PHARMACOLOGY PART 1: INTRODUCTION TO PHARMACOLOGY AND PHARMACODYNAMICS.

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Foot line: Introduction to Pharmacodynamics

Abstract

There is an emerging need for greater understanding of pharmacology principles amongst technical staff. Indeed, the responsibility of dose preparation and administration, under any level of supervision, demands foundation understanding of pharmacology. This is true for radiopharmaceuticals, contrast media and pharmaceutical interventions / adjunctive medications. Regulation around the same might suggest a need to embed pharmacology theory in undergraduate education programs and there is a need to disseminate that same foundation understanding to practicing clinicians. Moreover, pharmacology foundations can provide key understanding of the principles that underpin quantitative techniques (e.g. pharmacokinetics). This article is the first in a series of articles that aims to enhance the understanding of pharmacological principles relevant to nuclear medicine. This article will deal with the introductory concepts, terminology and principles that underpin the concepts to be discussed in the remainder of the series. The second article will build on the pharmacodynamic principles examined in this article with a treatment of pharmacokinetics. Article 3 will outline pharmacology relevant to pharmaceutical interventions and adjunctive medications employed in general nuclear medicine, the fourth pharmacology relevant to pharmaceutical interventions and adjunctive medications employed in nuclear cardiology, and the fifth the pharmacology related to contrast media associated with computed tomography (CT) and magnetic resonance imaging (MRI).

Introduction

Pharmacology is the scientific study of the action and effects of drugs on living systems and the interaction of drugs with living systems (*1-5*). Pharmacology includes the study of prescribed and over-the counter medications, legal and illicit drugs, natural and synthetic compounds, *exogenous* (sourced from outside the body) and *endogenous* (produced inside the body) drugs, and drugs that produce beneficial, harmful or both benefit and harm (*1-5*). As a generally speaking, pharmacology is divided into *pharmacodynamics* and *pharmacokinetics* (Figure 1) and these will be described in detail in parts 1 and 2 of this series respectively. It should, however, be recognized that some texts add the additional sub divisions (Table 1) of *pharmacogenetics*, *pharmacogenomics*, *pharmacoepidemiology*, *pharmacoeconomics* and *pharmacovigilance* (*1-5*). There has been a quantum shift in pharmacology since the mid-1900s with a leap from simply describing what effect a drug caused to an understanding of how drugs work.

A *drug* is simply a chemical or substance that causes a physiological effect when introduced to the body (*1-5*). Morphine is a good example of an exogenous drug that mimics endogenous morphine (endorphins). Obviously a wide variety of everyday chemicals (for example water) could be classified as a drug and, thus, drugs are generally defined based on key parameters like potency and selectivity. Importantly, some drugs elicit variable effects with varying doses; beneficial at one dose and harmful at another (hormesis). The basic principle of toxicology was captured by Paracelsus (1538) "*sola dosis facit venenum*" which translates as "only the dose makes the poison" (*6*). Thallium is an example of a chemical used for imaging in Nuclear Medicine but has also been used as a poison depicted in the odd black and white movie, more recently in the 2015 James Bond SPECTRE movie because it is highly toxic, colorless, odorless and tasteless. A *medicine* is a specific chemical preparation comprised of one or more drugs that is administered in order to elicit a therapeutic effect (e.g. disease or symptom treatment or prevention) (*1-3*).

Receptor Principle

Receptors are proteins (macromolecules) that can be found on cell surfaces or inside the cell that mediate drug activity (*1-3*). Receptors respond to specific neurotransmitters, hormones, antigens, chemicals or substances. A chemical (*ligand*) binds to a specific site (receptor) and triggers a response (signal) in the cells (*1-3*). The intra-cellular changes initiated by the ligand-receptor complex can be through direct or indirect action, however, the ligand generally functions as either an agonist or an antagonist (*1-3*). An *agonist* will mimic the endogenous ligand to produce a similar response (e.g. morphine is an agonist for opioid receptors) while an *antagonist* blocks the usual ligand and, thus, inhibits the physiological response (e.g. naloxone is an antagonist for opioid receptors) (*1-3*) (Figure 2). A more detailed classification of drug action includes (*1,2*):

- An *agonist* creates a conformation change at the site of action that mimics the physiological ligand. Potency is determined by affinity and efficacy. A full agonist has high efficacy. Dobutamine is an example of an adrenergic agonist.

