Development of reference blood concentrations

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ORIGINAL ARTICLE

Serum Concentrations of Antidepressant Drugs in a Naturalistic Setting: Compilation Based on a Large Therapeutic Drug Monitoring Database

Margareta Reis, PhD, Trond Aamo, MD,† Olav Spigset, MD, PhD,† and Johan Ahlner, MD, PhD**

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INTRODUCTION

Therapeutic drug monitoring (TDM) in the field of psychotropic drugs began with the tricyclic antidepressants (TCAs) in the 1960s. A common feature for all TCAs is a large interindividual variability of the serum concentrations of the respective drug.[1,2] They have a slow onset of action, and, initially, it was difficult to reveal any correlation between concentration and effect. However, a milestone was passed when the curvelinear concentration–effect relationship was described for nortriptyline.[3] Eventually, it was shown that the most important factor responsible for the interindividual concentration variations was the genetically determined metabolism. The metabolism of the selective serotonin

Why is this important?

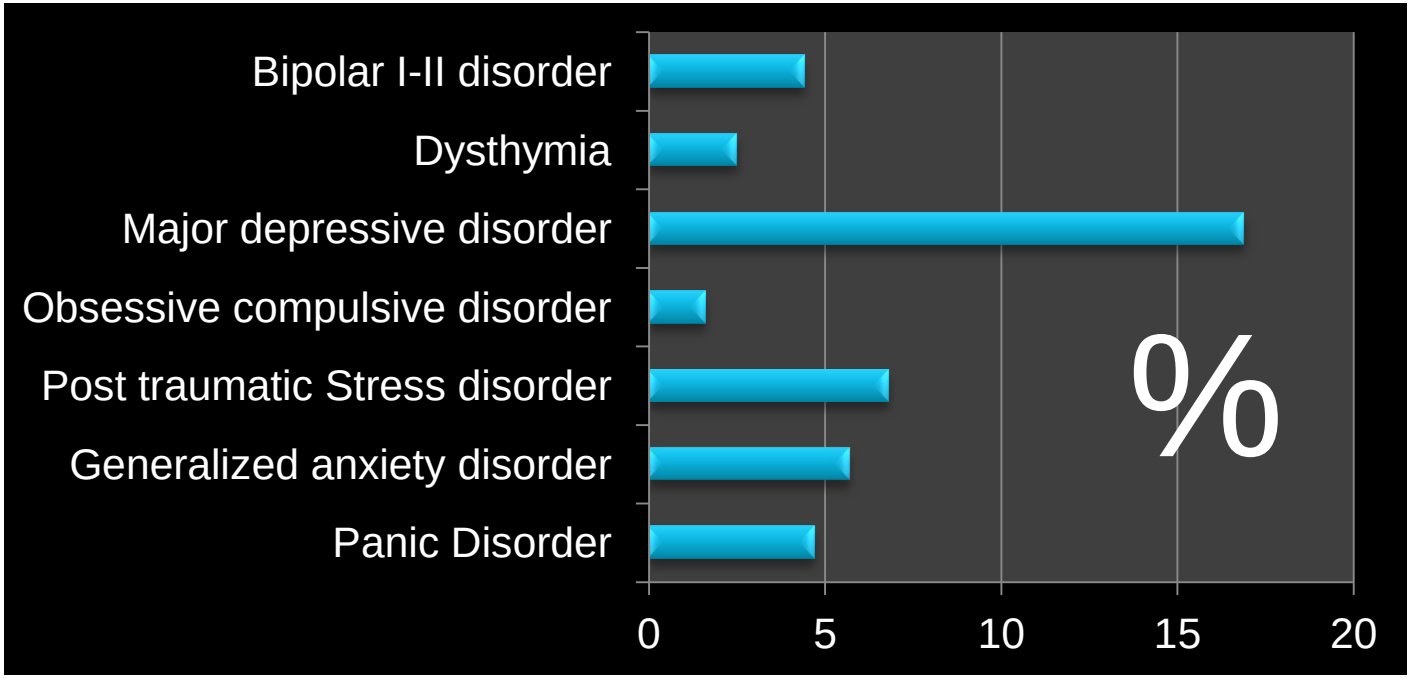
“Doctors pour drugs of which they know little,

to cure diseases of which they know less,

into human beings of whom they know nothing.”

Voltaire

Lifetime prevalence of some psychiatric disorders



Adaption from the National Comorbidity Survey (last update July 19, 2007)

Lifetime prevalence of major depression

Women 10% - 25% Men 5-12%

Prevalence before puberty: boys= girls

Suicide is a serious public health problem worldwide

More loss of life than all forms of war and interpersonal violence combined per year.

