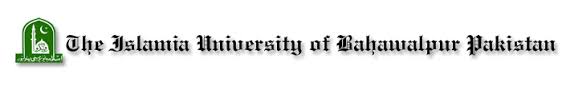


BIOPHARMACEUTICS

**PHARMACOKINETICS AND PHARMACODYNAMICS MODELLING**

**(**Fixed effect model, sigmoid Emax Model, Emax Model, Linear Adaptations of Emax i.e. Linear Model and Log linear Model**)**





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**PHARMACOKINETICS**

**Definition:**

**“**This refers to the movement of the drug in and alteration of the drug by the body**”**.

It includes:

* Absorption,
* Distribution,
* Metabolism (binding, storage, biotransformation)
* Excretion of the drug.

**PHARMACODYNAMICS**

**Definition:**

**“**The physiological and biochemical effects of the drug and their mode of action at organ system/subcellular/ macromolecular level**”**.

Drugs are in a dynamic state within the body as they move between tissues and fluids, bind with plasma or cellular components, or are metabolized. The biologic nature of drug distribution and disposition is complex, and drug events often happen simultaneously. The inherent and infinite complexity of these events requires the use of mathematical models and statistics to estimate drug dosing and to predict the time course of drug efficacy for a given dose. A model is a hypothesis using mathematical terms to describe quantitative relationships concisely. The predictive capability of a model lies in the proper selection and development of mathematical function(s) that parameterizes the essential factors governing the kinetic process.

The key parameters in a process are commonly estimated by fitting the model to the experimental data, known as **variables**.

A pharmacokinetic parameter is a constant for the drug that is estimated from the experimental data. Such mathematical models can be devised to simulate the rate processes of drug absorption, distribution, and elimination to describe and predict drug concentrations in the body as a function of time.

Pharmacokinetic models are used to:

1. Predict plasma, tissue, and urine drug levels with any dosage regimen
2. Calculate the optimum dosage regimen for each patient individually
3. Estimate the possible accumulation of drugs and/or metabolites
4. Correlate drug concentrations with pharmacologic or toxicologic activity
5. Evaluate differences in the rate or extent of availability between formulations (bioequivalence)
6. Describe how changes in physiology or disease affect the absorption, distribution, or elimination of the drug
7. Explain drug interactions

The concentration of the drug in the tank after a given dose is governed by two parameters:

1. the fluid volume of the tank that will dilute the drug,
2. the elimination rate of drug per unit of time.

For steady state condition, the most commonly used pharmacodynamics models are the

1. Fixed effect model
2. Linear model
3. Log linear model
4. Emax model
5. Sigmoid Emax Model
6. **FIXED EFFECT MODEL**

A fixed effect model, also known as quantal effect model, is a statistical approach based on a logistic regression analysis. It relates a certain drug concentration with the statistical likelihood of a predefined, fixed effect to be present or absent.

The simplest case of a fixed effect model is a threshold model, where the effect Efixed occurs after reaching a certain threshold concentration. C threshold, as

***E = Eeffect*** *if* ***C ≥ Cthreshold***

**E** is the measured **effect** and **C** is the measured **concentration**.

Since the threshold concentration will vary among patients, the probability of the effect to be present at a certain concentration will be a function of the threshold concentration in the populations.

**For example:**

Digoxin plasma concentration of **2.0 ng/ml** there is a **50%** probability to observe digoxin toxicity, where at a concentration of **4.01 ng/ml** the probability is **90%.** This approach may be useful in the clinical setting as an approximation of dose-response relationships but has major limitations for the prediction of complete effect-time profiles.

1. **LINEAR MODEL**

The linear model assumes a direct proportionality between drug concentration and drug effect.

For the correlation of salivary flow rate and plasma concentration after the pilocarpine infusions:

***E = m X C + Eo***

Where Eo is the baseline effect in the absence of drug and m a proportionality factor, that characterizes the Slope of a plot of effect E versus concentration C. Although the linear model is the one that intuitively is the most popular, it rarely applies.

1. **LOG LINEAR MODEL**

A much more common situation than the linear model is the log linear model with

**E = m X log C + b**

Where m and b are slope and intercept in a plot of effect E versus the logarithm of the concentration C.

