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Inter-Individual Variability in PK & PD A

General Overview

Division of Pharmacokinetics & Drug Therapy
Department of Pharmaceutical Biosciences
Uppsala University, Sweden

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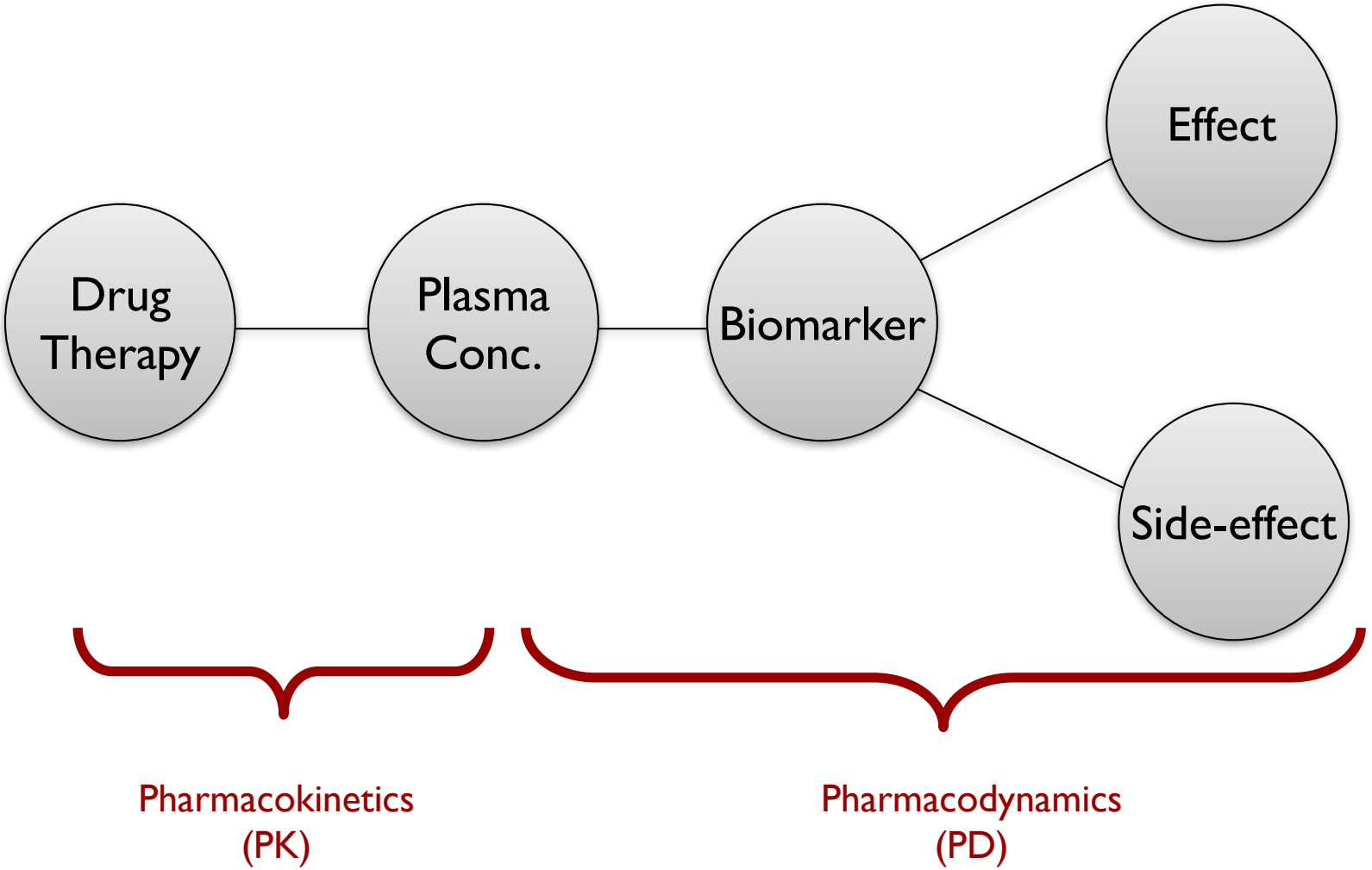
PKPD relationships

