INTRODUCTION TO POPULATION PHARMACOKINETICS

K. Arvind Nag

Pharm. D

Final Year

Department of Pharmacy Practice

JSS College of Pharmacy, Mysore

Introduction…

- Research in the last 40 years has uncovered significant differences among different populations in
  - Rates of drug metabolism
  - In clinical responses to drugs
  - In drug side effects

  } **Due to genetic variations**

- Genetic Variations of different Racial and Ethnic Groups ***cause*** → Difference in Proteins Encoding **(Enzymes)**

  cause ↓

  Difference in drug metabolism ***leads to*** ← Over dosing / Under dosing **(Toxic / Sub Therapeutic Levels)**

- To avoid this, substantial dosage adjustments may be necessary, particularly for - drugs of ***Narrow Therapeutic Index.***

Different Responses to Drugs among Different Population Groups

Aspect of difference	↑ Difference between ↓
Effect of Codeine as analgesic	More in Caucasians and Less in East Asians
Side effect of a Schizophrenic drug (Life threatening Blood disorder)	More in Caucasians and Less in Jewish
Dose requirement of Anti psychotic drug (for Schizophrenia)	Less in Asian, Hispanic and More in Non Hispanic White
Activity of several Phase I enzymes (CYP2D6, CYP2C Subfamily)	Difference between Caucasians and East Asians
Daily dose prescribed for many drugs	More in Japan and Less in US, Europe
Proportion of slow acetylators	More in Whites and Less in Chinese, Japanese
Allele frequency of CYP2D6 which encodes an enzyme with impaired activity	More in Black Americans, Africans and Less or absent in Whites, Asians
Two CYP2C9 alleles that produce a phenotype of poor metabolism	More in Whites and Less in Blacks
The phenotype of poor metabolism for CYP2C19	More in Asians and Less in Whites (in contrast to CYP2D6)
The frequency of CYP2C9*2 mutant alleles	**More in South Indians and Less in Chinese, Caucasians**
The frequency of CYP2C19*2 mutant alleles (Poor metabolizing genotype)	**More in South Indians (Over 28 million) and Less in other major Populations reported so far**
The distribution of CYP2C19*1/*1	**More in Caucasians, Africans, North Indians and Less in Tamilians**
The distribution of CYP2C19*1/*2	**More in Tamilians and Less in Other Populations**
The CYP2C19*1/*3 allele	**2.7% reported in Tamilians and not reported in North Indians and Caucasians**

Introduction...

- Now, an important recommendation by researchers is,

  "Pharmaceutical companies should include significant numbers of patients representing varied racial and ethnic groups in drug metabolism studies and clinical trials"

- Japanese authorities currently require clinical studies to be conducted in their own population. Because, they want evidence that their population metabolize a given drug in the same way as another population in which it was tested

- **ICH guidelines - E5**: Bridging study has to be conducted

- In light of these facts, drug therapy for specific populations and patients should be individualized to achieve the most effective health outcomes

- So, the future is most likely to be the development of drugs and their dosage regimen that work well with **certain population groups**

POPULATION PHARMACOKINETICS

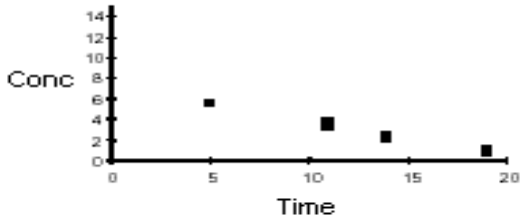
- **FDA:** Pop PK is "the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest".
- Pop PK originated as a TDM mechanism, and advent of new technologies and statistical methodologies expanded its role to almost the entire drug development process.

