Innovative trial designs including Bayesian approaches

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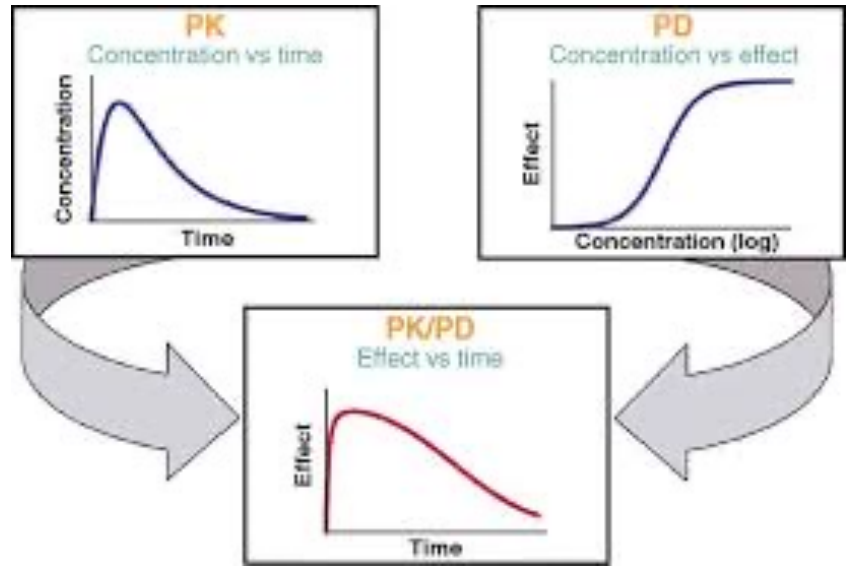
New Zealand



Learning Points

- Dose is based on PK, PD and adverse effects
- Variability affects response to medicines
- Major sources of usual variability are maturation, size, drug interactions and genes
- Modelling and simulation, using Bayesian approaches, can be used to predict dose, demonstrate effect and inform future studies

New Zealand: a land of sheep

4,000,000 people

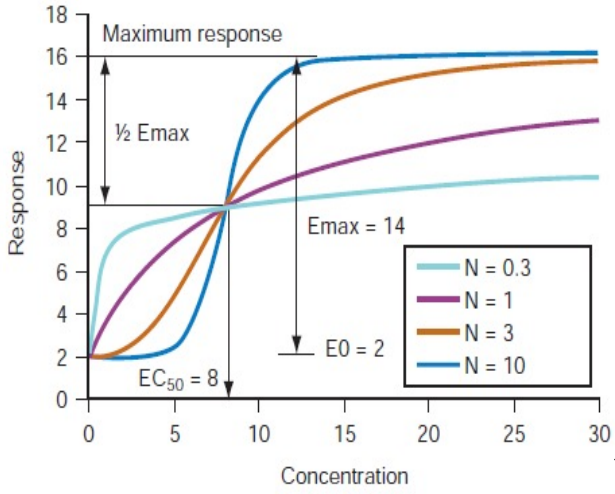
40,000,000 sheep

The Students in NZ

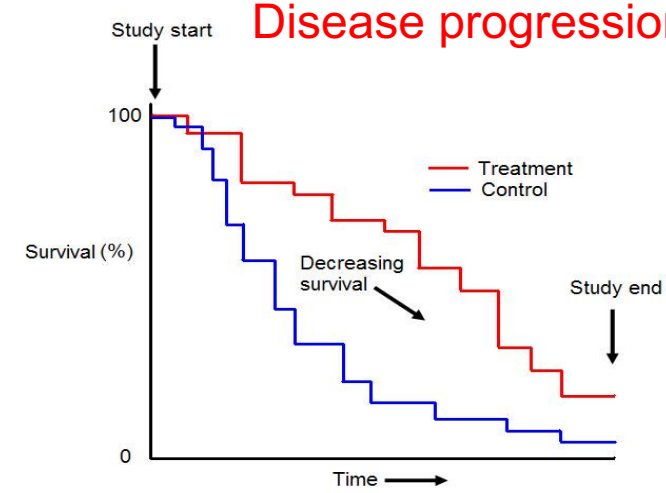
Assumptions

- Basic understanding of population modelling
  - Underlying theme is variability and prior knowledge (Bayesian)
  - Amy Cheung - PKPD
- Aware difficulties of study in children < 2 years