- A *partial agonist* demonstrates both agonist and antagonist action which produces a truncated response. The submaximal effects represent intermediate to low efficacy. Tamoxifen is a drug that nuclear medicine patients might encounter that is a partial agonist. While morphine is a full agonist for opioid receptors in the central nervous system, it is a partial agonist in other tissues like those associated with sphincter of Oddi contraction.

- An *antagonist* binds at the site of action but does not produce the conformational change. It does not produce a response and blocks an agonist from binding (zero efficacy). Patients present in nuclear medicine departments on a range of beta blockers (beta adrenergic antagonists) and captopril provide angiotensin converting enzyme antagonism (inhibition). A *competitive antagonist* represents displacement of the opportunity for the ligand or agonist to bind to the site of action.

- *Reversible competitive antagonism* reflects antagonist affinity and propensity for dissociation with a higher affinity ligand or agonist (or indeed by virtue of higher concentration) being able to displace the antagonist. The use of aminophylline to "reverse" dipyridamole is a classic example.

- *Irreversible competitive antagonism* results when the dissociation of the antagonist from the site of action occurs either slowly or not at all. Phenoxybenzamine is an irreversible antagonist and may be seen in pheochromocytoma patients for hypertension management.

- An *inverse agonist* produces a negative response and, thus, is more than simply antagonism. H_1 antihistamines like loratadine may have previously been thought of as histamine antagonists, however, they act as inverse agonists as do a number of common H_2 antihistamines like cimetidine and ranitidine.

- An *allosteric modulator* indirectly effect action with benzodiazepines being a typical example. They do not bind at the site of action but can produce an increase (*allosteric agonist*) or decrease (*allosteric antagonist*) in the action of the ligand or agonist. These may also be referred to as *non-competitive antagonists*.

Drug Action

There are a number of other important terms that need to be understood to characterize drugs. *Specificity* is the measure of a receptors ability to respond to a single ligand (*1-5*). Low specificity generally results in physiological responses not targeted or intended by the drug and side effects provide a good example. Indeed, it is not uncommon for a drug to be developed with a theoretical action but poor specificity for that action undermines efficacy while a side effect may emerge as the new targeted role. A classic example is sildenafil (Viagra) which was developed to treat hypertension and angina. It was not particularly effective but an observed side effect has become the new targeted role of the drug. *Selectivity* defines the ability of the receptor to distinguish between drugs and has the same implications as specificity; indeed the terms are often used interchangeably (*1-5*). Adenosine is non-selective (4 adenosine receptors with different actions) and as a result has unwanted effects potential bronchospasm (A_1 receptor) while regadenosan is selective for A_{2A} receptor (vasodilation and bronchodilation).

Affinity defines the strength of attraction between the drug and its receptor (*1-3,5*). A high affinity is generally associated with a lower dose requirement (compared to low affinity

for the same receptor). *Potency* describes the relationship between the drug dose and the magnitude of the effect (*1-5*). High potency induces a strong effect with a low drug dose. *Efficacy* is the invivo potency; the maximum response achieved from a drug (*1-3,5*). The interaction (e.g. absorption, metabolism, excretion) of the drug in the body may alter the relative *bioavailability* and thus, change the theoretical effect of the drug. Rapid metabolism of a high potency drug, for example, may render it low efficacy while rapid absorption, minimal first pass metabolism and delayed excretion may see higher efficacy despite much lower potency.

Generally speaking, the ideal drug will have easy administration, fully absorbed, not plasma bound, rapid onset, useful duration of action, high *therapeutic index* (no adverse effects), no interactions, spontaneous elimination, chemical stability, high selectivity and specificity, high affinity, high potency and high efficacy although there are no examples of synthetic or natural drugs that satisfy these criteria (*4*). Furthermore, there may be circumstances where these ideal properties are not wanted. For example, high affinity can also cause a prolonged action which may not be desirable (e.g. dipyridamole versus adenosine). High potency is not always desirable and poor selectivity might provide a good case example; that is, a drug that has non-selective biodistribution will have a poorer safety profile if it is also highly potent (versus a less potent alternative).