Effects of a drug involves PK and PD processes



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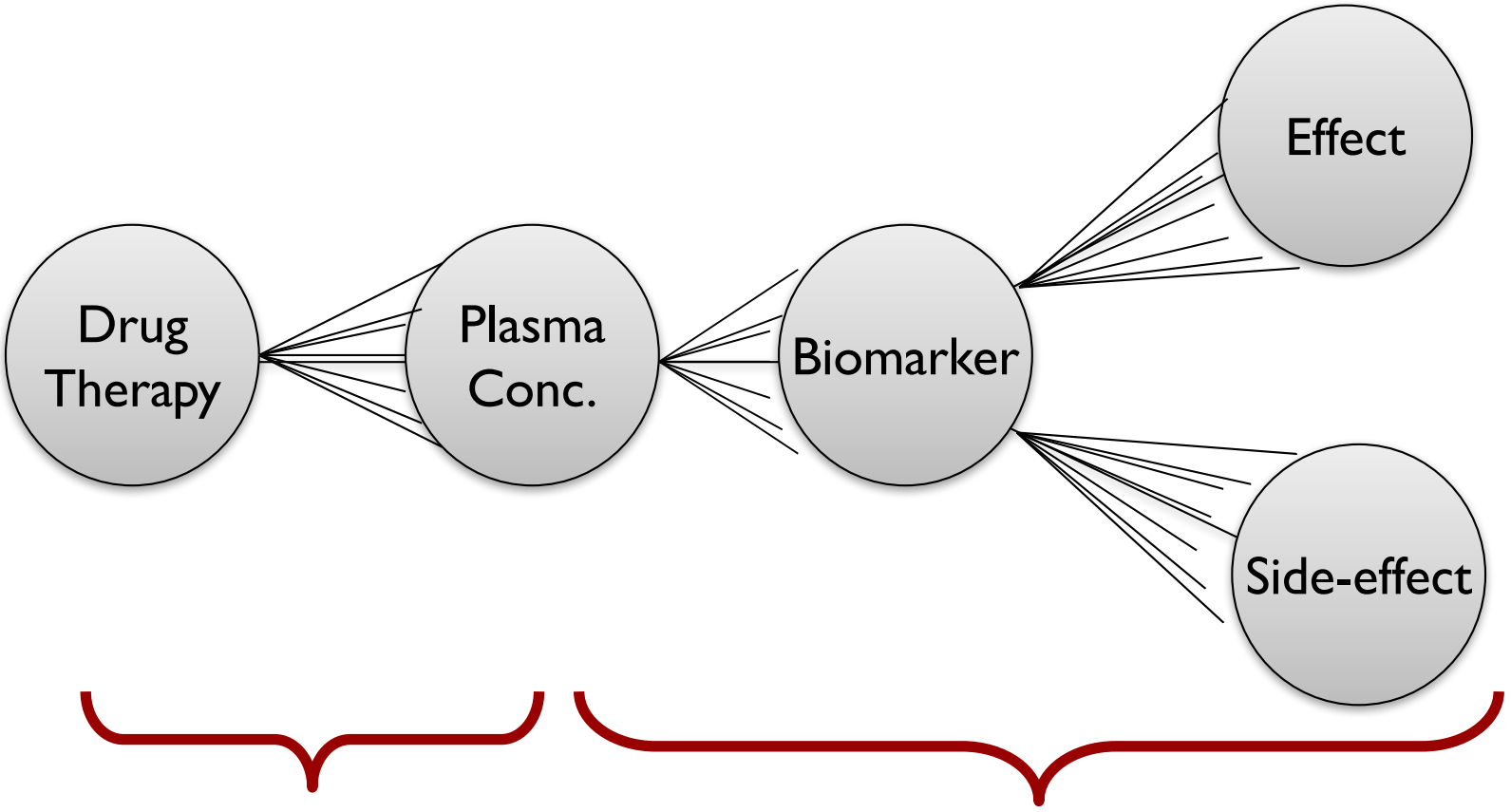
PKPD relationships

In each step is variability present



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Outline

- Parameters of PK and PD
- Measurements of variability
  - Magnitude of variability PK and PD
- Covariates explaining variability
- Contributing to PD variability

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Parameters

PK mainly depends on bioavailability and elimination rate

Treatment	Exposure measurement
Repeated (chronic)	$C_{av} = \frac{\text{Dose rate} \cdot F}{CL}$
Single	$AUC = \frac{\text{Dose} \cdot F}{CL}$

Bioavailability (F)

- Measurement of fraction absorbed

Clearance (CL)

- Measurement of elimination capacity

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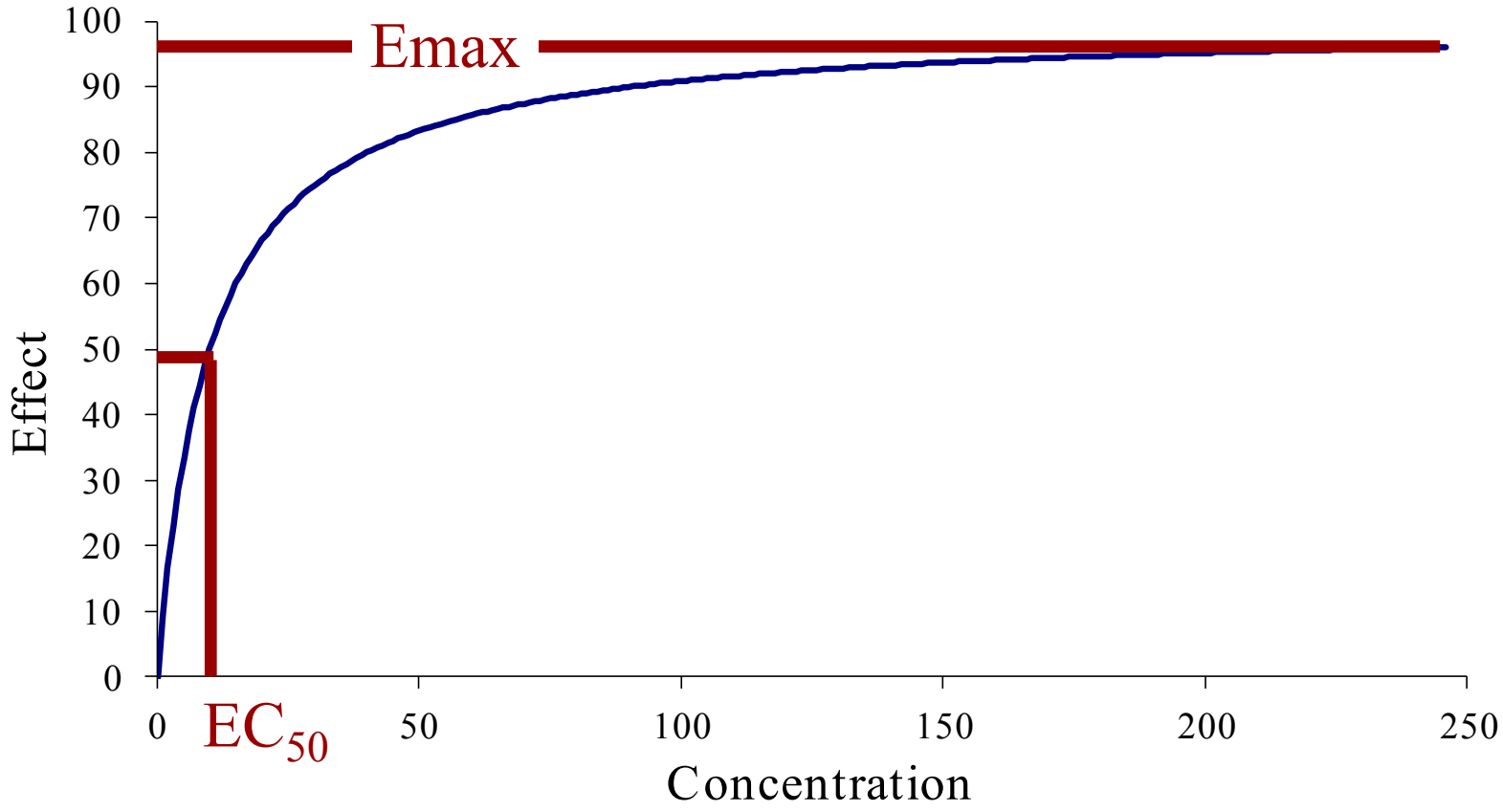
Parameters