Pharmacodynamics

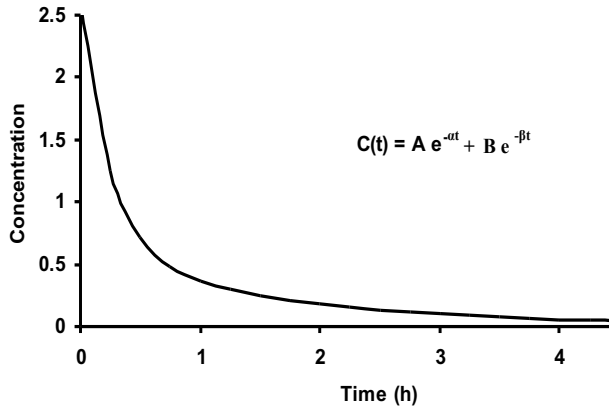


Survival analysis
Disease progression

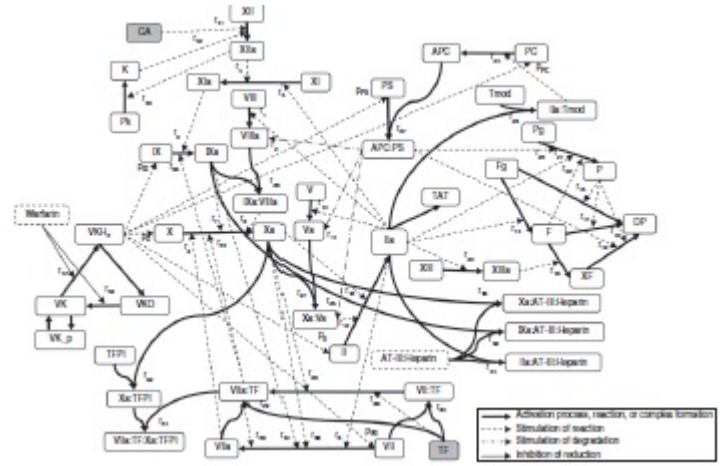


Pharmacometrics

Dose → Concentration → Effect → Response → Outcome



Pharmacokinetics



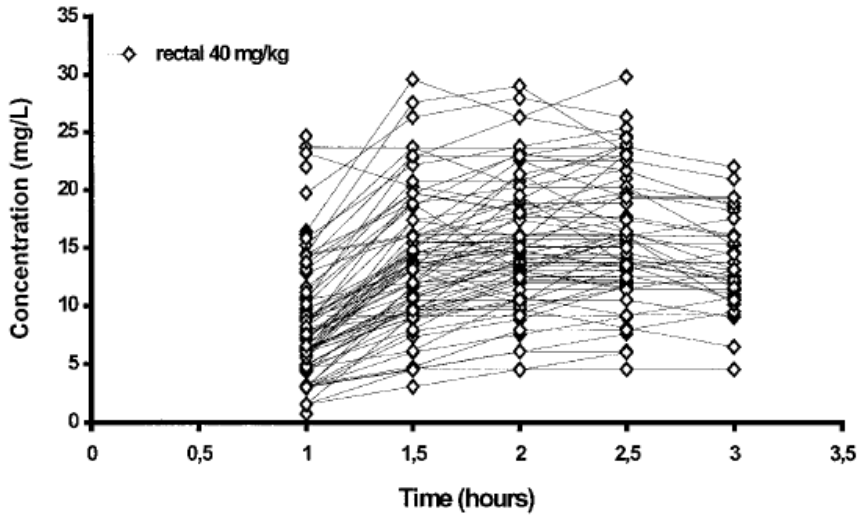
Quantitative Systems Pharmacology

Population Approach

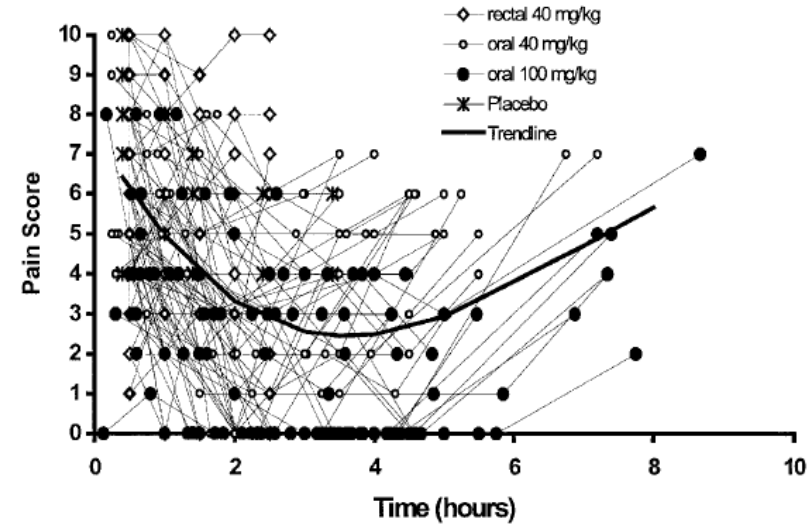
