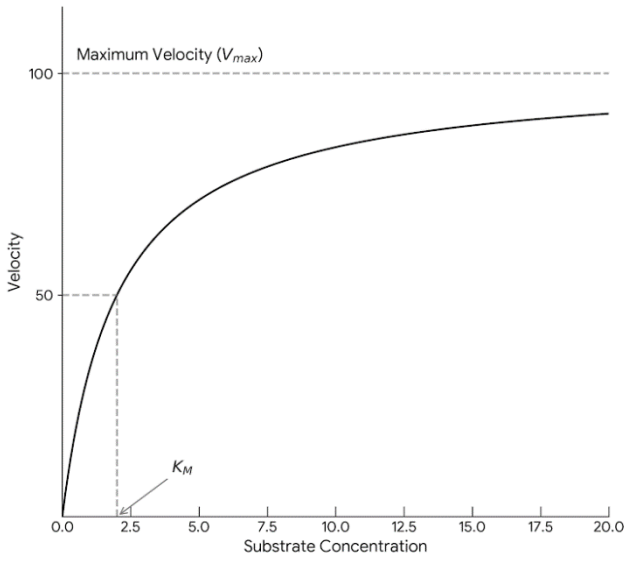
$$[L] + [R] \rightleftharpoons [LR]$$

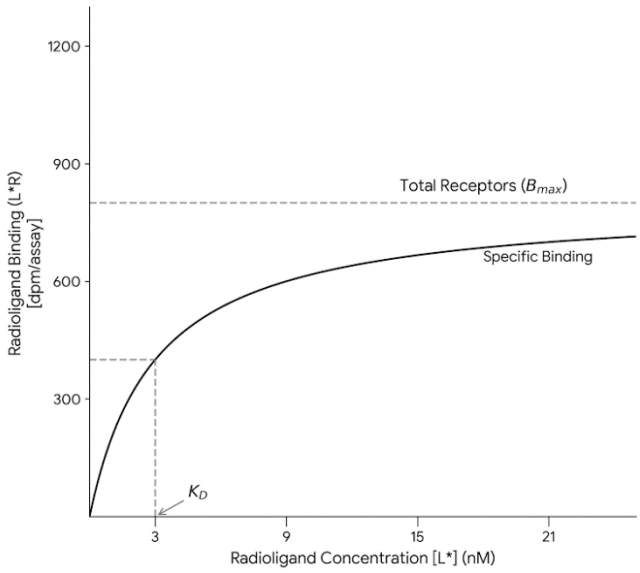
Where [L] is the concentration of the drug (Ligand), [R] is the concentration of free receptors, and [LR] is the concentration of the drug-receptor complex. It is from this simple equation that all the sigmoidal (dose-response) curves plotted later are derived!

Based on this model, three fundamental parameters are calculated to characterize the drug:

1. Affinity (Thermodynamic Parameter)

- **The Concept:** This is the measurement of the drug's attraction to, and binding strength with, its specific target.
- **Calculated Parameter:** The dissociation constant (K_d). The lower the K_d, the higher the affinity.





2. Efficacy or Activity (Biological Response)

- **The Concept:** This is the qualitative (type of response) and quantitative (intensity of the response) definition of the biological response induced once the drug binds to its target. This defines whether the molecule acts as an agonist (full/partial) or an antagonist.
- **Calculated Parameters:** Intrinsic activity (α), maximal effect (E_{max}), and potency or median effective concentration (EC_{50}).