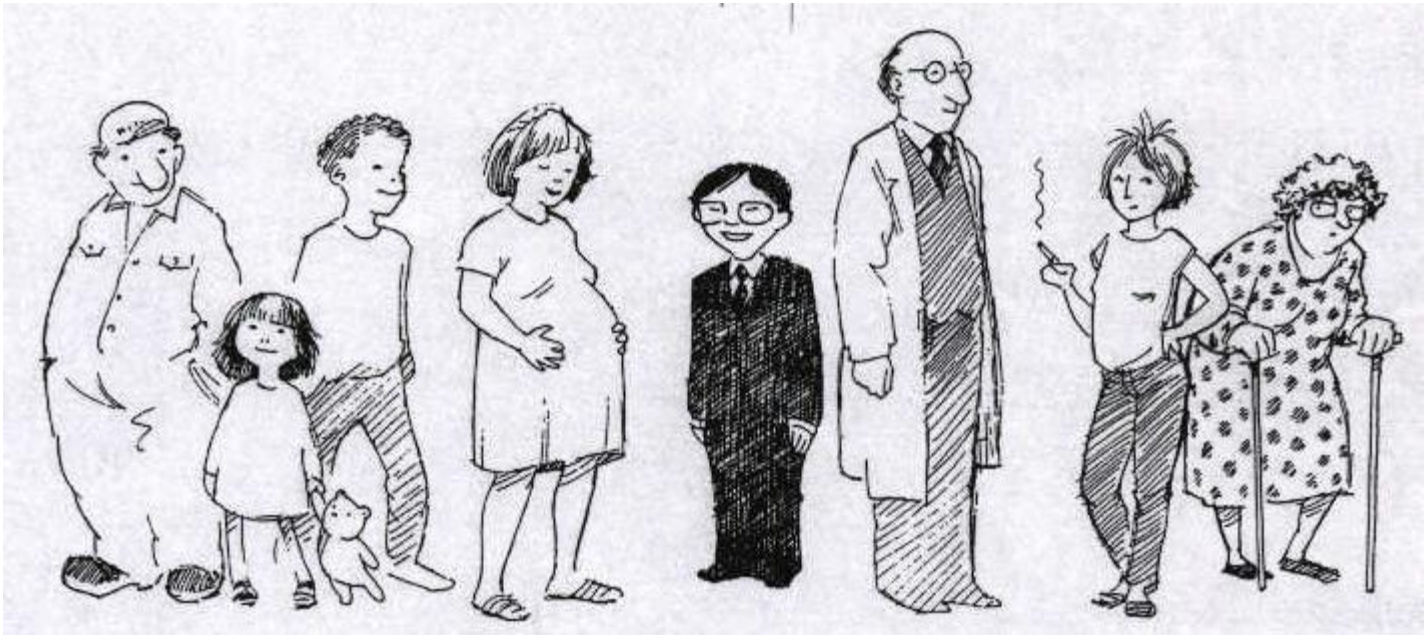
The number of suicides in Sweden, 2010, was 1442; a number which has decreased over the last 20 years.

Suicide attempts have increased over the same time

Suicide and suicide attempts are closely related to poor mental health.

Drugs are tested on these men

Drugs are given to these people….



Significant inter-individual concentration variation
50-100 x times in C_{ss} given the same dose!

For antidepressant drugs the

- non-response rate is high
- side effects are common

…..and in a naturalistic population:

- 5-10% are poor metabolizers of CYP 2D6 ,
- 2-3% are poor metabolizers of CYP 2C19
- 10 to 40 fold variation of CYP3A4

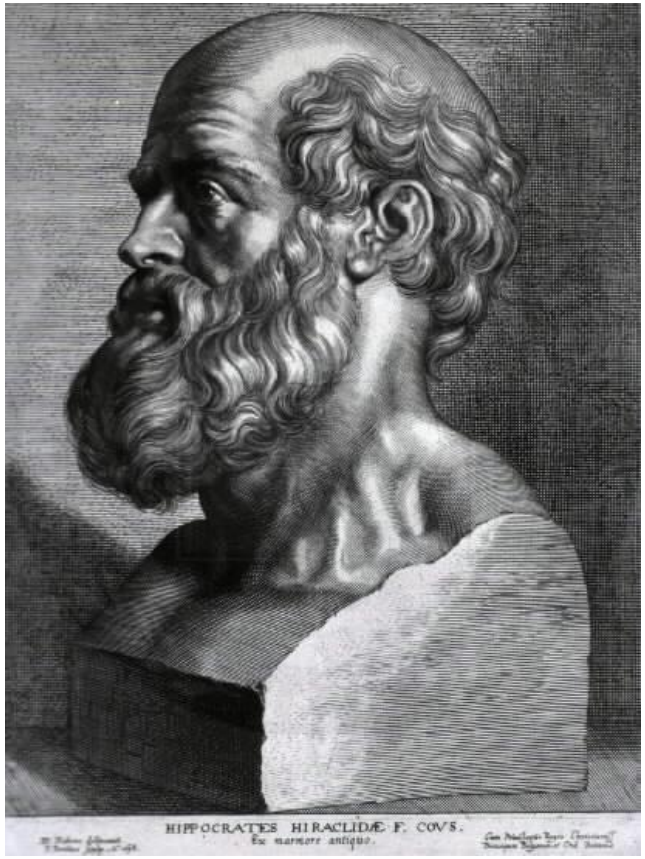
- Concomitant medication is common
- We smoke
- We drink

- Many of us are old

18% of the Swedish population are older than 65 years

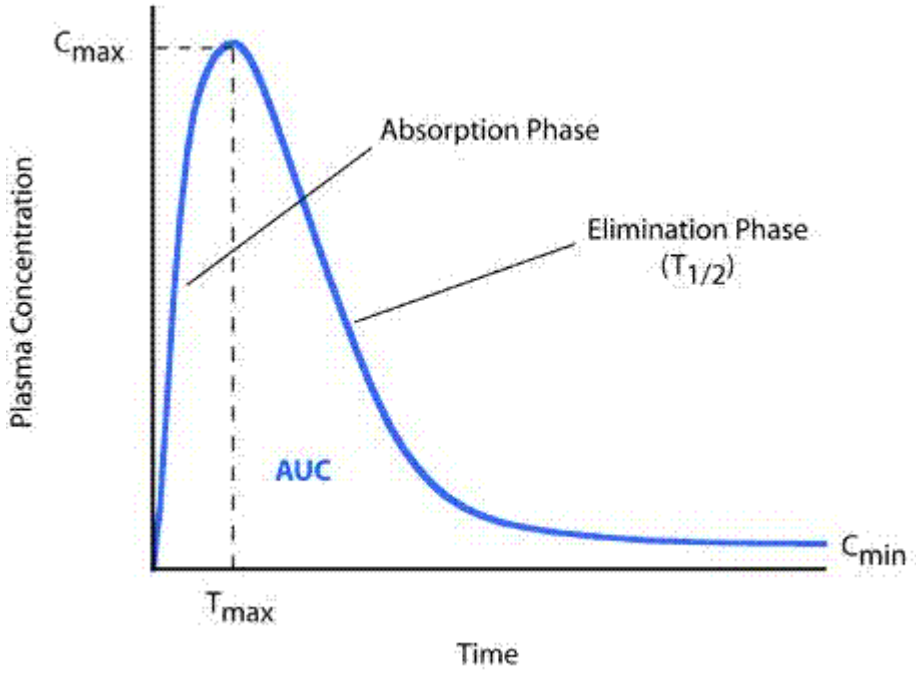
- The non-compliance rate is around 50%

"Keep watch also on the faults of the patients, which often make them lie about the taking of things prescribed."