Although b should have the unit of the effect, it is an empiric constant that has no real physiologic meaning, especially not that of a baseline value.

The log-linear model is applicable in many situations and can be considered a special case of the Emax-model, regarding the range between **20% to 80%** of Emax, where effect **E** and logarithm of the concentration **C** follow a linear relationship.

**For example:**

The synthesis rate of prothrombin complex activity to the plasma concentration of warfarin.

1. **Emax-MODEL**

In the maximum effect Emax-model, concentration **C** and effect **E** as related as

**E = Emax X C**

**E50 + C**

Where **Emax** is the maximum effect possible and **E50** is the condition that causes 50% of Emax. Emax refers to the intrinsic activity of a drug, E50 to its potency.

**For Example**

For applying Emax-model by describing the relationship between propranolol plasma concentrations and the resulting decrease in heart rate.

The equation of the Emax-model is based on the receptor theory relationship that can be derived for the equilibrium interaction of a drug (D) with its site of action (R)

**For example:**

A receptor, enzyme or ion channel, producing the effect E:

*[D] + [R] ↔ [DR] → Effect ⟹ [DR] = [Rtot] x [D]*

*Kd + [D]*

Where **Kd** the equilibrium constant and Rtot the total number of interactions sites. Under the assumption, that the observed effect **E** is directly proportional to the number of occupied interaction sites DR.

**Kd** is the concentration at which half of the concentration sites are occupied and, hence equivalent to **E50**.

The Emax-model describes the concentration effect relationship over a wide of concentration from zero effect in the absence of a drug to the maximum effect at concentration much higher than E50 (C >> E50).

In the presence of a baseline effect Eo, this term can simply be added

***E = Eo + Emax x C***

***E50 + C***

The clear non-proportional concentration effect relationship of Emax-model as linear and semilogarithmic plot. Whereas small increases in concentration may result in significant increases of the effect for low concentrations, this is much less profound for higher concentrations where only small changes in effect will result from changes in concentration.

From the semilogarithmic presentations, it is apparent that in the range from 20% to 80% of the maximum effect, the relationship between effect and the logarithm of the concentration is linear.

The slope of the linear phase can be calculated as Emax/4, the respective X intercept as In E50 – 2, and the y-intercept b as Emax x (2-In E50)/4.

At concentrations below 20% and above 80% of the maximum effect the Emax-model clearly deviates from the linear model. For concentrations much smaller than E50 (C<<E50), it reduces to a linear model with a slope m of Emax/E50. Hence, both, the log-linear as well as the linear model may be interpreted as special case of the Emax-model.

The Emax-model assumes an increase of the effect with increasing concentartions, i.e. a stimulated effect. Opposite, inhibitory effects can be