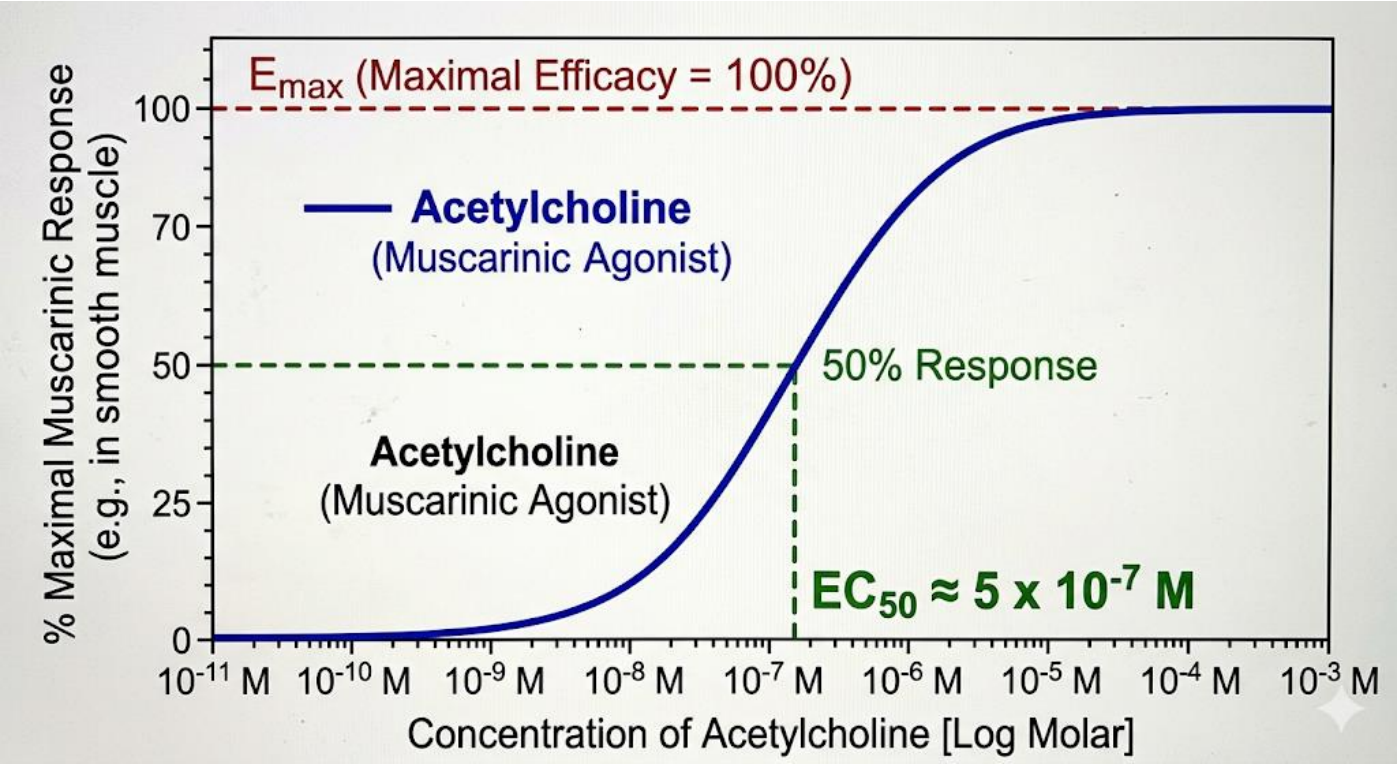
3. Selectivity (Safety Profile)

- **The Concept:** This approaches the molecule's ability to bind preferentially to its primary target rather than other "off-target" receptors.
- **Calculated Parameter:** The selectivity ratio (e.g., comparing the K_d or EC_{50} values between two different receptors). This step is crucial for anticipating the molecule's tolerance profile and predicting any potential side effects.

II-Graded Effect (*Effet Graduel*)

The **graded effect** is measured in a **single biological system** (one patient, one isolated organ, or one cell culture).