PD depends on maximum effect and potency



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Measurements of variability

Shape and magnitude of variability is equally important

Two components of variability

- Shape

- Magnitude

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Measurements of variability

Shape informs about what the variability looks like

Two components of variability

- Shape
  - CL and EC_{50} log-normally distributed
  - Individual F bounded between 0 and 1
  - Emax depends on effect
  - Consider bimodal and other distributions
  - Determination of shape requires a large sample

- Magnitude

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Measurements of variability

Magnitude informs about how large the variability is

Two components of variability

- Shape
  - CL and EC_{50} log-normally distributed
  - Individual F bounded between 0 and 1
  - Emax depends on effect
  - Consider bimodal and other distributions
  - Determination of shape requires a large sample

- Magnitude
  - Standard deviation (SD)
  - Coefficient of variation (CV = SD/mean)
  - Interquartile or percentil range
  - Range or max/min-ratio

} most common in life-science

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Measurements of variability

Comparison of max/min ratio and CV

Max/min ratio and CV are unit less

- unlike SD, percentiles and range

CV may not have any meaning on variable that ranges across zero.

CV ranges $[0, \infty)$

commonly expressed in %

Max/min ratio ranges $(-\infty , \infty)$

in our area commonly $[0, \infty)$

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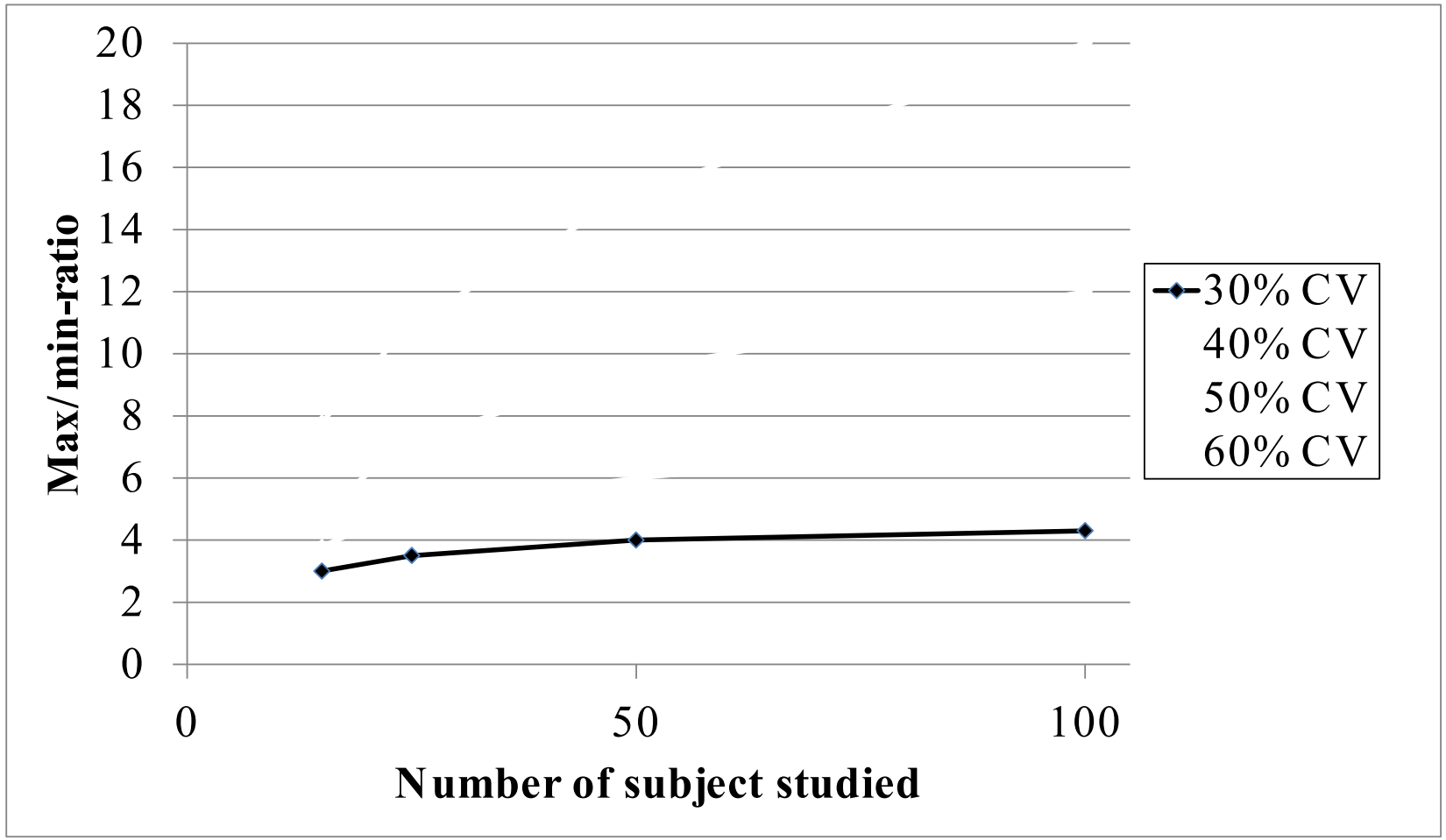
Magnitude of variability