***E = Eo + Emax x C***

***E50 + C***

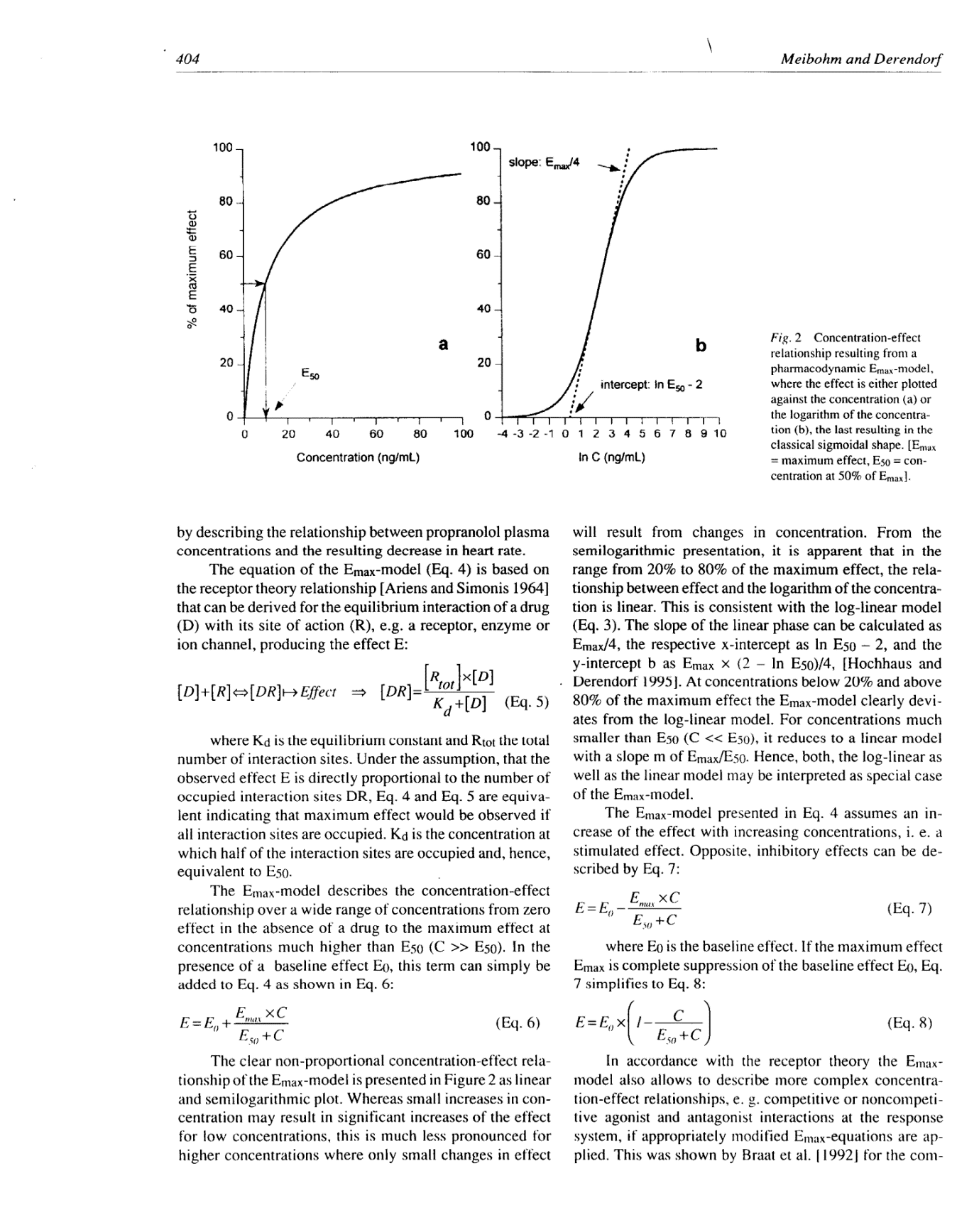
Where Eo is the baseline effect. If the maximum effect Emax is complete suppression of the baseline effect Eo

***E = Eo x ( 1 – C\_ )***

***E50 + C***

In accordance with the receptor theory the Emax-model also allows to describe more complex concentration-effect relationships,

e.g.

Competitive or noncompetitive agonist and antagonist interactions at the response system, if appropriately modified Emax-equations are applied. This was shown for the competitive effect of dexamethasone and hydrocortisone on lymphocytes.

1. **SIGMOID Emax-MODEL**

The sigmoid Emax-model is an expansion of the Emax-model. Effect and concentration are related as

**E = Emax x Cn**

**E50 + Cn**

Theoretically, this relationship can be dived to describe the interaction between n drug molecules and one interaction site similar.

However, in most cases n has no molecular basis and is merely used as an operational shape factor that allows a better data fit. This also explains why in many studies non-integer values for n are reported which could not be possible based on the mentioned derivation.