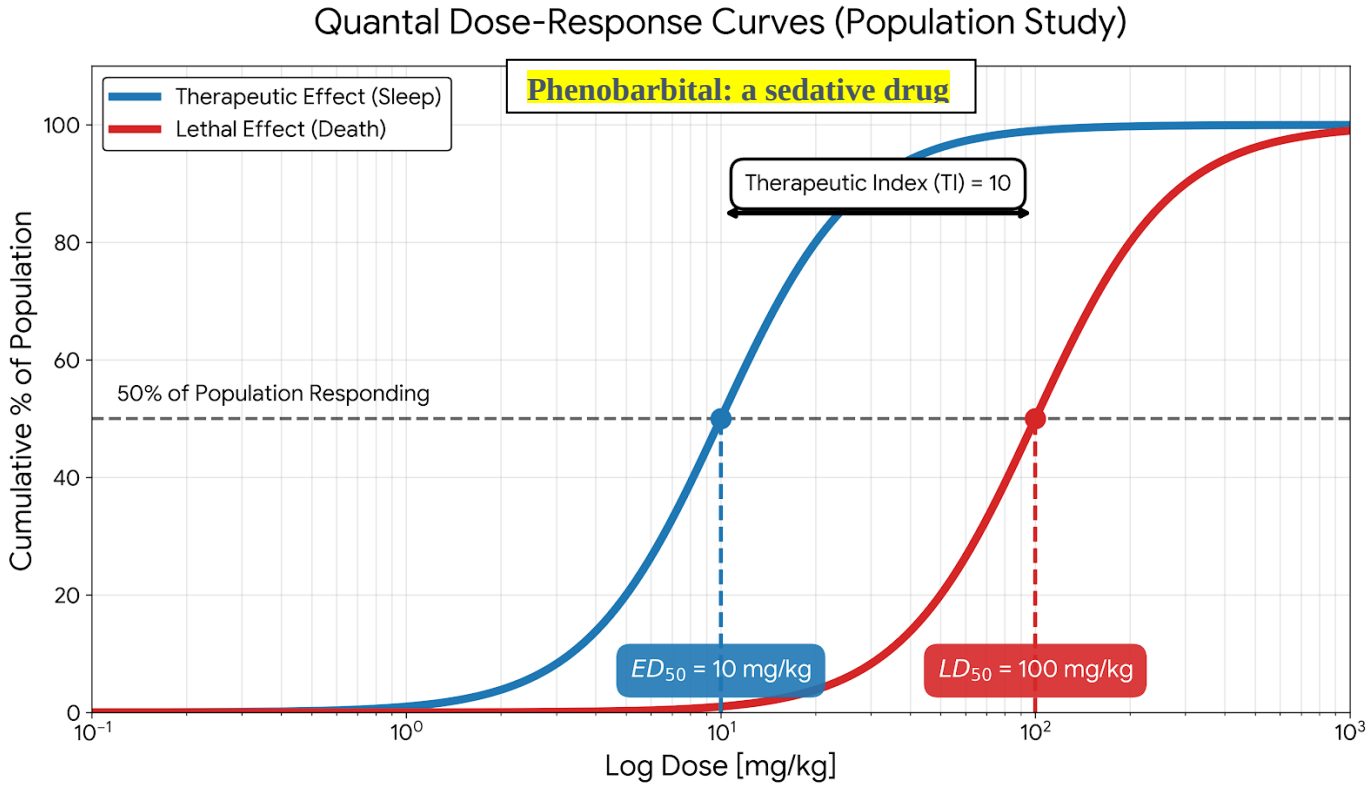
- **Definition:** As the dose increases, the **intensity** of the response increases. It is a continuous scale.
- **Key Question:** How much of an effect are we seeing?
- **Examples:** A drop in blood pressure (measured in mmHg).
    - The percentage of enzyme inhibition.
    - The reduction of vessel growth in your **CAM Assay**.
- **Parameters:**
    - **E_{max} (Efficacy):** The maximal effect the drug can produce.
    - **E_{C50} (Potency):** The concentration required to reach 50% of the E_{max}.



2. Quantal Effect

The **quantal effect** is an **"all-or-none"** response measured across a **population** of subjects.