Drug Receptor Interactions

Human receptors are generally proteins so it is worth reviewing protein structure. Nonetheless, receptors are not the only targets for drug binding with other targets including; ion channels, enzymes and transporters (*1*). While there are about 300 amino acids present in various animals, plants and microbial systems, only 20 amino acids are coded by DNA to appear in proteins in humans. Cells produce proteins with different properties and activities by joining the 20 amino acids in many different combinations and sequences. The properties of proteins are determined by the physical and chemical properties of the amino acids. Proteins can be large molecules with complex three dimensional shapes and structures. Protein structure is best considered in terms of primary, secondary, tertiary and quaternary structures. The primary structure simply

relates to the protein configuration associated with the amino acid sequence; the order of amino acids in the polypeptide chain (peptide bonds). The secondary structure relates to the way the polypeptide chain is folded (hydrogen bonds) creating pleated sheets and helices. The tertiary structure relates to the interactions between amino acid side chains (hydrogen bonds, disulphide binds, ionic binds and hydrophobic interactions). The quaternary structure relates to interactions between different polypeptide chains within the same protein. Perhaps a simple way to consider protein structure would be that primary structure are an array of letters, secondary structure would be creation of words from the letters, tertiary structure a sentence from the words, and then quaternary structure a paragraph of multiple sentences woven together. From a nuclear medicine context, beta amyloid plaque arises from a folding error (secondary structure) that results in cleavage of the protein.

All types of bonding are involved in drug receptor interactions (*1,5*). While figure 2 uses physical characteristics to schematically represent receptors, each drug / binding site has a unique chemical characteristic which is largely defined by the amino acids at the binding site (*1,5*). How the drug and receptor interact (structure, shape, and reactivity) determines how tightly they bind. A short direction of action for a drug is generally associated with weaker bonds while stronger bonds produce longer duration drug-receptor interactions (potentially irreversible). In decreasing strength, the binding forces associated with drug – receptor binding include (*1,5*):

- Covalent bonds
- Ionic interactions
- Hydrogen bonds
- Hydrophobic effects
- van der Waals forces

In most cases, a combination for these interactions are involved for each drug-receptor interaction (*5*).

When considering the drug-receptor binding, the rate at which the association between drug and receptor occurs relative to the rate of dissociation will define affinity; the

strength of attraction. Low affinity, and thus higher dose requirements, are associated with drugs where the rate of dissociation is appreciably higher than the rate of association. Conversely, high affinity drugs requiring lower doses for effect tend to be associated with a rate of association (k_1) well in excess of the rate of dissociation (k_2). The dissociation constant (k_d) is simply the ratio k_2 / k_1 (smaller means higher affinity) and provides an insight into both the drug effect and half maximal effect.

Dose-Response Relationship

The effect of a drug is a product of the concentration of the drug at the binding site, however, specific responses to drug concentrations are typically non-linear and considering that drug effect is a function of dose and time, there is a significant level of complexity. To simplify this concept, dose-response curves are generated using logarithmic X-axis scale for drug dose and a linear Y-axis for effect at a specific time point (e.g. equilibrium / steady state, or at maximum effect) (Figure 3). The time to steady state is influenced by a number of factors, including the rate of dissociation (k_2). It should be kept in mind that the drug-response curve will vary between individuals for the same drug and dose across gender, weight, race and age demographics, and for an individual (e.g. level of hydration, blood pressure, and self-limiting illness). Thus, a drug-response curve represents a mean response that can be generally applied to a population. The dose-response curve provides a valuable insight into drug characteristics and allow understanding of specific pharmacodynamic concepts (*1-3,5*):

- Dose response, slope of the curve, maximal effect (Figure 3),
- Potency and efficacy (Figure 4A),
- 50% effective dose (ED_{50}), 50% lethal dose (LD_{50}), therapeutic window (TW) and therapeutic index (TI) (Figure 4B),
- Tolerance (Figure 5A),
- Sensitization (Figure 5B),
- Activation and antagonism (Figure 6).

Drug Interactions

Drug interactions can cause harm due to either increased drug effect (toxicity) or decreased drug effect leading to therapeutic failure (*1-5*). There are a number of strategies that can be used to reduce the impact of drug interactions, however, the most appropriate for those in nuclear medicine include:

- recognizing potential interactions between drugs (e.g. assessing patient medication history prior to administration of interventional medication),
- recognizing factors that might potentiate drug interaction (e.g. age, diet, hydration level, comorbidity, environmental factors), and
- recognizing drugs with a narrow therapeutic index.