Phase	Reason for doing Pop PK
1	To estimate population parameters of a response surface model
2a	To gain information on drug safety
2b	how the drug will be used in subsequent stages of drug development
3	To gather additional information on drug pharmacokinetics in special populations, such as the elderly
4	Postmarketing surveillance studies

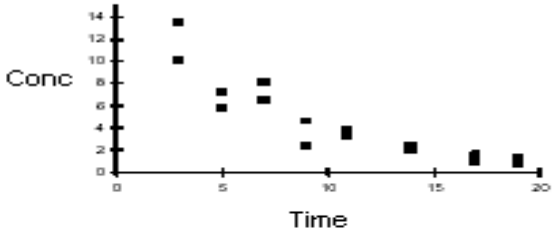
A comparison of Population Pharmacokinetics and Classical Pharmacokinetics Approach

Pop PK Approach

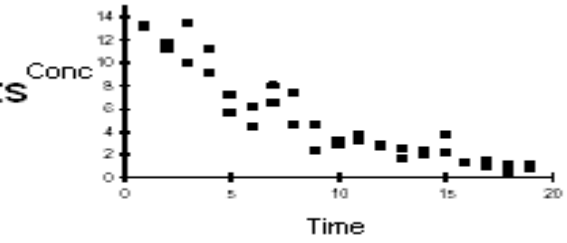
One subject



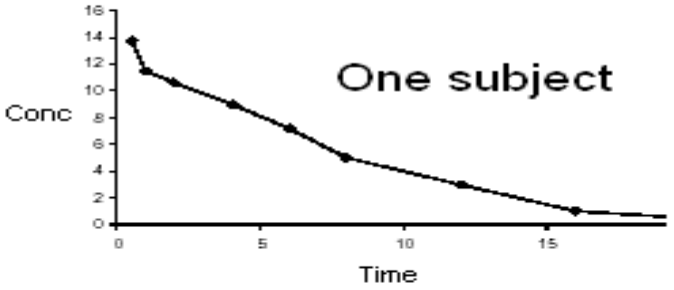
2-3 subjects



many subjects



Classical PK Approach



Advantages of Pop PK

- Overcomes many limitations of traditional PK studies
- Provides a better understanding of the dose-response relationship among the target patient population
- Mostly, drug is administered in clinically relevant doses and under routine therapy conditions
- The sample population mimics the real target population at large
- Multiple factors may be studied in one Pop PK study.

Advantages of Pop PK…

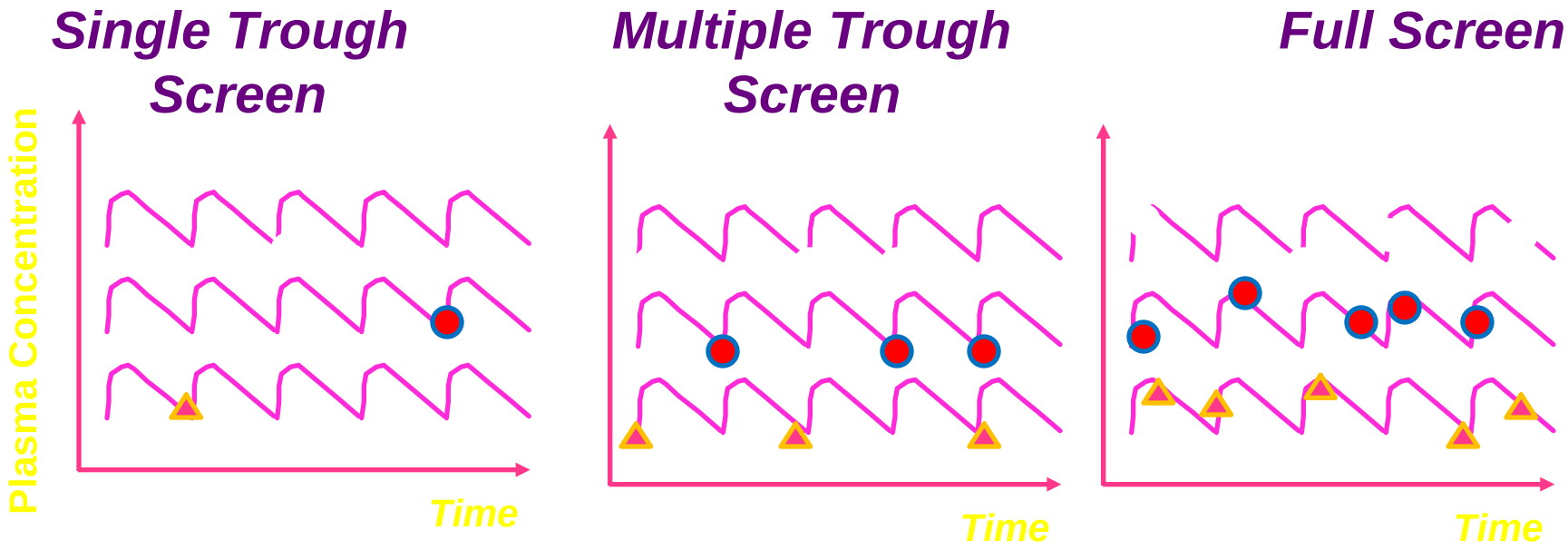
- Diversity of patient characteristics in population PK studies and large sample sizes
- A priori dose adjustment can be made by using Pop PK data
- Data on studies of different designs, dosing regimens, dosages and formulations can be pooled
- Data can be used to support labeling claims, drug - concentration relationships and also to seek regulatory approval of a new use of a drug