- **Definition:** The effect is either present or absent. We don't measure the "intensity" in one person; we count how many people in a group reached a specific "threshold."
- **Key Question:** Does the subject show the effect? Yes or No?
- **Examples:**
    - **Therapeutic:** Did the headache disappear?
    - **Toxic:** Did the subject experience a seizure?
    - **Lethal:** Is the embryo in the CAM Assay dead or alive?
- **Parameters:**
    - **ED_{50} (Median Effective Dose):** The dose at which 50% of the population shows the desired effect.
    - **TD_{50}/LD_{50}:** The dose that is **toxic** (**TD_{50}**) or **lethal** (**LD_{50}**) to 50% of the population.



Comparison Table: Gradual vs. Quantal

Feature	**Graded Effect (Graduel)**	**Quantal Effect (Quantal)**
Scale	Continuous (0 to 100%)	Binary (Yes/No)
Subject	Single individual/system	Entire population
Information	Drug's **Efficacy** and **Potency**	Drug's **Safety** and **Variability**
Key Metric	EC_{50}	ED_{50}, LD_{50}

Why does this matter for Biotech?

We use **Quantal Effects** to calculate the **Therapeutic Index (TI)**.

$$\mathbf{TI = LD_{50}/ED_{50}}$$

The larger the TI, the safer the drug. In a lab setting, if you are looking for a "nuisible" (harmful) effect, you are often looking at a quantal dose-response curve to see at what concentration your biotech candidate starts killing cells vs. curing them.

Graded effects are used to calculate cellular-level metrics: **Potency**, **Efficacy**, and the **In Vitro Selectivity Ratio**.

Think of it as a timeline in drug development: you use *graded effects* in the petri dish to find out if the molecule works, and *quantal effects* later in animal/human trials to see if it safe for a population.

you calculate the **Selectivity Ratio** (sometimes called the *In Vitro Therapeutic Index*).

To do this, you map two different graded curves in the lab:

1. The graded curve for your **desired target** (e.g., enzyme inhibition).
2. The graded curve for an **off-target or toxic effect** (e.g., cell death/cytotoxicity in a cell viability assay).

$$\text{Selectivity Ratio} = \frac{EC_{50}\ (\text{Toxic or Off-target Effect})}{EC_{50}\ (\text{Therapeutic Effect})}$$

Example:

If your biotech candidate inhibits a tumor growth pathway with an EC_{50} of $2\ \text{nM}$ (therapeutic), but it also inhibits a healthy heart cell enzyme with an EC_{50} of $2000\ \text{nM}$ (toxic off-target):

$$\text{Selectivity Ratio} = \frac{2000\ \text{nM}}{2\ \text{nM}} = 1000$$

Interpretation: The drug is 1000 times more selective for the tumor than the heart. This is a massive "therapeutic window" at the cellular level, making it a great candidate to move forward to animal testing (where you will finally measure quantal effects).

Summary: Graded vs. Quantal Math

Dimension	Graded Curve Metric	Quantal Curve Metric
Safety Variable	**Selectivity Ratio** ($\frac{EC_{50}\text{ toxic}}{EC_{50}\text{ therapeutic}}$)	**Therapeutic Index** ($\frac{TD_{50}}{ED_{50}}$)
Location	In vitro (test tubes, cell cultures, organ baths)	In vivo (populations of animals, clinical trials)
What it guards against	Molecular off-target binding / cross-reactivity	Whole-organism toxicity, side effects, and death

Quick check: If you are measuring exactly how many millimeters a tumor shrank in response to a drug, is that a **graded** or a **quantal** measurement?

III-Agonist vs antagonist Ligands

This is where the concepts of affinity and efficacy (intrinsic activity) come to life. In pharmacology, we classify ligands based on what they do to the receptor *after* they bind.

Think of the receptor as a molecular switch. Agonists flip the switch, while antagonists jam the mechanism so nothing else can flip it.