Max/min ratio increases with increasing no of studied subjects



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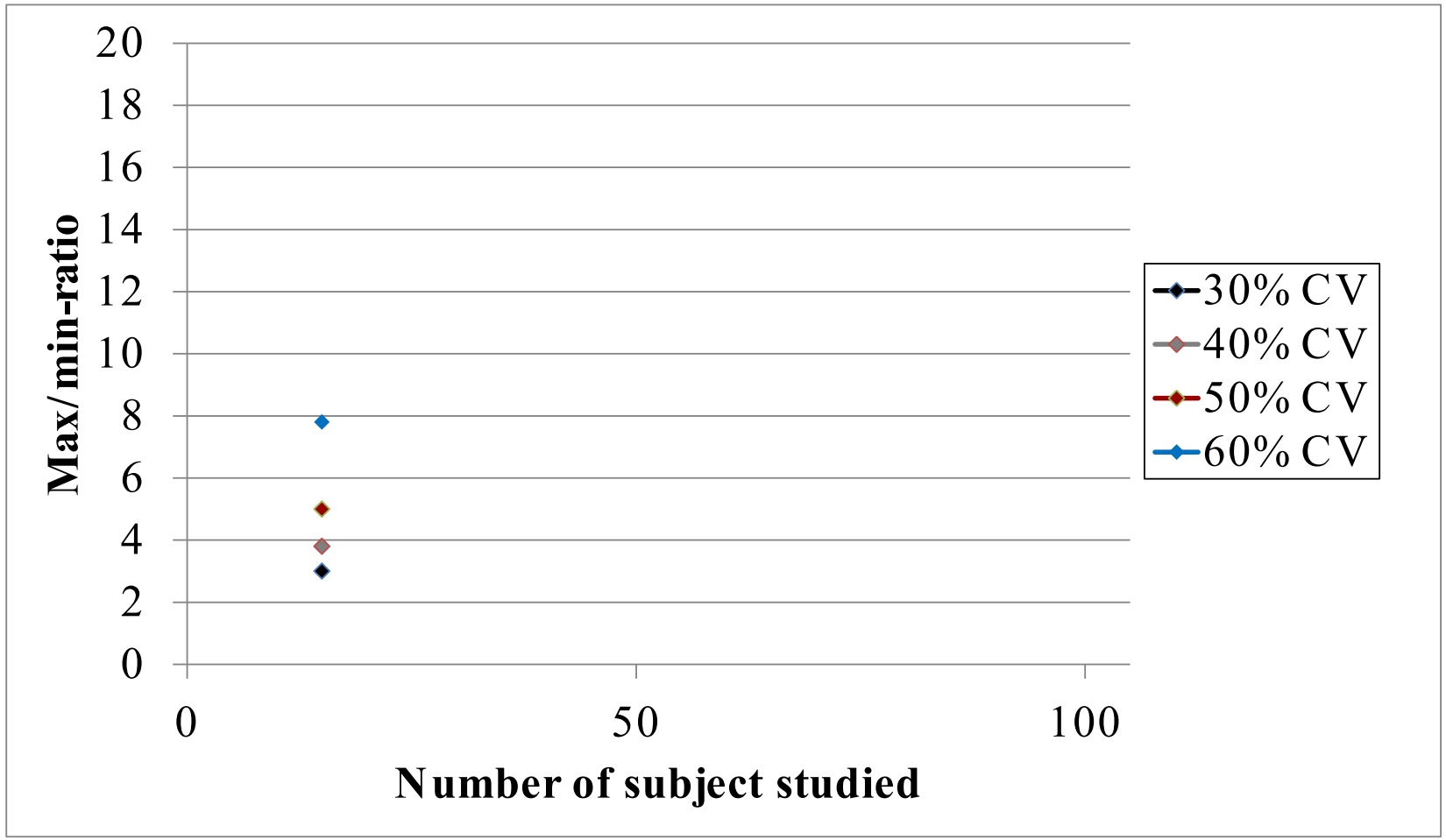
Magnitude of variability