Pre-requisites to conduct Pop PK studies

- A valid assay for the relevant analyte
- Structural PK model, developed from early phase I studies
- Determine the parameters to be observed
- Suitable protocol for the study

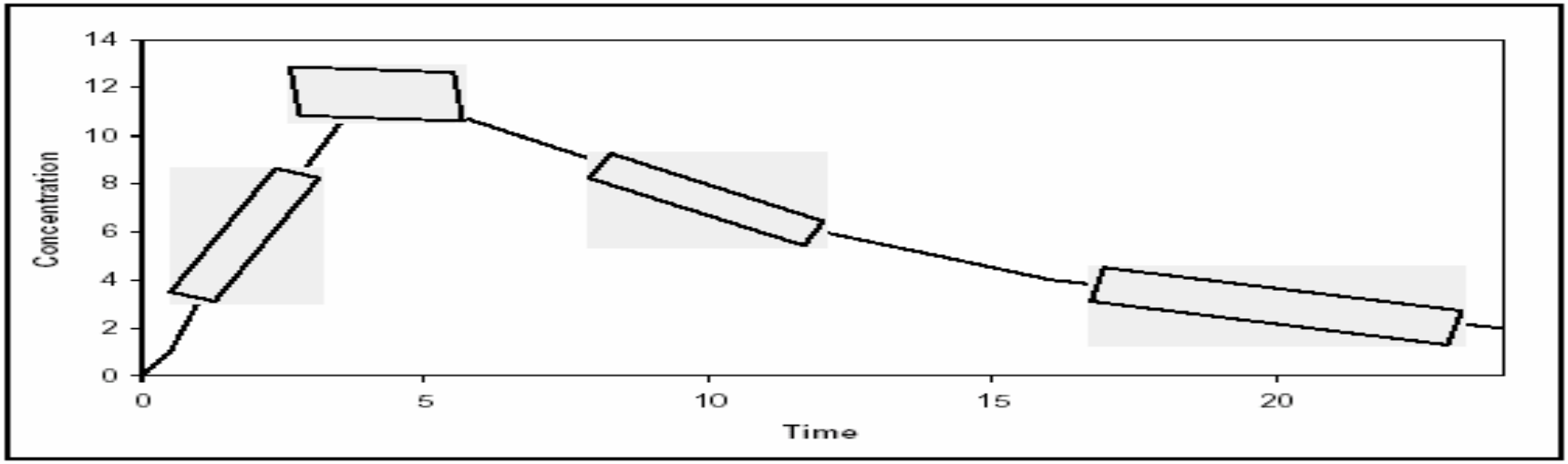
Sampling Designs

- Single pre-dose (or "trough") sampling
- Multiple-trough sampling
- Full PK screen design / experimental Pop PK design (2-6 samples)



Sampling Designs

- Full screening can take all kinds of flexible forms such as fixed sampling, random sampling and window sampling



- Accurate clinical data are very important
- The times, routes, and doses preceding sample collection, and the times at which the samples are drawn must be accurately recorded.