Describing the Signal and the Noise

… and it is the noise (variability) that is important

$$C = {Dose.F}/{V} \times e^{-CL/V \; x \; t}$$



$$Effect = \frac{Emax \; x \; C^N}{C_{50}^N + \; C^N}$$



Anderson BJ. EJCP 2001

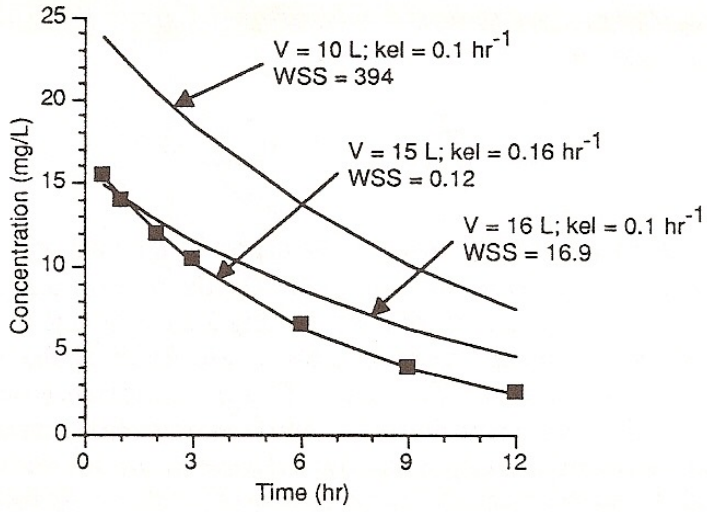
Mixed Effects Modelling

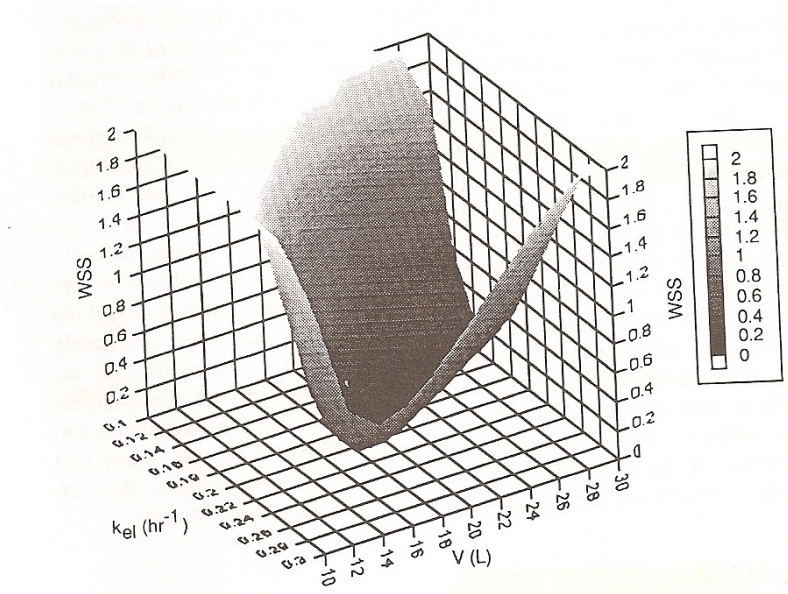
Fixed Effects (predictable variability)