4th century B.C., Hippocrates recognized the difficulties of patient compliance

All those factors affect the pharmacokinetics of a drug



Those were some reasons for the importance of developing reference blood concentrations

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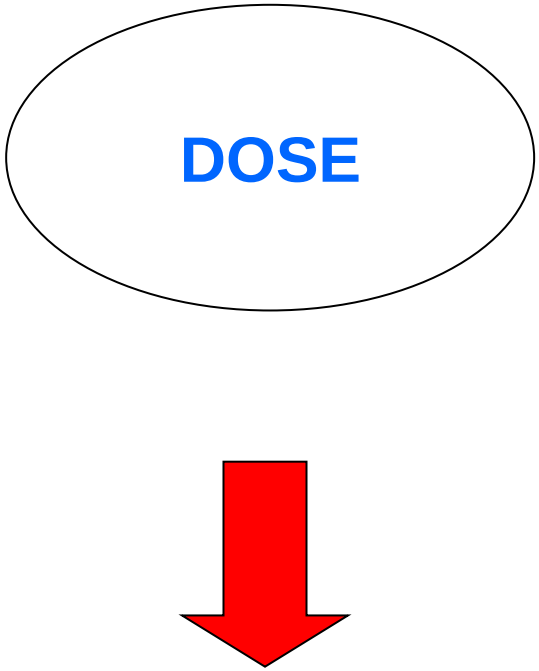
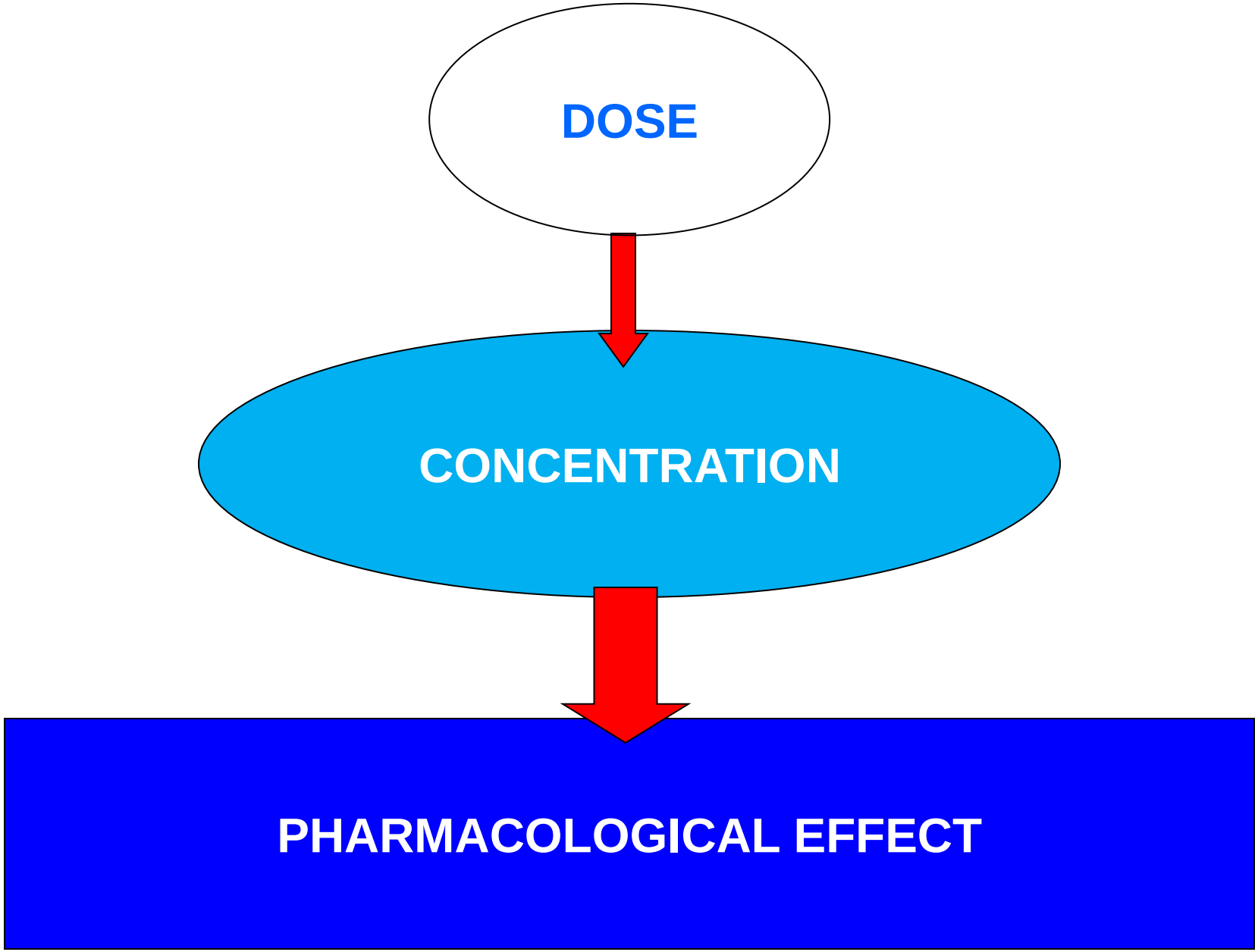
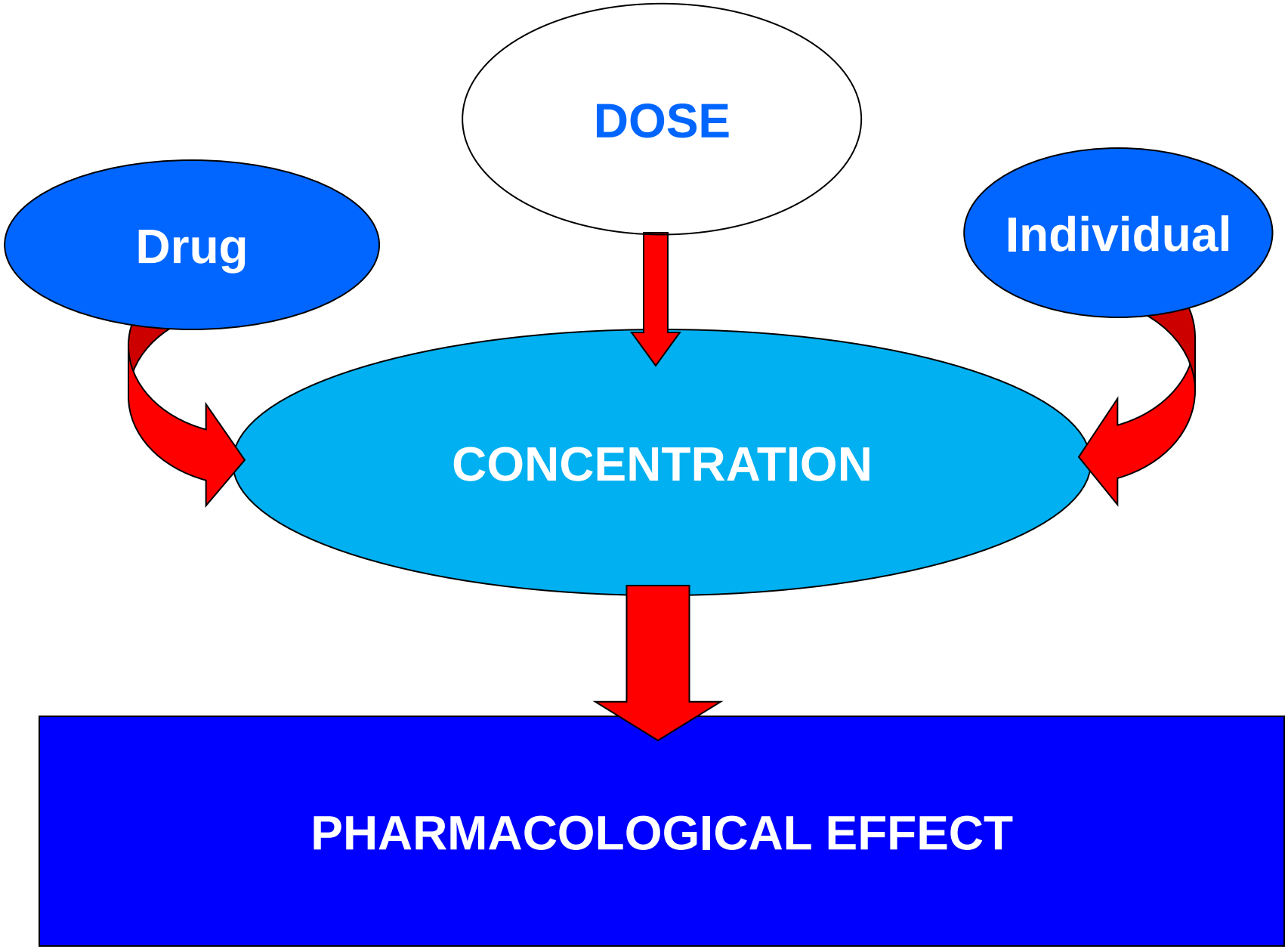
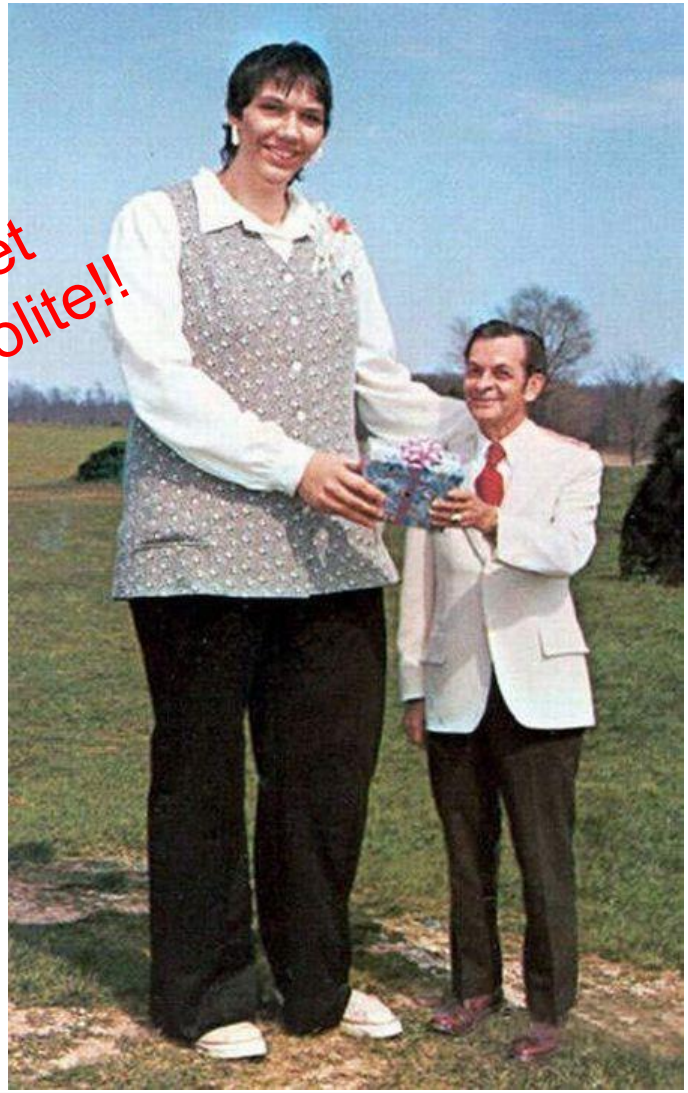