Methods in Population pharmacokinetics:

Methods of Population pharmacokinetics:

Traditional-

- standard two stage method
- Naive Pooling Method

Newer Methods-

- Mixed Effects Modelling

Nonparametric methods-

- Nonparametric Maximum Likelihood (NPML)
- Nonparametric Expectation Maximization (NPEM)
- Semi-nonparametric method (SNP)

- involves a relatively small number of individuals subjected to intensive sampling.
- The period of study often short since the subjects are usually institutionalised.
- Each individuals data analysed on a case by case basis using WLS/ELS regression to determine individual pharmacokinetic parameters.
- In the second stage, individual parameters are pooled to provide measures of central tendency (means) and variability (variances) for the population.

Advantages:

- Simple method.
- Capable of producing estimates of typical values for members of a population that are similar to those found with the direct population approaches.
- Well tried and straightforward to implement.
- Many software packages are available for this method.
- The statistics are straightforward and familiar to investigators.
- Gold standard method in case of rich data.

Disadvantages:

- A controlled study design therefore very expensive and requires careful planning and implementation.
- Difficult to study a sufficiently large number of individuals to adequately represent the population.
- Ethical issues associated with obtaining extensive samples in the more fragile sub-populations, where it is more important to apply population pharmacokinetics to optimize drug therapy.
- Gives unreliable results in case of sparse data.

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The Naive Pooling Method

- It is another traditional approach to population analysis. Here the data from all the individuals are pooled and analysed simultaneously without consideration of the individual from whom specific data were derived.

Advantages:

- Sometimes the only viable approach in certain situations like in the case of animal data where each animal provides only one data point.

Disadvantages:

- Generally this method is considered the least favourable.
- It is most susceptible to bias.
- It produces inaccurate estimates of Pharmacokinetic parameters.

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Mixed Effects Modelling

- It is viewed by many as the optimum population modelling method. It is a direct population approach in which the population parameters are determined in a single stage of analysis applied simultaneously to the data from many individuals.

Non Linear Mixed Effects Modeling (NONMEM)® - Overview

- **NONMEM®** is a computer program developed by the NONMEM project group at the University of California at San Francisco written in FORTAN 77, designed to fit general statistical (nonlinear) regression type model to data for analyzing population pharmacokinetic data in particular

- Proper modeling of these data involves accounting for both unexplainable inter- and intra-subject effects **(random effects)**, as well as measured concomitant effects **(fixed effects)**

Fixed effects are the components of the structural pharmacokinetic model. The structural model itself takes on the usual form. For example,

- **$Cp = D/Vd\ e^{-Cl/Vd\ t}$**
- Where, Cp = Concentration of drug in plasma (Observation or dependent variable)

D = Dose (Fixed effect)

T = time (Fixed effect)

→ They quantify the influence of a fixed effect on the dependent variable.

(NONMEM)® - Overview...

Fixed Effects:

- The known, observable properties of individuals that cause the descriptors (PK Parameters) to vary across the population are called “fixed” effects”. For example, if we know that clearance is proportional to body weight, then body weight has a “fixed effect” on clearance

Random Effects:

- These are “random” in that they can’t be predicted in advance (otherwise, they would become part of the fixed effects)
- In general, there are two sources of random variability when dealing with biological data
  - “interindividual” / “between-subject” variability (not ‘Noise’ / ‘Error’, It is BIOLOGY)
  - “intraindividual” / “within-subject” variability (includes ‘Error’ / “noise” in the assay, errors in drug dose, errors in the time of measurement, etc.