Interactions between drugs (drug-drug interaction) are an important cause of patient harm and are particularly important to consider in the nuclear medicine patient because the mean age of a nuclear medicine patient exceeds 60 years and both polypharmacy (concurrent use of multiple medications) and the degenerative effects of aging on organ function increase the risk of interaction. Pharmacokinetic drug-drug interactions will be discussed in part 2 of this series of articles. Pharmacodynamic drug-drug interactions result in cumulative (e.g. ACE inhibitors act on potassium sparring diuretics to lead to hyperkalemia), additive (e.g. ACE inhibitors and loop diuretics reduce blood pressure), synergistic (e.g. alcohol and sedatives have an effect greater than the sum of the individual drugs) or antagonistic effects (e.g. non-steroidal anti-inflammatory reduced the effect of ACE inhibitors on blood pressure) (Figure 7).

Conclusion

While dose-response curves provide some translational principles to therapeutic nuclear medicine, the tracer principle associated with radiopharmaceuticals generally relegates pharmacodynamics to the periphery. Pharmacodynamics is the study of how the drug affects the body and by design, radiopharmaceuticals should have little or no effect on the body. Nonetheless, pharmacodynamics provides essential insights into the effects of interventional and adjunctive medications on the nuclear medicine patient. Furthermore, understanding of pharmacodynamic principles provides the tools to mitigate drug interactions between adjunctive / interventional medications and those medications the

patient may have prescribed. This article provides foundational understanding for a more detailed examination of adjunctive and interventional medications in subsequent articles in this series.

References

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6. Stumpf WE. The dose makes the medicine, *Drug discovery today*. 2006; 11: 550-555.

List of tables

Table 1: Definitions of pharmacology terms.

Pharmaco-	Is the study of …………..
-dynamics	……… how the drug affects the living system
-kinetics	……… how the living system affects the drug
-genetics	……… variations in drug response due to genetic influences
-genomics	……… genetic factors to guide drug therapy
-epidemiology	……… variability of the drug response across a population
-economics	……… the comparative cost:benefit ratios of treatment strategies
-vigilance	……… the adverse effects of drugs