DOSE
Pharmacological effect


DOSE
CONCENTRATION
PHARMACOLOGICAL EFFECT


DOSE
Drug
Individual
CONCENTRATION
PHARMACOLOGICAL EFFECT

Never ever forget
the major metabolite!!



TDM-data of fifteen antidepressant drugs from naturalistic settings collected during the years 1999-2006

Drug	Samples (n)	Samples with no detectable parent substance (%)
Amitriptyline	927	10%
Citalopram	10324	4%
Clomipramine	938	9%
Escitalopram	5113	4%
Fluoxetine	1511	4%
Fluvoxamine	446	4%
Mianserin	1891	5%
Mirtazapine	2370	4%
Moclobemide	427	7%
Nortriptyline	463	14%
Paroxetine	3154	6%
Reboxetine	139	1%
Sertraline	5659	4%
Trimipramine	353	15%
Venlafaxine	3214	3%

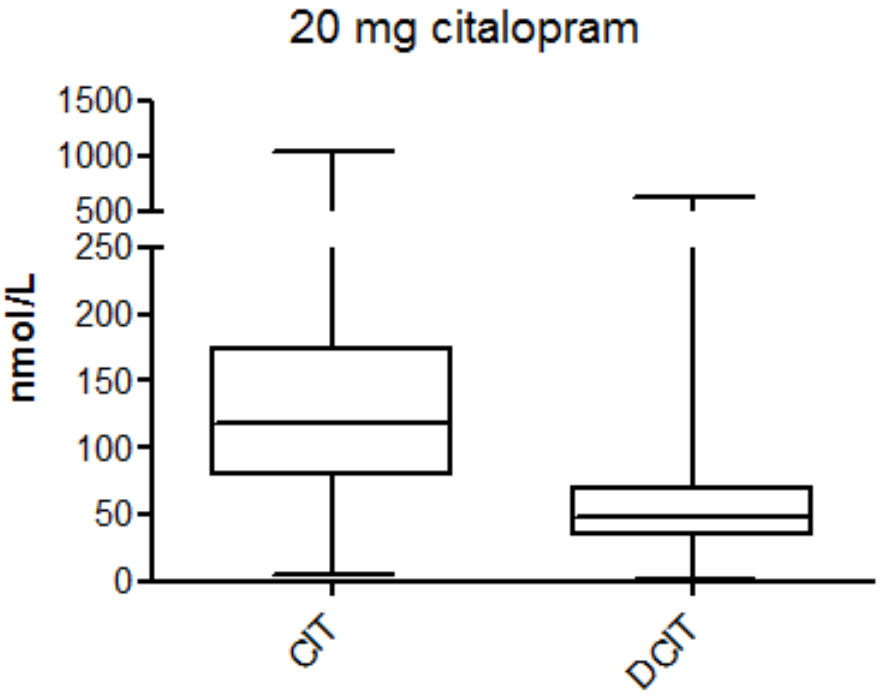
Number of samples included in the analyses

Drug	Samples	Women	≥ 65 years	Median dose
Citalopram	5457	64%	20%	30 mg
Escitalopram	3066	63%	15%	10 mg
Mirtazapine	1427	54%	21%	30 mg
Paroxetine	1677	66%	17%	30 mg
Sertraline	2998	66%	16%	100 mg
Venlafaxine	1781	60%	13%	150 mg

General outcomes

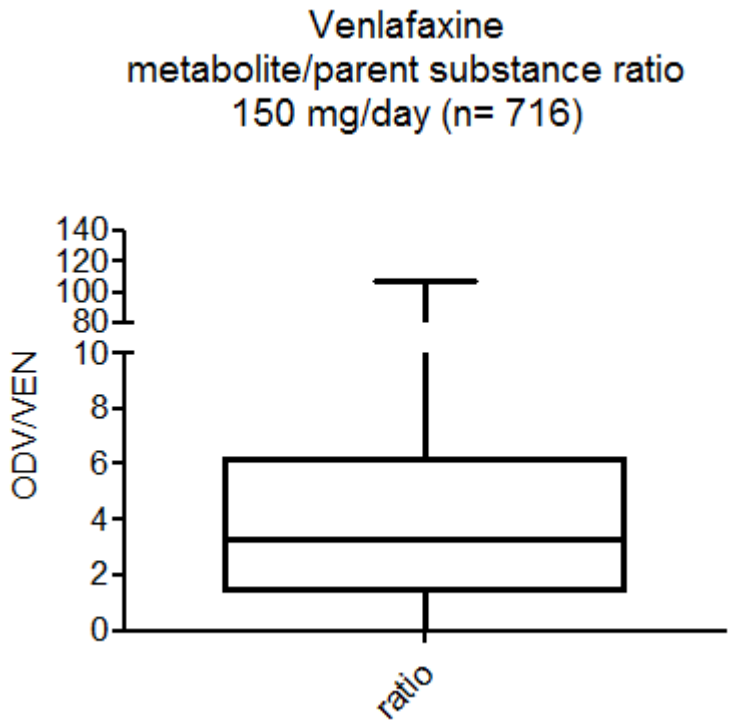
Drug (most common dose/day)	seum concentration women vs. men	seum concentration old vs. young
Amitriptyline (100 mg)	ns	ns
Citalopram (20 mg)	+ 25% ***	+ 84%***
Clomipramine (150 mg)	ns	+ 71%*
Escitalopram (10 mg)	+ 9%*	+ 91%***
Fluoxetine (20 mg)	ns	+ 61%**
Fluvoxamine (100 mg)	ns	#
Mianserin (30 mg)	+ 42%***	+ 62%***
Mirtazapine (30 mg)	+ 16%***	+ 44%***
Moclobemide (600 mg)	ns	ns
Nortriptyline (100 mg)	ns	+ 72%**
Paroxetine (20 mg)	+ 32%***	+ 74%***
Reboxetine (8 mg)	ns	#
Sertraline (100 mg)	ns	+ 35%***
Trimipramine (150 mg)	ns	ns
Venlafaxine (150 mg)	+ 42%***	+ 38%***