(NONMEM)® - Overview...

- Let's say I give a subject a drug, and then measure a concentration. I know with 100% confidence that the concentration won't be precisely what I expected to see. There are two reasons for this:

  1) The model describes the typical (or most representative) individual, not anyone in particular. This particular subject's volumes and clearances are different from those in the model.

  2) Even if the subject happened to be exactly like the typical individual, the measured concentration wouldn't be the same as the concentration predicted by the subject's volumes and clearances. There are two reasons for this:

  1) There is always measurement error

  2) There is misspecification in the model. In other words, it is illogical that biology can be reduced to a few simple equations. This misspecification in the model is considered part of the error, and gets lumped, together with assay error, as residual error

(NONMEM)® - Overview...

- Let's say that P is a parameter of a pharmacokinetic model (Cl / V)
- Regardless, the value of P in the i^{th} subject could be related to the typical value of P in the population by the following model:

$$Pi = PTV + \eta i \qquad \text{where}$$

Pi is the value of the parameter in the ith individual

ηi is the difference between Pi and the value of P for the typical individual, PTV

- The average ηi is **NOT** very interesting, because it should be 0.
- However, the variance of η, ω^2 (Omega squared) is very interesting, because it is the variance of P in the population, that is what NONMEM will estimate. Illy, Variance of ε is σ^2

P. ID	POP – 1 Clearance (L/hr)	POP – II Clearance (L/hr)
1.	20	22
2.	19	17
3.	18	21
4.	21	18
Mean SD	19.5 1.29	19.5 2.38
Variance	**1.66**	**5.66 (SD = √ Variance)**

Advantages:

- NONMEM is especially usefull for sparse, randomly collected data.
- the individuals are still identifiable, which permits different numbers of repeated measures for individuals inspite of the data being pooled into one data set.
- The inclusion of covariates during the estimation procedure offsets unbalanced data.
- NONMEM is able to derive population models when only a few samples are available from each individual.
- It is ideal for studying the populations such as the very old, very young or very sick, which are very difficult to address using STS.

Ideal for sparse data and Ideal for studying special population.
Able to derive population models from few samples available from individuals.

Disadvantages:

- The study design does not call for the collection of samples at specific times, resulting in imprecise estimates, therefore some thought must be given to optimal collection times.

  However, somewhat biased estimates have been reported especially when the data contain a large amount of random error. A modification implemented in the most recent version of NONMEM reduces this bias.

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Non parametric methods:

- Nonparametric approaches do not assume any specific underlying distribution of the parameters about the population values, but rather allow for many possible distributions. In this method the entire population distribution of each parameter is estimated from the population data.

Nonparametric Maximum Likelihood (NPML):

this method permits all forms of distributions, including those containing sharp changes, such as discontinuities and kinks.

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Nonparametric Expectation Maximization (NPEM):

- It is Another for this type of estimation which uses expectation maximisation as the estimator is Nonparametric Expectation Maximization (NPEM).
- It includes one and two compartment model capabilities with oral or intravenous dosing.
- NPEM is preferred to any parametric approaches when there is an unexpected multimodal or non-normal distribution of at least one of the model parameters.
- NPEM eliminates the need for initial guesses which are required for non linear least squares procedure; however, NPEM is highly dependent on selection of initial boundaries for the 2D grid base of the joint probability density function (pdf). NPEM is preferable to traditional methods in the event of sparse data.

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Semi-nonparametric method (SNP):

- As opposed to NPML and NPEM, SNP places some restrictions on the types of parameter distributions considered, but not to the extent of the parametric methods.
- The functions which are not permitted are those containing sharp edges or discontinuities, thereby imposing the property of smoothness to the pdf.
- This is justified since it is likely that the underlying parameter distributions of the population (as opposed to a sample of the population) are smooth.
- Although the NPML and NPEM distributions are discrete, they may also be smoothed after the estimation procedure is complete.