List of figures

Figure 1: Schematic representation of the relationship between pharmacokinetics and pharmacodynamics.
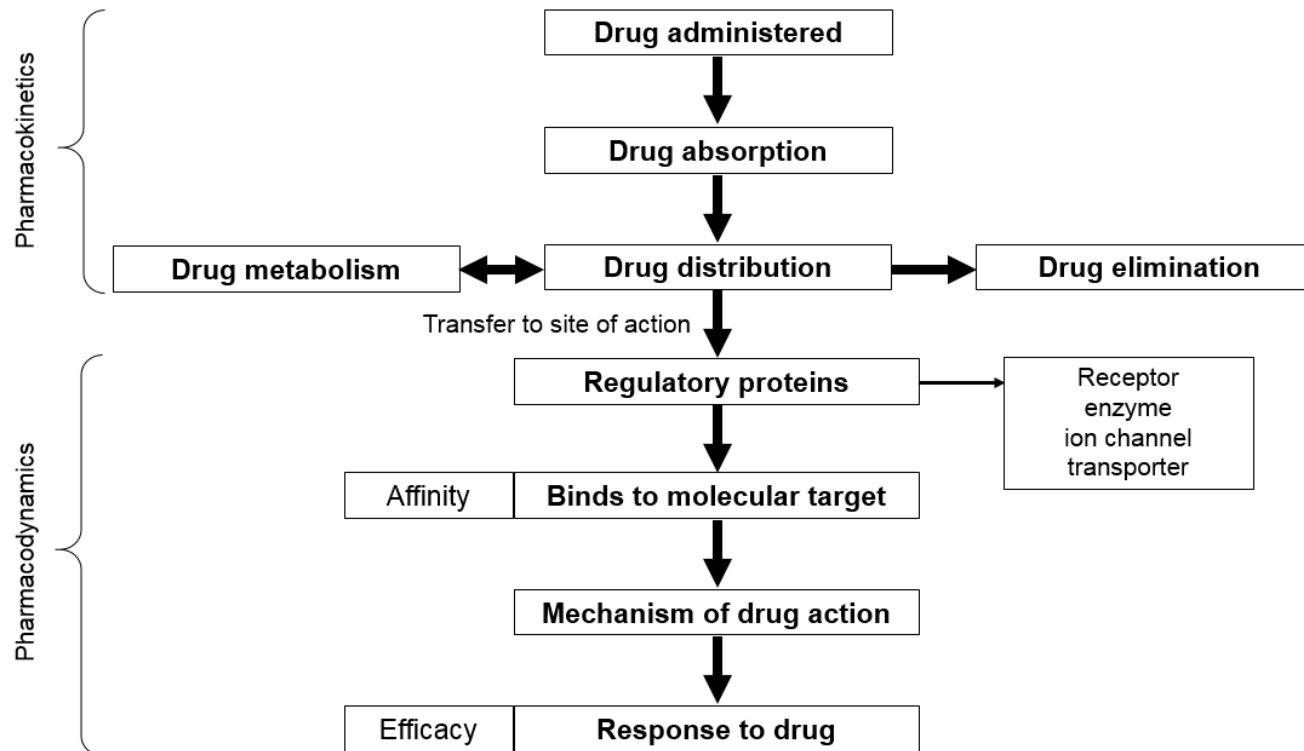
Figure 2: Schematic representation of the receptor concept. Ligands specific for a receptor may produce a response across the cell membrane, a partial response or block a response.
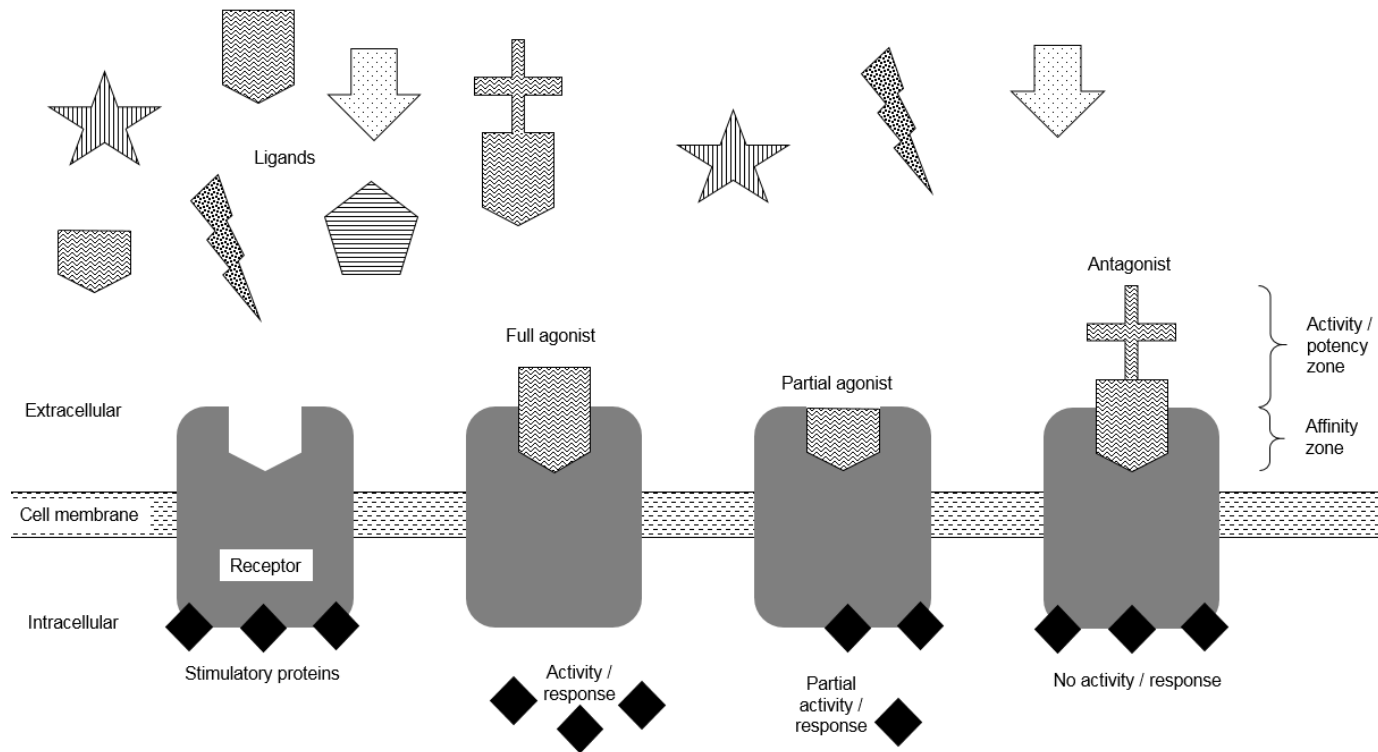
Figure 3: Steady state dose-response curve. The plateau (arrow) represents the dose for which maximal effect is achieved and above which additional dosage does not change the effect. There is also a drug dose below which no noticeable effect will be observed. The slope of the line provides an indication of how small (steep) or large (flat) a change in dose is required to observe increased effects.
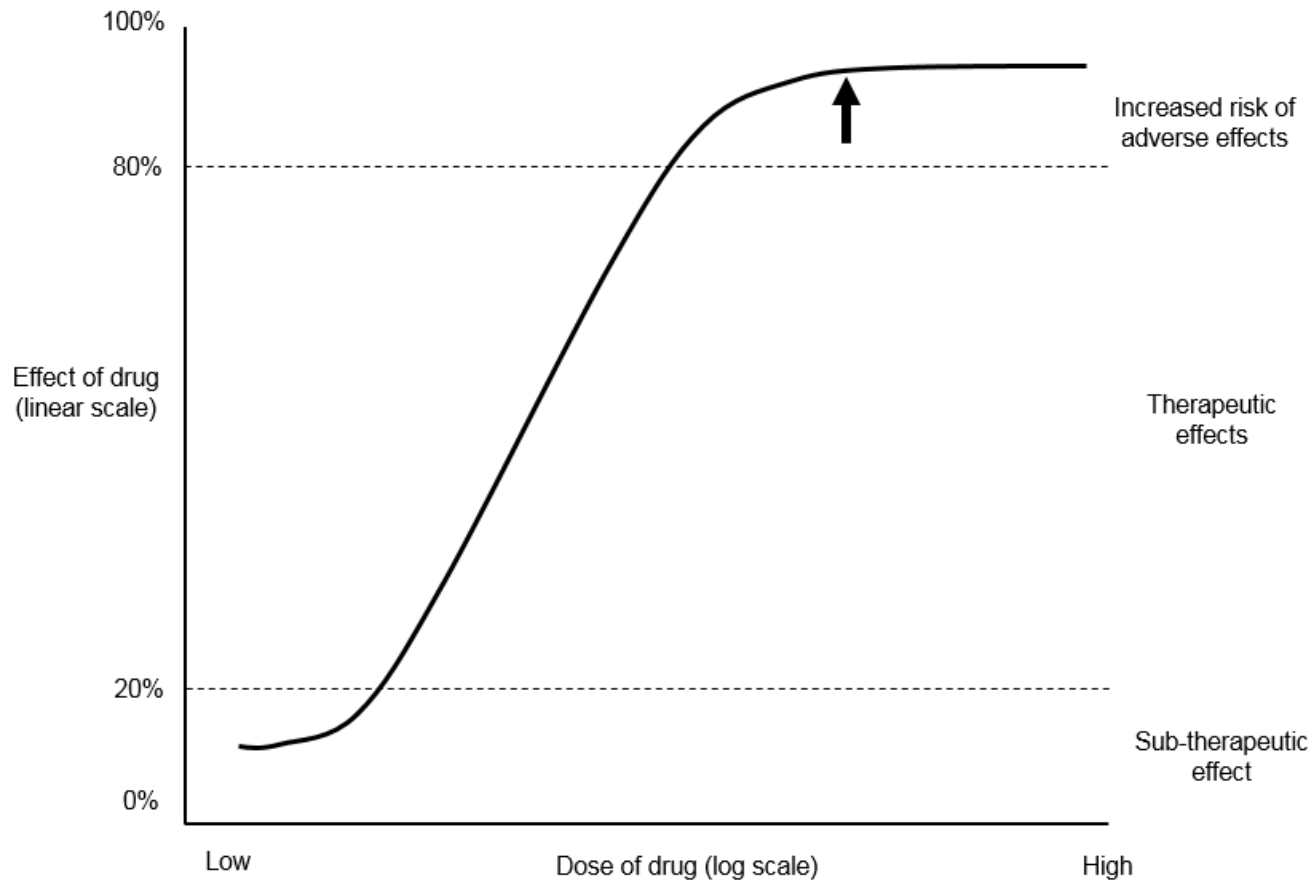
Figure 4: Dose-response curve representing the concepts of potency and efficacy (A on left). High potency (drug A) is represented by a shift to the left from drug B; strong effect with low dose. Sub-maximal effect (drug C) despite increasing dose demonstrates lower efficacy compared to drug A. The dose-response curve can also be used to represent the same drug but with different outcomes (B on right). Curve A represents the targeted therapeutic effect and ED_{50} (50% effective dose) is a dose that produces an effect in 50% of the population. Curve C represents the same drug but more dire effects and LD_{50} (50% lethal dose) is a dose that produces death in 50% of the population. The difference between curves A and C is the therapeutic window (TW) or the margin of safety and can be represented as the therapeutic index (TI) by expressing the ratio LD_{50}/ED_{50}. Curve B provides an example of a drug that would have a narrow therapeutic window or lower TI.