The serum concentration variation was high



example

.....as was the ratio metabolite/parent substance



example

The concentration variation was great

Drug (mg/day) M / P ratio	*Intra*-individual CV (%)	*Inter*-individual CV (%)
Citalopram (20 mg)	34	53
Desmethylcitalopram/citalopram	*33*	*46*
Escitalopram (10 mg)	41	64
Fluoxetine (20 mg)	47	62
Norfluoxetine/fluoxetine	*31*	*56*
Mirtazapine (30 mg)	50	45
Desmethylmirtazapine/mirtazapine	*26*	*43*
Paroxetine (40 mg)	52	65
Sertraline (100 mg)	54	73
Desmethylsertraline/sertraline	*38*	*37*
Venlafaxine (150 mg)	87	66
O-desmethylvenlafaxine/venlafaxine	*71*	*93*

CV = coefficiant of variation

- The intra-individual CVs were significantly lower than respective overall CVs

- In general, the CV was lower for the metabolite/parent substance ratio than for the parent substance

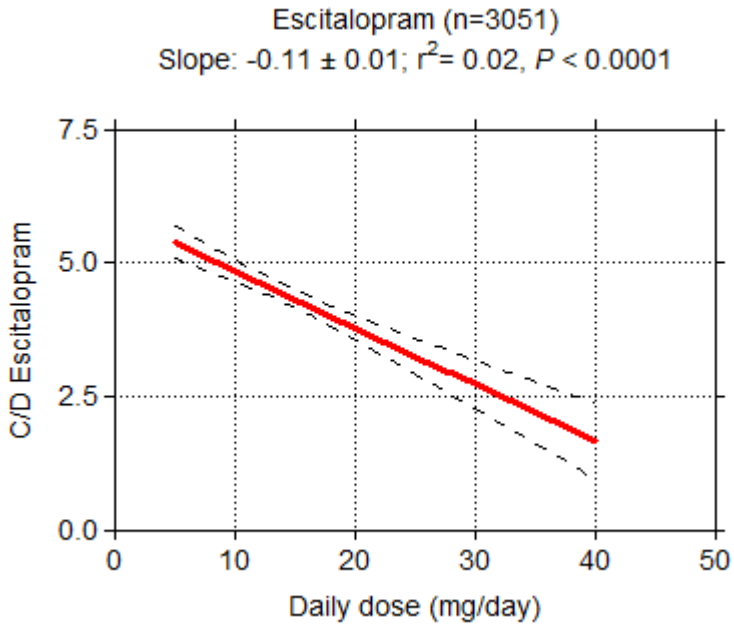
The relationship between daily doses and dose-normalized parent substance concentrations (C/D ratios)

All drugs with linear (1st order) kinetics (but reboxetine) described a significantly negative correlation between dose and C/D whereas a straight horizontal line would have been expected:

- An increased clearance with higher dose for several of the substances.

……..example:

Escitalopram exhibited a decreasing concentration of 0.11 nmol/L per mg/day



TDM

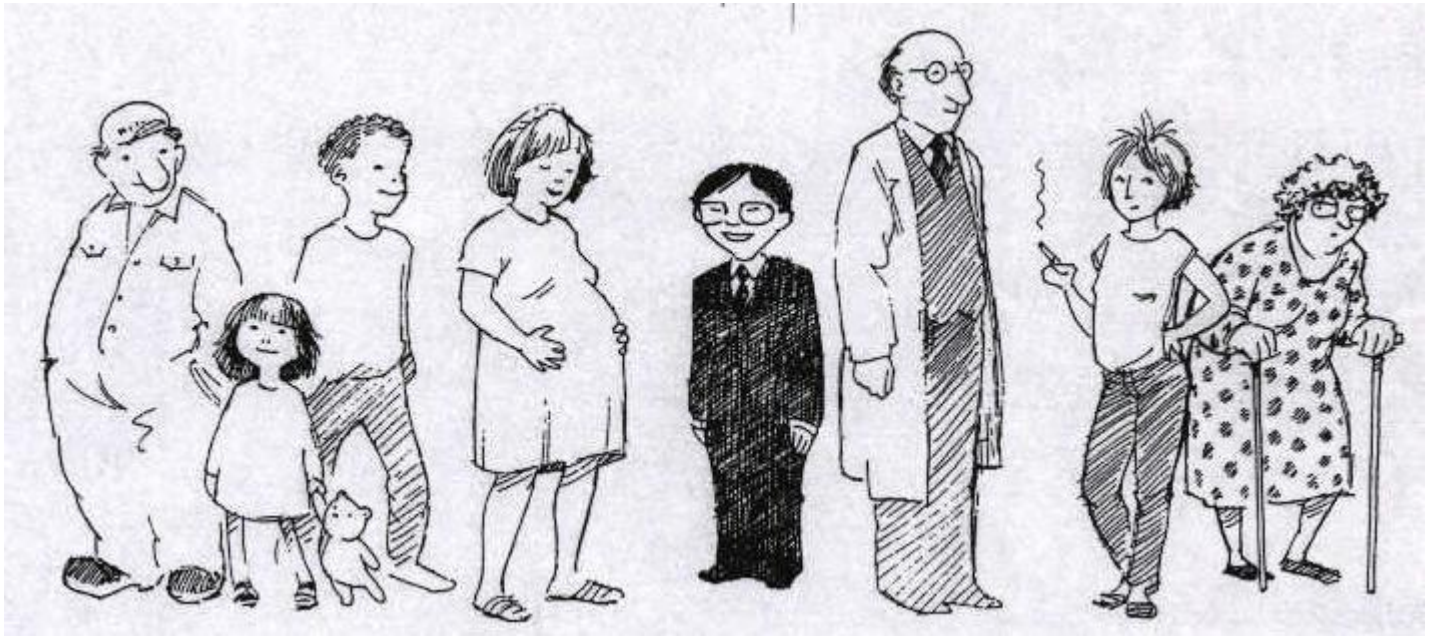
Therapeutic Drug Monitoring

Indications for TDM in Psychiatry

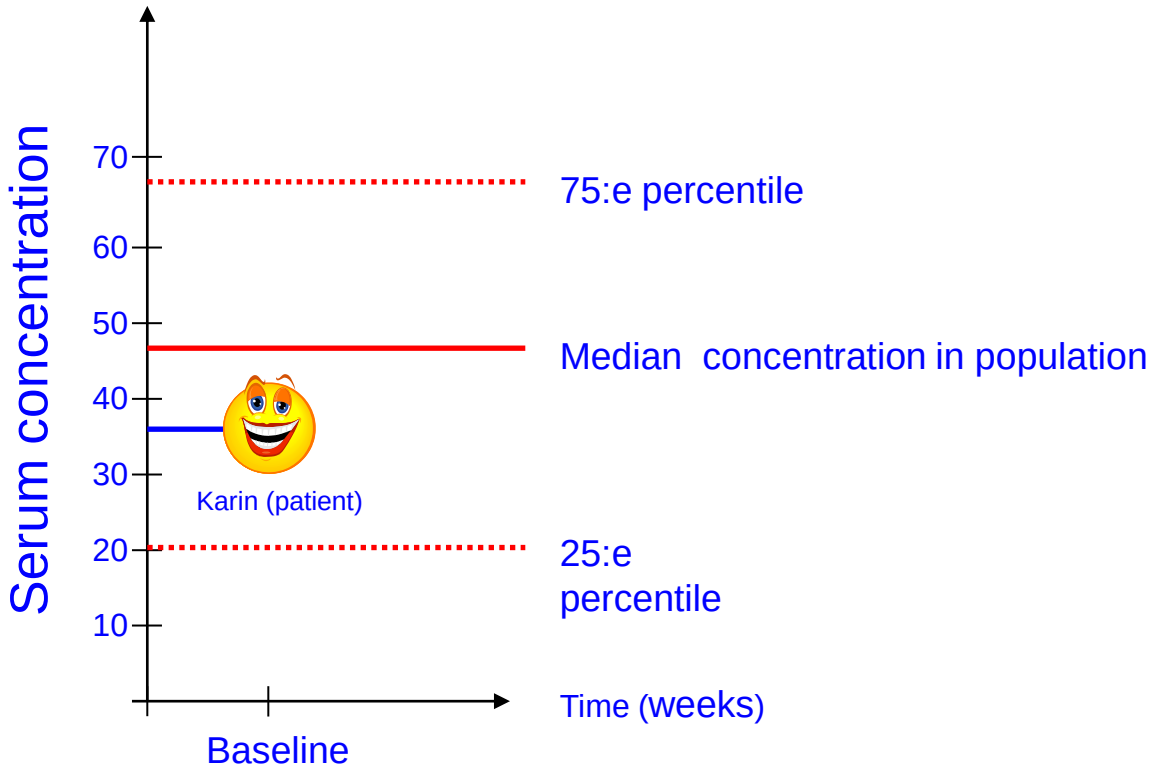
- Dose optimization after initial prescription or after dose change
- Drugs, for which TDM is mandatory for safety reasons (e.g. lithium)
- Suspected complete or partial non-adherence to medication
- Lack of clinical improvement under recommended doses
- Adverse effects and clinical improvement under recommended doses
- Combination treatment with a drug known for its interaction potential or suspected drug interaction
- Relapse prevention under maintenance treatment
- Recurrence under adequate doses
- Presence of a genetic particularity concerning drug metabolism
- Pregnant or breast feeding patient
- Children and adolescent patient
- Elderly patient (> 65 y)
- Individuals with intellectual disabilities
- Patients with pharmacokinetically relevant comorbidities
- Forensic patient
- Problems occurring after switching from an original preparation to a generic form