Max/min ratio increases with increasing CV



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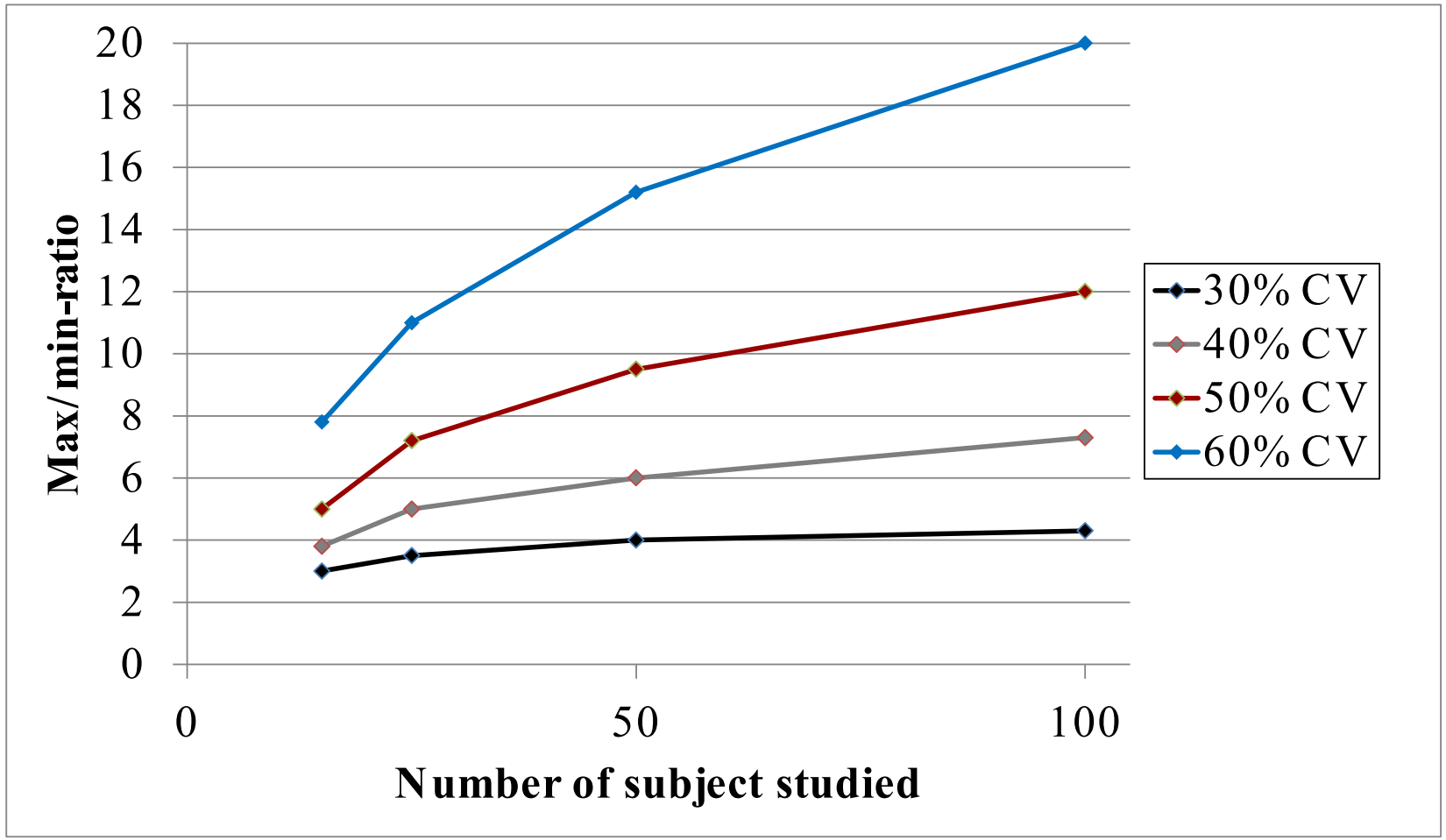
Magnitude of variability