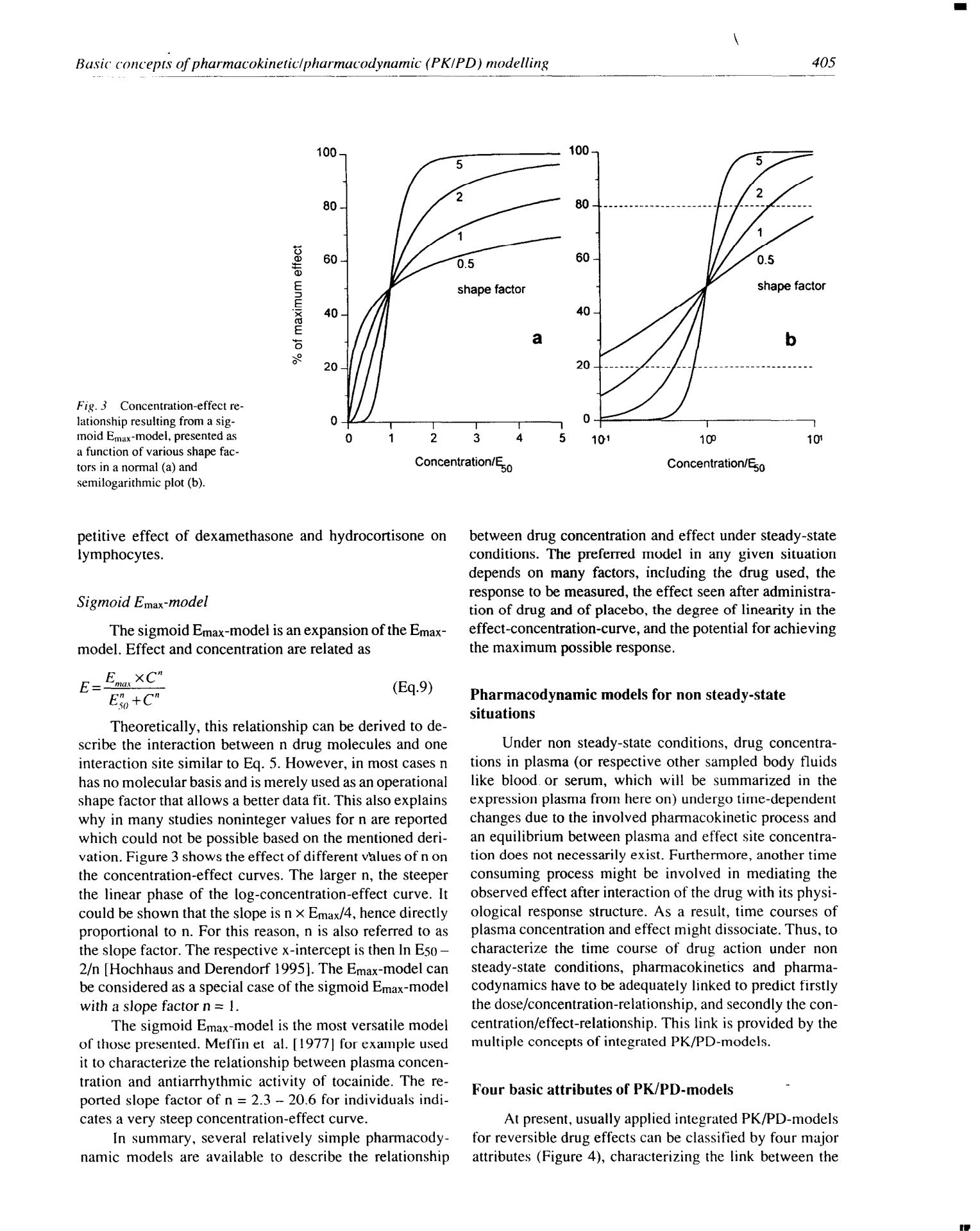
The effect of different values of n on the concentration – effect curves. The larger n, the steeper the linear phase of the log – concentration- effect curve.

It could be shown that the slope in n x Emax/4, hence directly proportional to n. for this reason, n is also referred to as the slope factor. The respective x-intercept is then In E50-2/n. the Emax-model can be considered as a special case of the sigmoid Emax-model with a slope factor n=1. The sigmoid Emax-model is the most versatile model of those presented.

**For example:**

The relationship between plasma concentration and antiarrhythmic activity of tocainide. The reported slope factor n=2.3 – 20.6 for individuals indicates a very sleep concentration-effect curve.

In summary, several relatively simple pharmacodynamic models are available to describe the relationship between drug concentration and effect under steady-state conditions. The preferred model in any given situation response to be measured, the effect seen after seen administration of drug and of placebo, the degree of linearity in the effect-concentration-curve, and the potential for achieving the maximum possible response.



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