A. potency and efficacy

100%

A

B

Efficacy

C

Effect of drug (linear scale)

Potency

0%

Low

Dose of drug (log scale)

High

B. effective dose

100%

A

B

C

TW

Effect of drug (linear scale)

ED_{50}

LD_{50}

LD_{50}

TW

0%

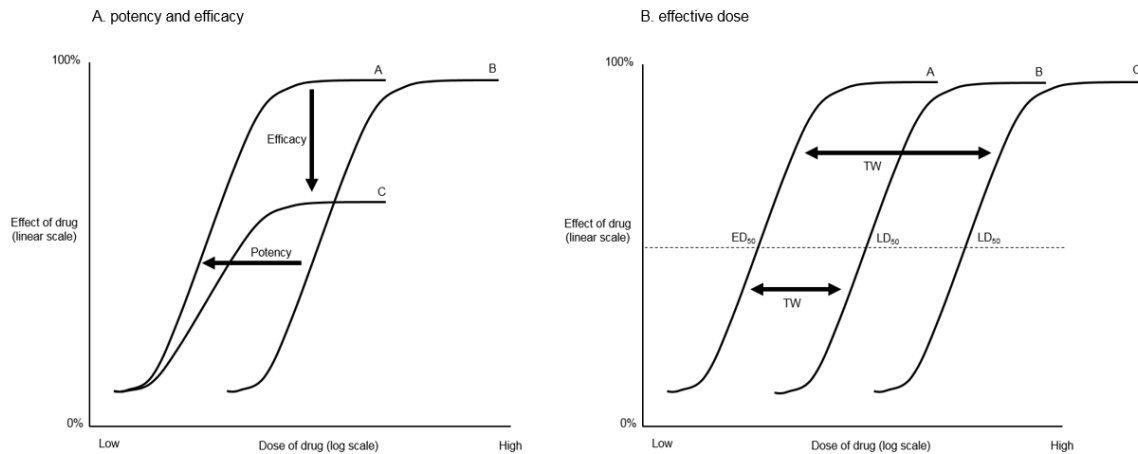Low

Dose of drug (log scale)