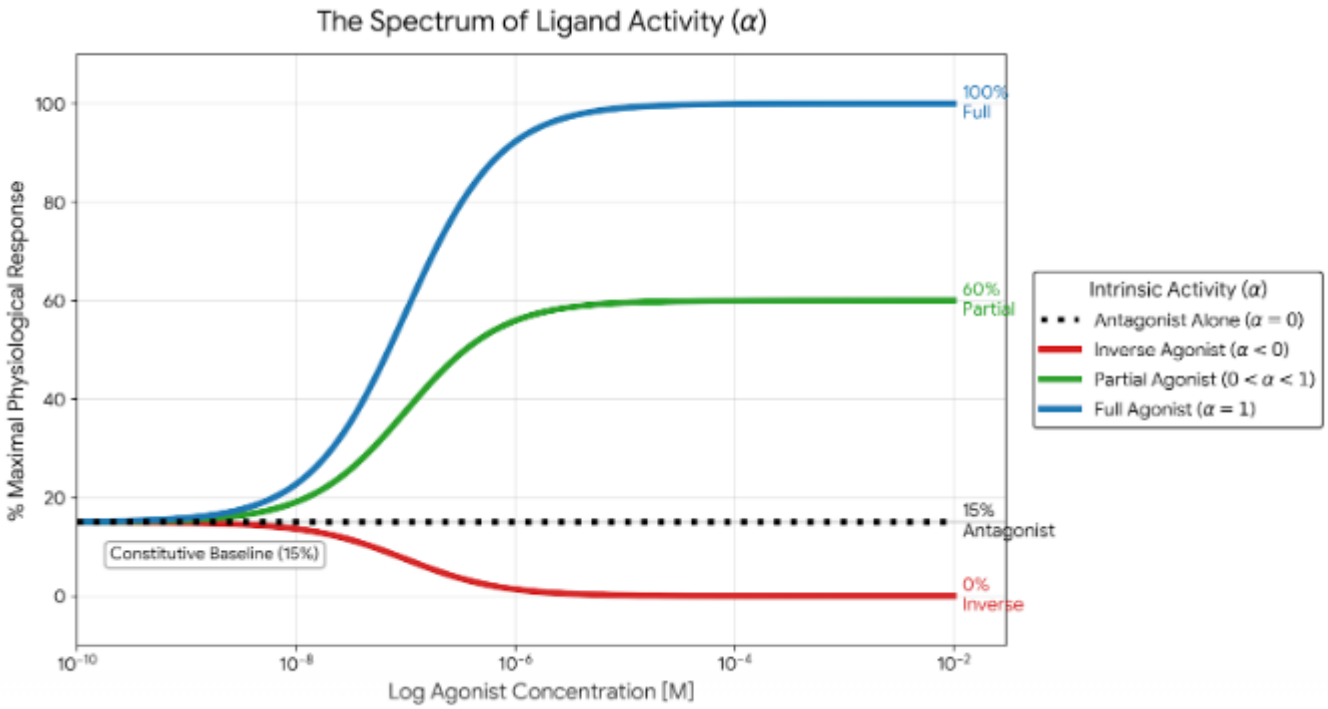
1. Agonists: The Activators

An agonist is a molecule that possesses both affinity (it binds to the receptor) and efficacy (it stabilizes the receptor in its active conformation, triggering a biological cascade).

However, not all agonists are created equal. We measure their power using the intrinsic activity variable, α.

- **Full Agonists (α = 1):** These molecules bind to the receptor and induce a conformational change that produces the maximum possible biological response (100% E_{max}). Acetylcholine at the muscarinic receptor is a classic full agonist.
- **Partial Agonists (0 < α < 1):** These bind to the exact same receptor, but they cannot induce the fully active conformation. Even if you flood the system and occupy 100% of the receptors, the biological response might plateau at 40% or 60% of the E_{max}.
- **Inverse Agonists (α < 0):** This is a specialized concept for receptors that exhibit "constitutive activity" (meaning they fire at a low baseline level even when nothing is bound). An inverse agonist

binds and forces the receptor into an *inactive* state, actively driving the biological response below the normal resting baseline.



