Unit IV: Pharmacodynamics:

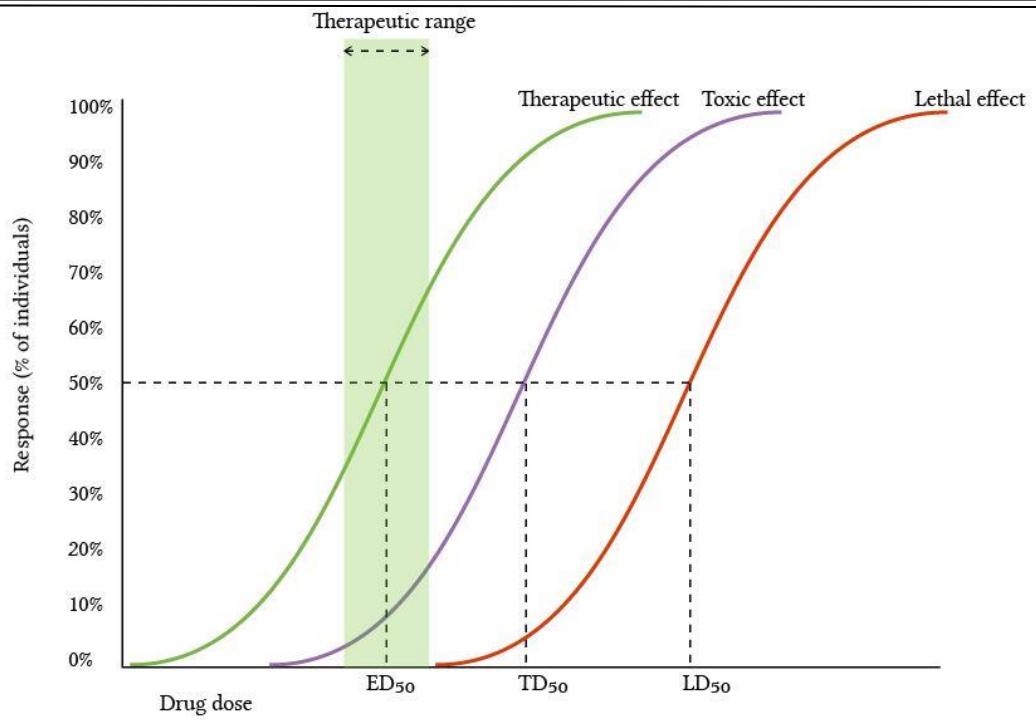
Concept of LD50, LC50, TD50 and therapeutic index

Quantal dose-response graphs can be characterised by the median effective dose (ED_{50}). The median effective dose is the dose at which 50% of individuals exhibit the specified quantal effect. The median toxic dose is the dose required to produce a defined toxic effect in 50% of subjects. The median lethal dose is the dose required to kill 50% of subjects. The therapeutic index is the ratio of the TD_{50} to the ED_{50}, a parameter which reflects the selectivity of a drug to elicit a desired effect rather than toxicity. The therapeutic window is the range between the minimum toxic dose and the minimum therapeutic dose, or the range of doses over which the drug is effective for most of the popuation and the toxicity is accceptable.

Anatomy of the quantal dose-response graph contain the following elements:

- Three sigmoid curves
- The median effective dose (ED_{50})
- The median toxic dose (TD_{50})
- The median lethal dose (LD_{50})
- The therapeutic window

The end result should look something like this:



❖ Median effective dose, ED_{50}

This thing is distinct from the identical ED_{50} in graded dose-response curves, where it corresponds to a measure of the potency of a drug, being the dose of a drug required to produce 50% of that drug's maximal effect. In quantal dose-response curves, the Katzung textbook defines ED_{50} as

"the dose at which 50% of individuals exhibit the specified quantal effect"

The International Union of Pharmacology Committee on Receptor Nomenclature and Drug Classification (Neubig et al, 2003) give an "official" definition as "*the dose of a drug that produces, on average, a specified all-or-none response in 50% of a test population*" which is essentially the same as the Katzung one, and in fact all the textbooks generally use a similar selection of words to express exactly the same content.

So, what is the point of this metric?