Hiemke C, personal communication Jan. 2012

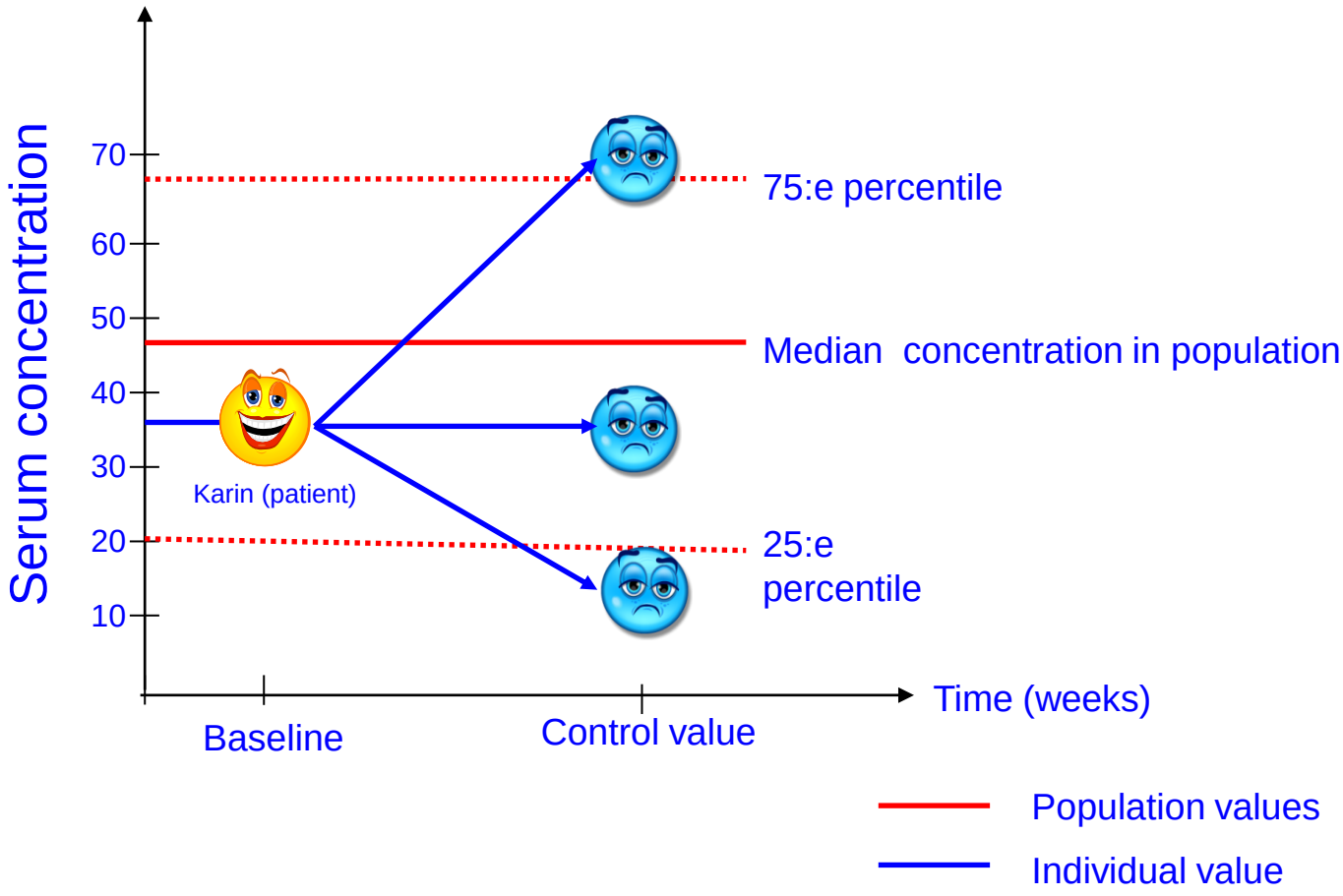
That means for almost all of us!



Serum samples of parent substance compared with reference values; **population values**

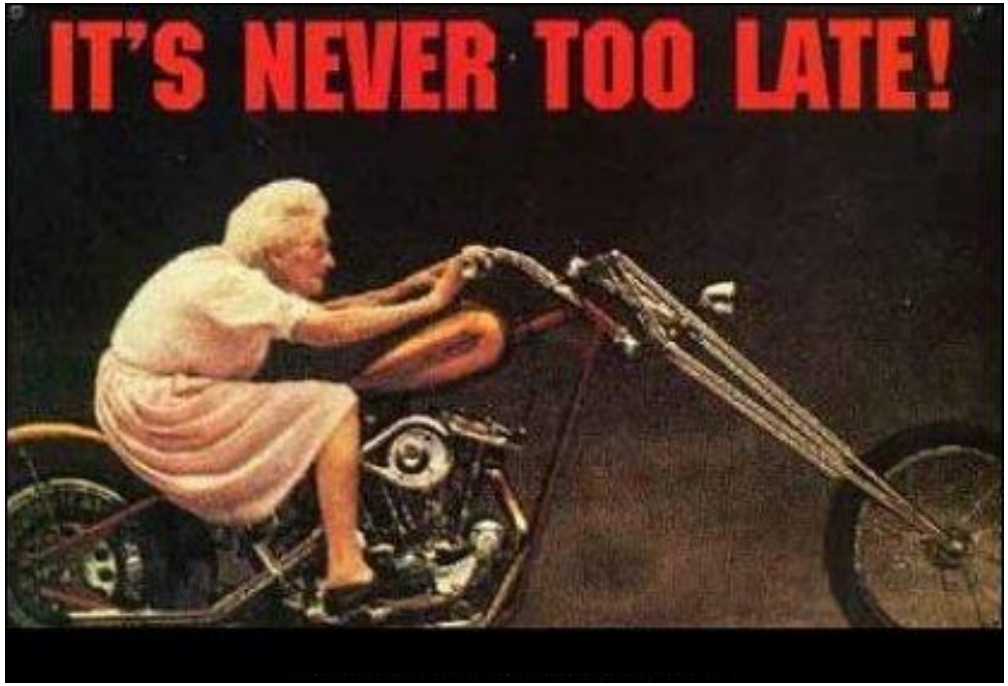


TDM with an intra-individual perspective (the patient as her own reference)



The long term goal is an individual treatment

and the development of reference blood concentrations is one way to go



Thanks!