2. Antagonists: The Blockers

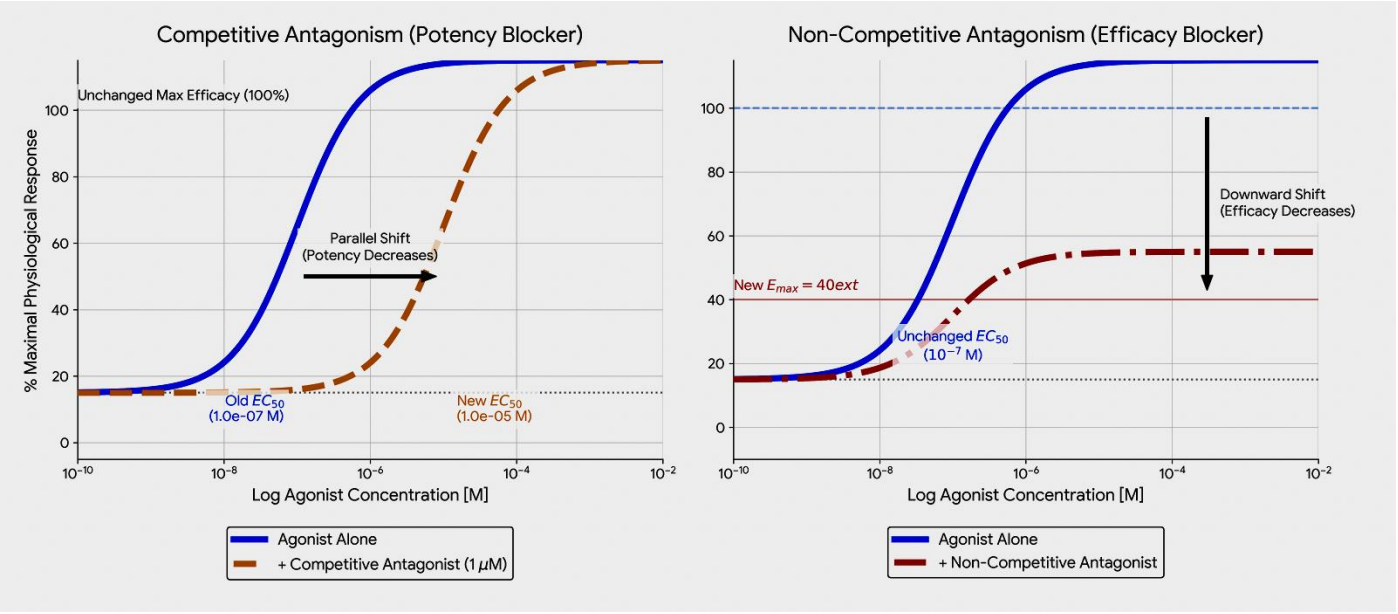
An antagonist has affinity (it binds beautifully to the receptor) but absolutely zero efficacy (α = 0). By itself, an antagonist does nothing. You only see its effect when you try to add an agonist and realize the agonist is blocked. As we mapped out in our earlier plot, antagonists fall into two main categories:

Competitive (Reversible) Antagonists:

They bind to the primary (orthosteric) binding site. They compete physically with the agonist for the exact same parking spot. Because the binding is reversible, adding a massive dose of agonist can "outcompete" the antagonist and restore the full response (shifting the EC50 to the right).

Non-Competitive Antagonists:

They either bind permanently (covalently) to the main site, or they bind to a secondary (allosteric) site. If they bind to an allosteric site, they warp the shape of the main receptor site so the agonist can no longer fit. No matter how much agonist you add, you can never overcome this block (lowering the overall E_{max}).



Summary of Intrinsic Activity (α)

Ligand Type	Intrinsic Activity	Biological Effect
Full Agonist	$\alpha = 1$	Maximum physiological response
Partial Agonist	$0 < \alpha < 1$	Sub-maximal physiological response
Antagonist	$\alpha = 0$	No response (maintains baseline, blocks agonists)
Inverse Agonist	$\alpha < 0$	Negative response (suppresses baseline activity)