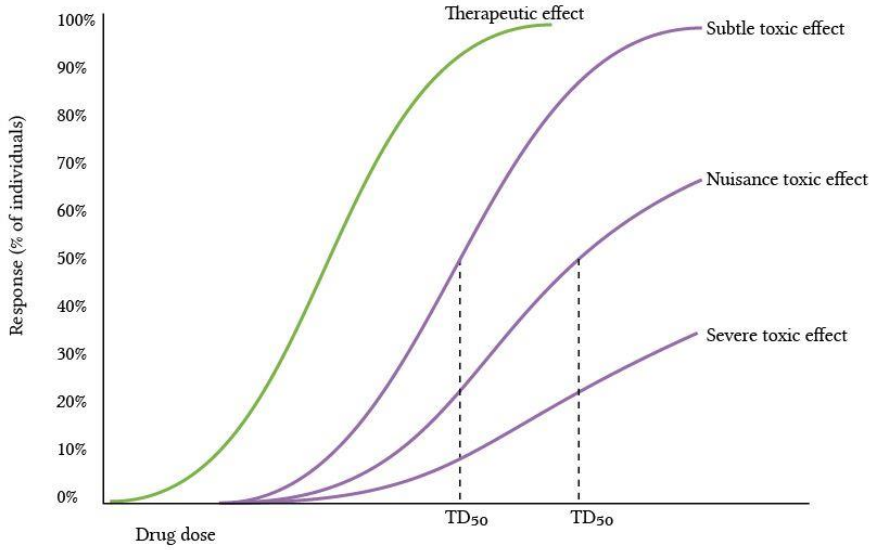
- It permits drug effect to be anticipated by clinicians
- It allows manufacturers to recommend dose ranges for safe prescribing.

However:

1) **It depends entirely on the definition of the quantal response.** When studying an antibiotic, is the endpoint complete elimination of bacteria from the blood, or is it clinical resolution of infection, or is it the inhibition of bacterial growth? Reported ED_{50}s are therefore potentially completely different among published investigators.
2) **It does not necessarily represent a clinically relevant dose**, which is the dose you actually prescribe. That might be higher or lower. For instance, when looking at cardiovascular mortality prevention as the end-point for quantal effect, one might discover that one is occasionally prescribing candesartan in doses which are 32 times the ED_{50} (Dimmitt et al, 2017).

❖ Median toxic dose, TD_{50}

This is the dose at which some clinically relevant toxic effect is reported in 50% of the tested population. To borrow credibility from von Zastrow, it is *"the dose required to produce a particular toxic effect in 50% of animals"* Like for all quantal dose-response relationships, many different interpretations are available of what a toxic effect is, and numerous TD_{50}s for each drug may be generated.



There are all sorts of problems with determining the TD_{50}:

1) **The TD_{50} may be difficult to model or measure experimentally.** A toxic effect may be predictable (for example, the extension of the drugs' therapeutic effect, such as warfarin and anticoagulation) or it may be completely unpredictable and idiosyncratic (eg. statins and rhabdomyolysis). In the latter case, toxicity becomes difficult to study.
2) **The toxicity may develop only after years of post-marketing data.** Carcinogenesis would not be revealed by 12-month follow-up in a clinical trial of cigarettes,
3) **The toxicity may be completely unrelated to dose.** For some toxic effects (eg. anaphylaxis), the TD_{50} is completely meaningless because even a minute dose will produce the effect in susceptible individuals, and in the non-susceptible population the likelihood of toxicity does not increase with dose, no matter how much of the drug you give.

❖ Median lethal dose, LD_{50}

LD stands for "Lethal Dose". LD_{50} is the amount of a material, given all at once, which causes the death of 50% (one half) of a group of test animals.

The LD_{50} is one way to measure the short-term poisoning potential (acute toxicity) of a material. J.W Trevan first introduced the concept of *minimum* lethal dose.

> *"I would suggest that the term " minimal lethal dose," with its variable meaning, should be dropped altogether, and that toxicity should be stated primarily in terms of the " median lethal dose," that is the dose which kills 50 per cent, of a large group of animals. As a convenient abbreviation I would suggest for this the symbol LD 50"*

Toxicologists can use many kinds of animals but most often testing is done with rats and mice. It is usually expressed as the amount of chemical administered (e.g., milligrams) per 100 grams (for smaller animals) or per kilogram (for bigger test subjects) of the body weight of the test animal. The LD_{50} can be found for any route of entry or administration but dermal (applied to the skin) and oral (given by mouth) administration methods are the most common.

Obviously, as with everything, there are some problems with the usefulness of LD_{50} as a means of comparing drugs. For example:

1) **Death may not represent a useful endpoint:** toxicity is a continuum, and functionally for the purposes of the clinician there is only a trivial practical distinction between the states of "dead from cocaine" and "almost dead from cocaine".
2) **Pharmacokinetics change the LD_{50}:** the rapid administration of phenytoin may be fatal, whereas the same dose administered slowly may have no toxic effects whatsoever. Nonlinear pharmacokinetics (eg. where increasing the dose also increases or decreases the clearance) factors into this.