Increase in max/min with no of subjects is dependent on CV



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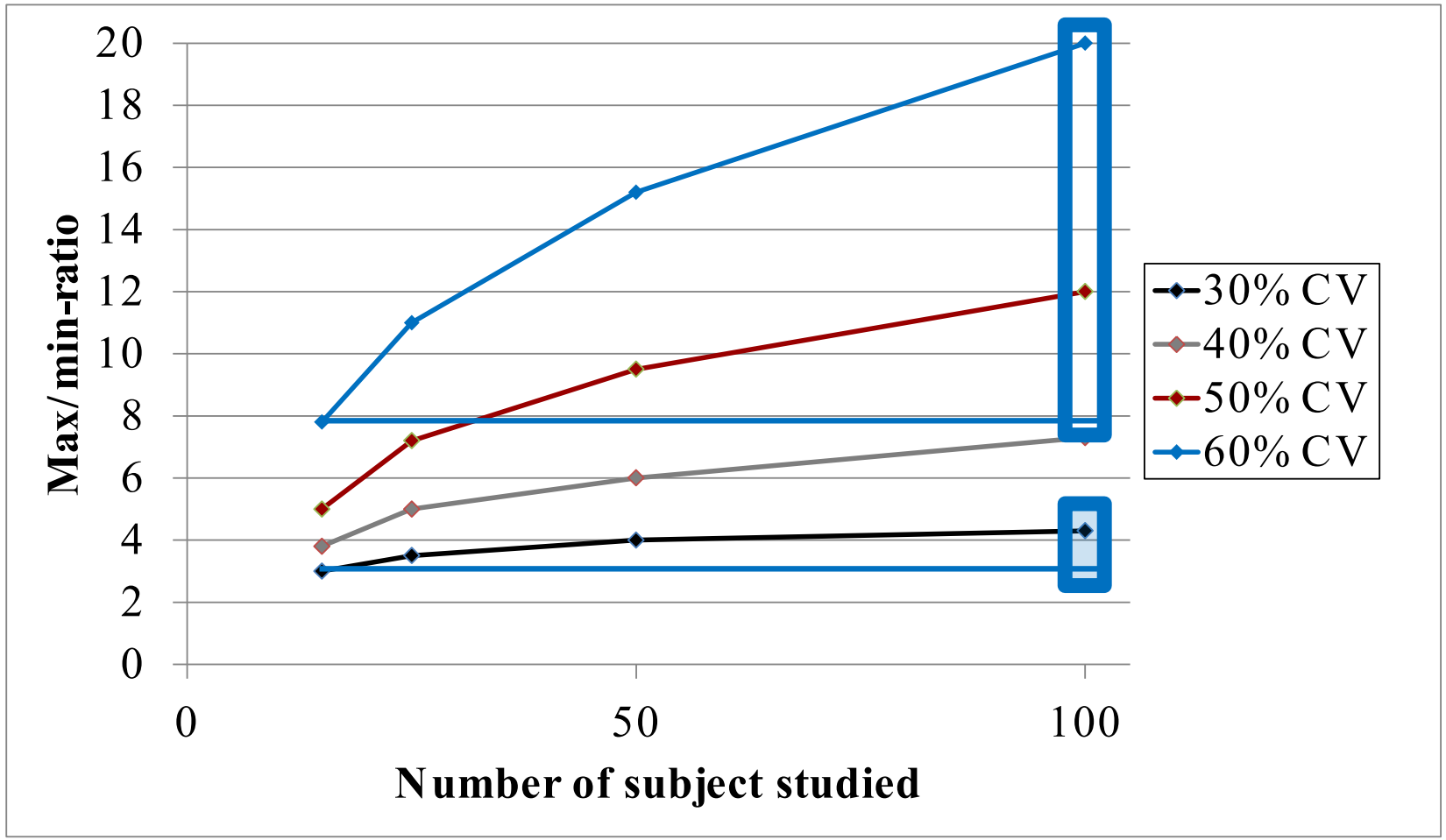
Magnitude of variability

Increase in max/min with no of subjects is dependent on CV



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Magnitude of variability

Everolimus is considered a drug with high PK variability

”There was evidence for longitudinal stability in AUC of everolimus during the course of the study. The interindividual pharmacokinetic variability for AUC was **85.4%** and intraindividual, interoccasion variability was **40.8%**. Age (range, 17-69 years), weight (range, 49-106 kg), and sex (65 men and 36 women) were **not significant contributors** to variability.”

* Kovarik JM *et al*., *Clin Pharmacol Ther* 2001 69:48-56

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Magnitude of variability

ThioTEPA is considered a drug with low PK variability

”Clearance of thioTEPA was 34 L/h with an IIV and IOV of **18** and **11%**, respectively. CL of thioTEPA **was correlated** with alkaline phosphatase and serum albumin.”

*Huitema *et al*., *Br J Clin Pharmacol* 2001 51:61-70

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Magnitude of variability

Effect variability of the same drug could be vary

SR33671 – a calcium antagonist metabolite
Has 1 PK (AUC) and 4 PD measurements

- Heart rate, PR interval, Artery flow, Vascular resistance

Subject	AUC (CL/F)	Heart rate (slope)	PR interval (slope)	Artery flow (C_{50})	Vascular resistance (C_{50})
1	587	-0.18	0.40	10	4.3
2	517	-0.18	0.46	1.5	1.9
3	459	-0.18	0.67	5.3	4.7
4	513	-0.16	0.49	14	6.0
5	368	-0.30	0.62	2.4	2.0
Mean	**535**	**-0.20**	**0.53**	**9**	**5.8**
CV	**25%**	**28%**	**22%**	**82%**	**88%**

*Bellisant, Giudicelli, *Br J Clin Pharmacol* 1999 48:801-10

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Magnitude of variability

Variability of parameters describing the same effect could vary

SR33671 – a calcium antagonist metabolite
For artery flow and vascular resistance potency and maximum effect has been estimated.

Subject	Artery flow (C_{50})	Vascular resistance (C_{50})	Artery flow (Emax)	Vascular resistance (Emax)
1	10	4.3	40	-34
2	1.5	1.9	43	-31
3	5.3	4.7	49	-26
4	14	6.0	49	-23
5	2.4	2.0	35	-29
Mean	**9**	**5.8**	**42**	**-28**
CV	**82%**	**88%**	**14%**	**14%**

*Bellisant, Giudicelli, *Br J Clin Pharmacol* 1999 48:801-10

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Magnitude of variability

PK variability is usually lower than PD variability

Fentanyl, alfenanil and trefentanil are PK and PD for 3 anesthetic agents

Drug	CV(CL)	CV(C_{50},EEG)
Fentanyl	20	85
Alfentanil	17	47
Trefentanil	16	73

*Lemmens *et al*., *Clin Pharm Ther* 56:261-71 (1994)

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Covariates explaining variability

Variability may be unidentified patients characteristics

- Sex (Gender)
- Age
- Race
- Body size (WT, BSA, BMI, IBW, LBW, HT)
- Genotype (mainly fast and slow metabolisers)
- Renal function (creatinine-, inulin-, CrEDTA CL)
- Hepatic function (bilirubin, albumin, ASAT, ALAT, ALKP)
- Disease parameters
  - Baseline, etiology, common complications, sub-diagnosis
- Therapy related
  - Co-medication, pre-treatment, dialysis
- Habits / Environmental factors
  - Smoking, alcohol, food, diet