High

Figure 5: Following repeated doses of a drug, a patient may develop tolerance (A on left) which means the patient needs higher doses to generate the same effect (move from curve A to B) or has lower effects from the same dose (curve A to C). It should be noted that an individual may develop tolerance to the targeted effect of a drug without developing tolerance to side effects which changes the TI. Following repeated doses of a drug, a patient may also develop sensitization (B on right) which means the patient generates greater effects from the same dose (move from curve A to B) or has same effects from a lower dose (curve A to C). It should be noted that an individual may develop sensitization to one effect of a drug without developing sensitization to other effects.
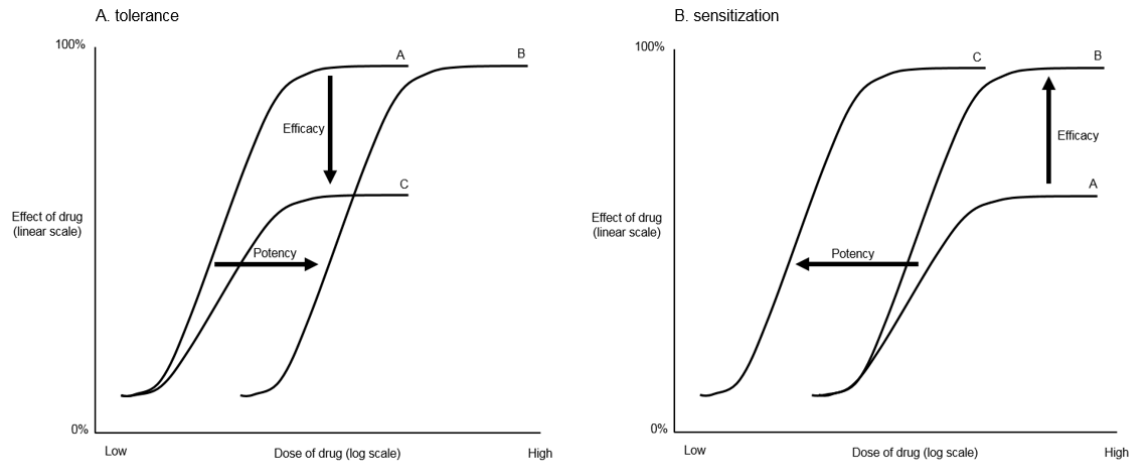
Figure 6: Agonist activity at a receptor may be altered by an antagonist, potentiated by allosteric activation of other receptors or inhibited by allosteric inhibition at other receptors.
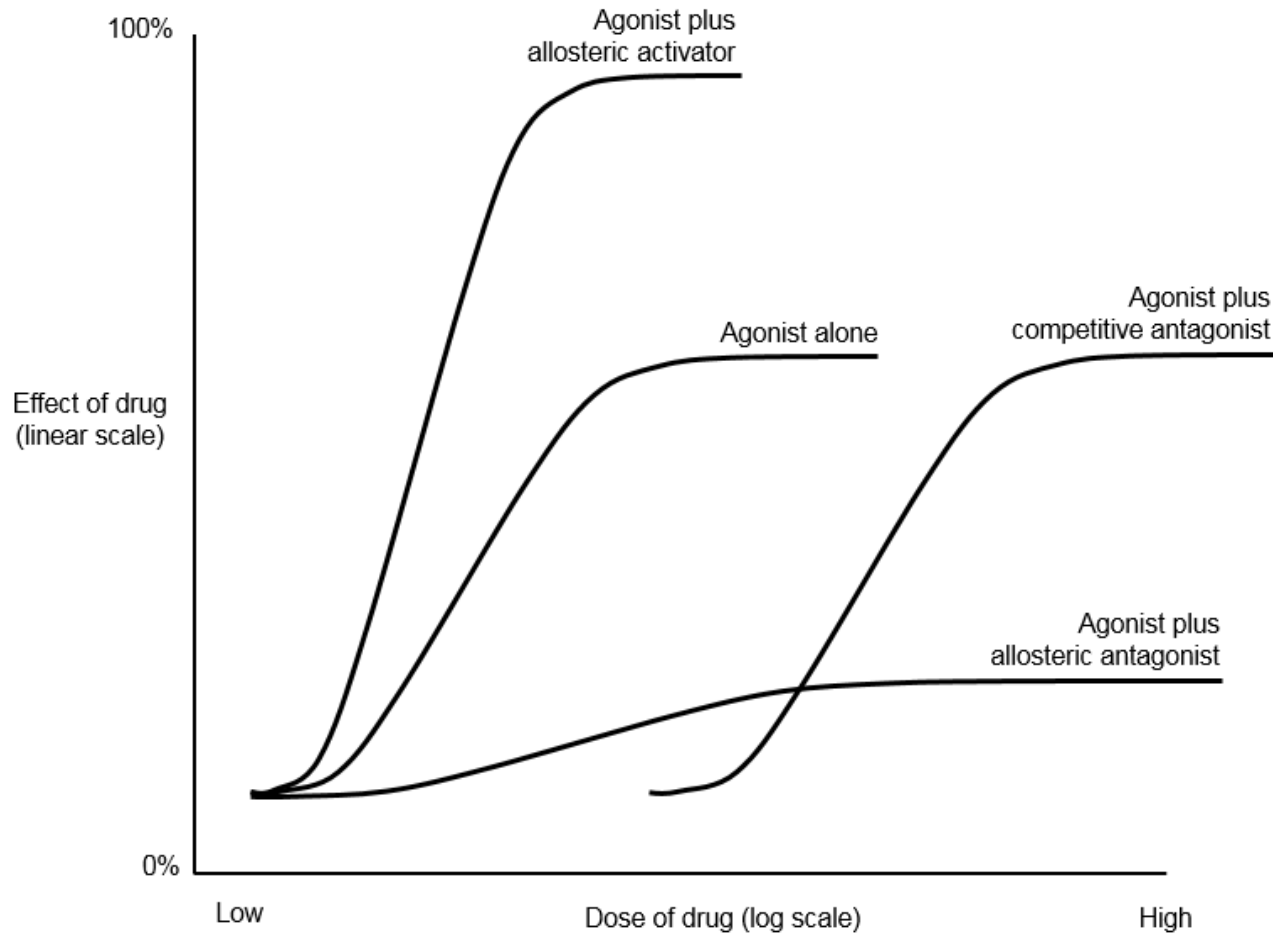
Figure 7: Schematic representation of pharmacodynamic drug-drug interactions.