Application of Population Pharmacokinetics:

Postapproval phase-

- Dose adjustment based on the population average dose for an individual depending on the variability of the pharmacokinetic and pharmacodynamic parameters.
- Dose individualization for individuals whose pharmacokinetic parameters are most likely to deviate from the population typical values.
- Dose individualization for drugs possessing narrow therapeutic ranges.
- Stochastic control of drug therapy.

Preapproval Phase – Drug Development:

- Developing dosage regimens
- Evaluating dosage requirements of special populations (III)
- Investigate potential disease and drug interactions (II)
- Studying Drug concentration-acute toxic effect relationships (I-IV)
- Predicting outcomes of various forms of drug administration like multiple doses, special patient groups and controlled release formulations (I)
- Construction of a population pharmacokinetic model (I)
- Evaluating pharmacokinetic versus pharmacodynamic variability(I)

Indian Studies

- Amiodarone *
- Clozapine *
- Glibenclamide *
- Gentamycin *
- Theophylline *
- Phenytoin
- Carbamezipine
- Valproate
- Omeprazole *
- Metformin
- Rifampin *

*** Work done in TDM lab**

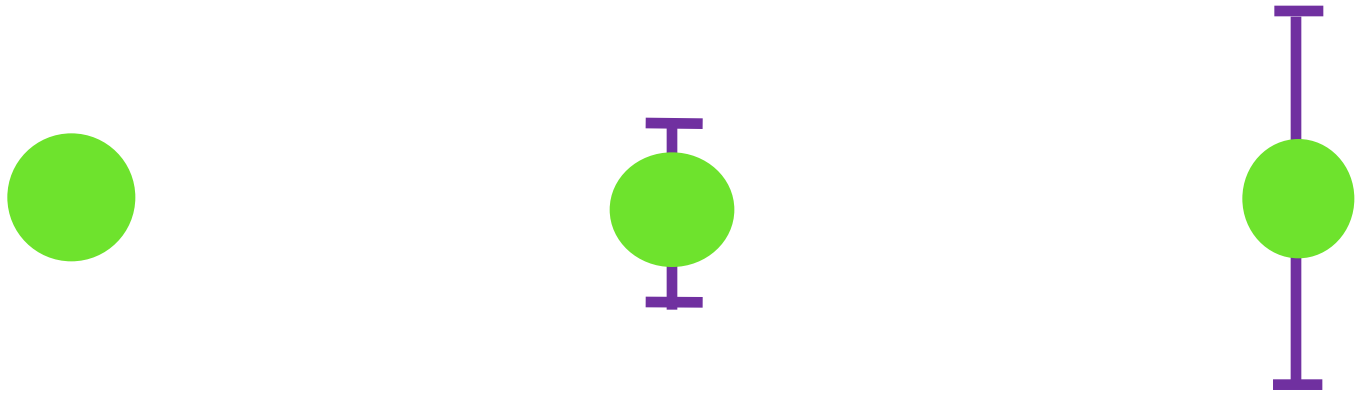
CONCLUSION

Empirical Dosing:

Dose

Concentration

Effect(s)



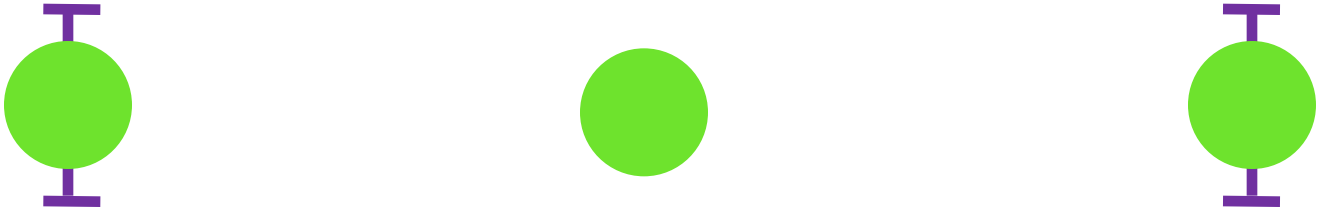
CONCLUSION…

Pharmacokinetic Dose Adaptations:

Dose

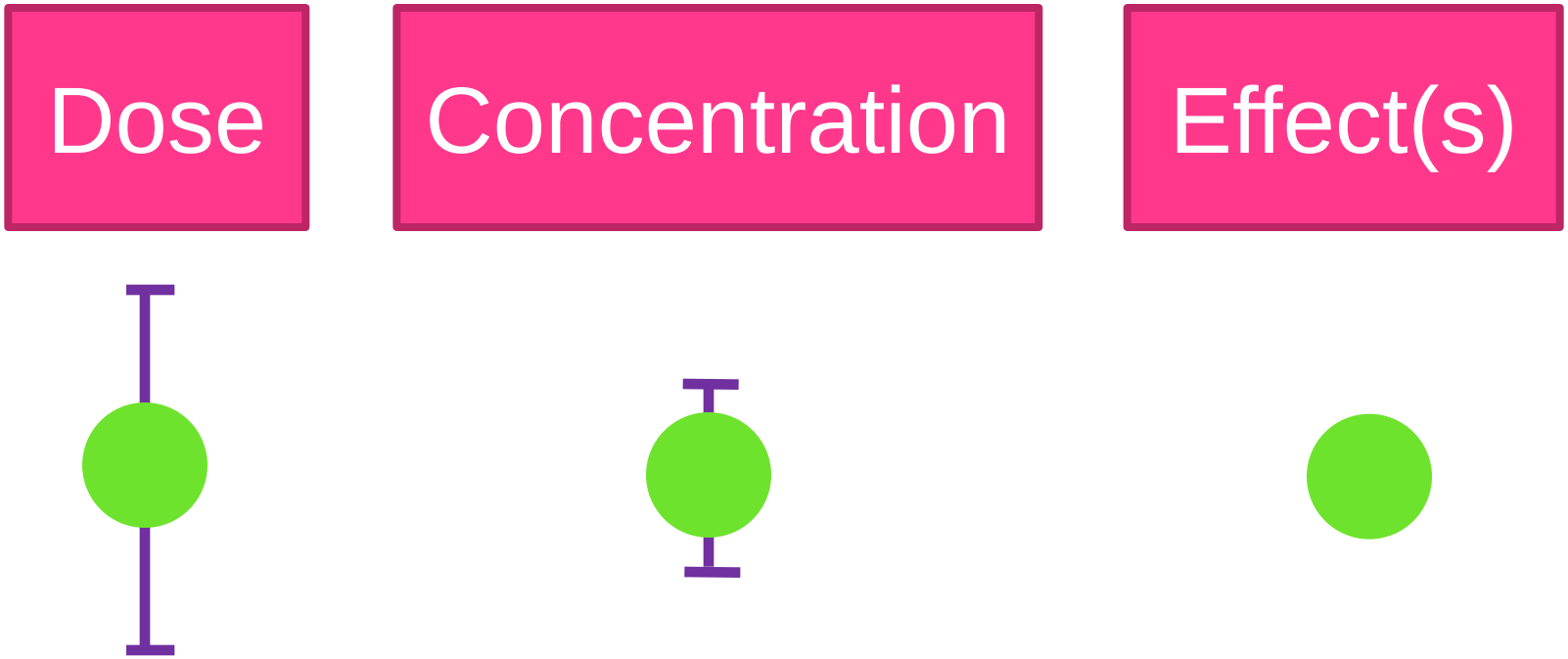
Concentration

Effect(s)



CONCLUSION…

Pharmacodynamic Dose Adaptation (Pop PK):



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