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Covariates explaining variability

For PK variability some major covariates can be identified

Major

- Renal function (CrCL) - renally eliminated compounds
- Size/age in pediatric studies
- Geno-/phenotype for compounds eliminated mainly via polymorphic enzymes (e.g. CYP2D6, CYP2C19)

Sometimes clinically significant

- Drug interactions
- Body size (in adults)
- Hepatic function (via lab values)
- Age
- Feeding status
- Race
- Sex

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Covariates explaining variability

PD covariates are highly correlated to the effect used as PD

Major

- None

Sometimes clinically significant

- Disease severity / subtype
- Performance status
- Drug interactions
- Genotype
- Age
- Race
- Sex

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Covariates explaining variability

Example of covariate for PD of remifentanil for anesthesia

Remifentanil C_{50} for adequate anesthesia in abdominal surgery (n=40)

- 4.1 ng/ml in men
- 7.5 ng/ml in women
- CV of unexplained variability in C50 was 57%

*Drover *et al*., *Anesthesiology* 89:869-77, 1998

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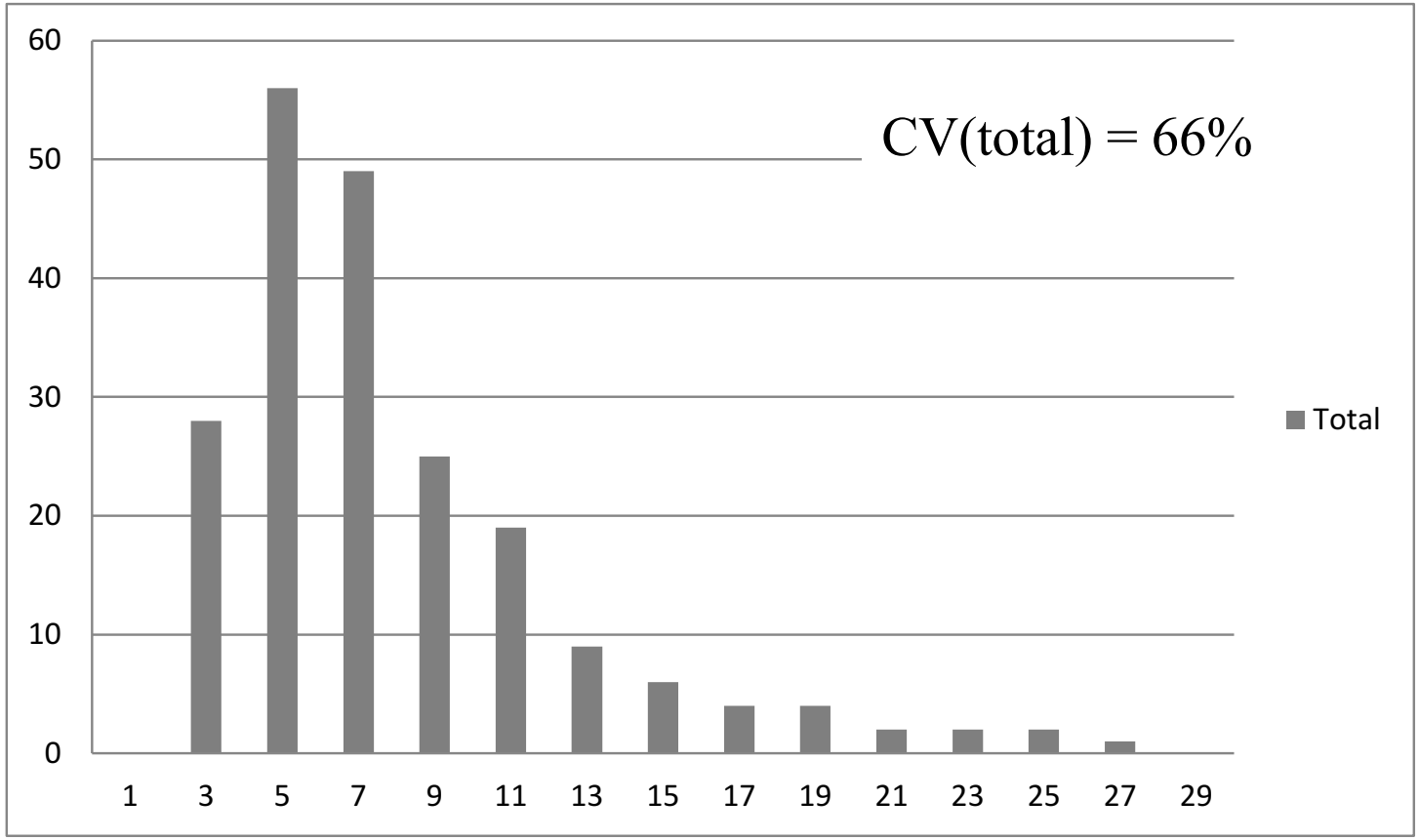
Covariates explaining variability

Example of impact of remifentanil sex difference



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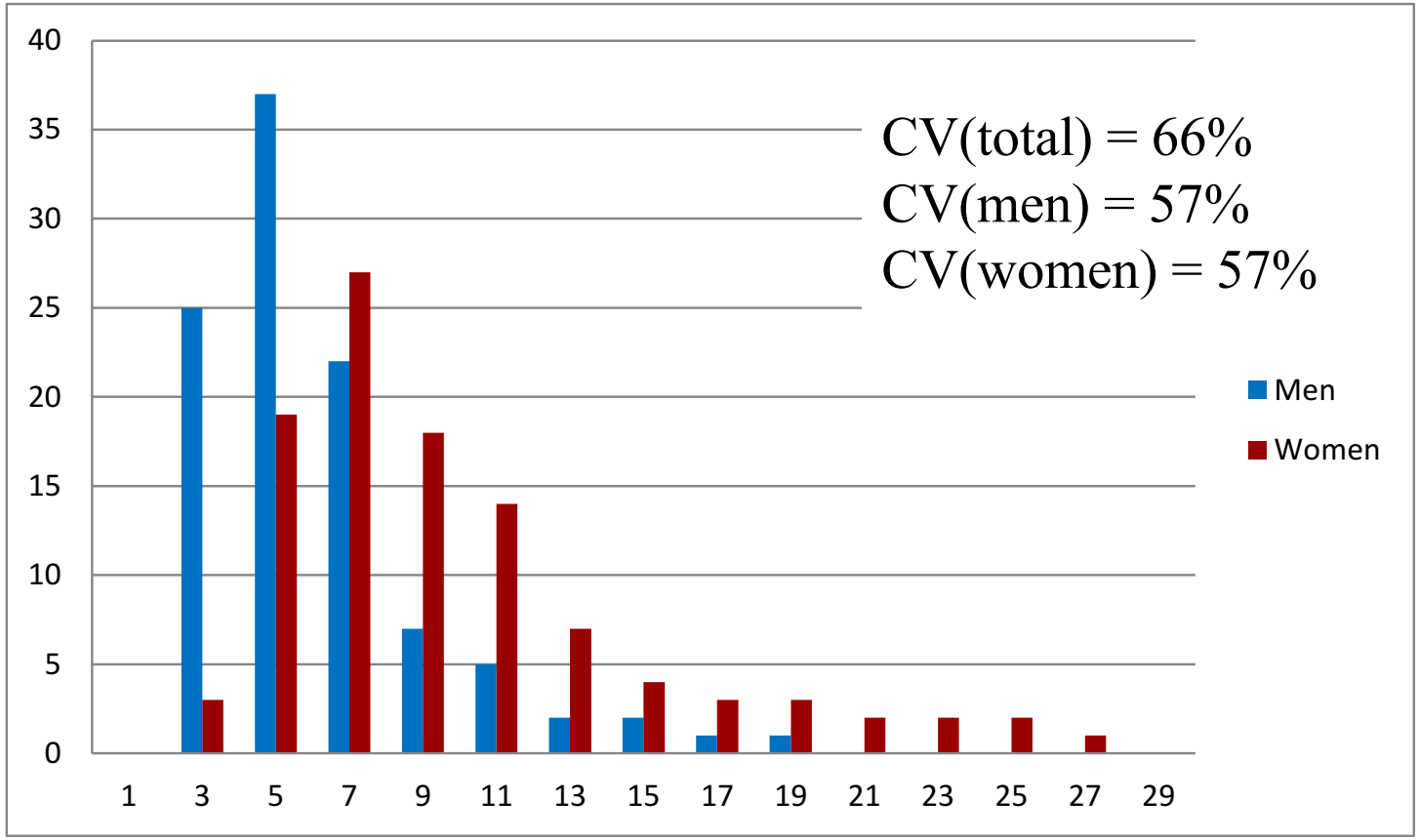
Covariates explaining variability

Example of impact of remifentanil sex difference



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Contributing to PD variability

Depends on:

- Who we study
- What we study
- How we perform the study

- PD processes we can't affect

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Contributing to PD variability

Who – What population is studied?

Study population

- Healthy volunteers (male, young, average sized, non-smoking,…)
- Patient population (or ”healthy” part of it)
- Adults and/or children
- General population

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Contributing to PD variability

What – Which measurement is used to assess effect?

Remifentanil

	Adequate anestesia (Clinical endpoint)*	EEG spectral edge (Biomarker)**
CV(EC_{50})	66%	25%

*Drover et al., Anesthesiology, 89:869-77, 1998

**Egan et al., Anesthesiology, 81:821-33, 1996

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Contributing to PD variability

How – What does the study design look like?

Small study

- Experimental
- Rich data
- Not representative
- Well-controlled conditions
- Too small for detecting covariate effects
- Often too small for reliable determination of variability

Large study

- Observational
- Sparse data
- Varying data quality
- Methodological difficulties to determine parameter values
- Representative

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Contributing to PD variability

Determinants of PD variability – things we can't affect

Measured conc ≠ "Active" conc
- free fraction, metabolites, isomeres

Transporters
- influx and efflux

Level of endogenous agonist
- production/elimination

Receptor characteristics
- density, heterogeneity

Post-receptor events

Homeostasis and feedback mechanisms

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Contributing to PD variability

A drug is not just a chemical substance

Selection bias towards

- Low between-subject variability
  - Avoiding polymorphic metabolism pathways
  - Avoiding low (= more variable) bioavailability
- Specific targets
- Low toxicity
- Stability (or not)
- ”One dose fits all”

Activity assured by special delivery

Promising compounds exist with characteristics very different from those of drugs

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Summary

Between-subject variability is an important measurement of PK and PD

PD variability is larger than PK variability

Part of the variability can be predicted using covariates

Think: who, what, how to estimate variability