Covariates and parameters
e.g. renal function and clearance

Random Effects (unpredictable variability)

Parameter variability e.g. in clearance
Residual error e.g. measurement error, process noise, model misspecification, assay error, transcription





Minimisation successful

Bourne D. mathematical modeling of PK data 1995

Population Modeling – a logical processor

Paediatric Studies Difficult

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Pain. 2018 February ; 159(2): 193–205. doi:10.1097/j.pain.0000000000001104.

Clinical trial designs and models for analgesic medications for acute pain in neonates, infants, toddlers, children, and adolescents: ACTTION recommendations

Gary A. Walco[a,b], Ernest A. Kopecky[c,d], Steven J. Weisman[e] Stevens[d], Paul J. Desjardins[f], Charles B. Berde[g], Elliot J. Kr Myron Yaster[j], Carlton D. Dampier[k], Robert H. Dworkin[l], Ian Lynne G. Maxwell[n], Srinivasa Raja[j], Bernard Schachtel[o], and

Pediatric Analgesic Clinical Trial Designs, Measures, and Extrapolation: Report of an FDA Scientific Workshop

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The Lancet Child & Adolescent Health Commission

l practical challenges
sponsored by the US
ensus on aspects of
dard parallel-placebo
has ethical and prac-
d of subjects experi-

Delivering transformative action in paediatric pain: a *Lancet Child & Adolescent Health* Commission

Christopher Eccleston, Emma Fisher, Richard F Howard, Rebeccah Slater, Paula Forgeron, Tonya M Palermo, Kathryn A Birnie, Brian J Anderson, Christine T Chambers, Geert Crombez, Gustaf Ljungman, Isabel Jordan, Zachary Jordan, Caitriona Roberts, Neil Schechter, Christine B Sieberg, Dick Tibboel, Suellen M Walker, Dominic Wilkinson, Chantal Wood

Clinical studies difficult and Sheiner proposed alternative approach

Clin Pharm Ther 1991

The intellectual health of clinical drug evaluation

Lewis B. Sheiner, MD *San Francisco, Calif.*

"We have to trust the scientific judgement of the scientists . . . Statistics should be their handmaiden, not their jailer."

—D. Salsburg[1]

Let me introduce my topic by presenting three symptomatic examples of an intellectual illness from which I believe clinical research in general, and drug trials in particular, is suffering.

1. An irrelevant analysis. Fig. 1 is redrawn from a recent article in our Society's journal, CLINICAL PHARMACOLOGY & THERAPEUTICS.[2] The error bars are drawn on only one point on each curve, but these are typical of the rest of the points.

The figure shows a characteristic time course of drug action, independent of dose, and a clear progression of pain relief as the dose of bromfenac increases. Rather than stressing this compatibility with expectation and rather than deriving a dose-response curve from which the (time course of) response to any dose could be predicted, why do the authors confine themselves to pairwise comparisons of the mean (over time) response between doses and deem it relevant to tell us, for example, that "No significant distinction was achieved between the 10 and 25 mg bromfenac doses"?[2]

2. A great waste. It seems that Smith Kline & French Laboratories (Philadelphia, Pa.) studied about surely many tens, if not hundreds, of millions of dollars. Although proving unequivocally that the drug was effective, all those studies apparently did not reveal the minimum effective dose. This is not just an isolated instance. Temple[3] has pointed out that for many drugs the dose approved initially is considerably greater than that ultimately found to be adequate. This has been true, for example, for many β-blockers and more recently for zidovudine.

3. An excessive conservatism. Imagine a double-blind crossover placebo-controlled study of a new drug for the prophylaxis of angina. Fig. 2 shows both the placebo and active drug data on one hypothetical patient. Here the intended dose of the new drug was one per day, and if the patient had taken the new drug as intended, there would be no reason to think it was superior to placebo on the basis of the similar frequency of anginal attacks on both treatments.

But what if a medication monitor had been used,[4] and the pattern of dosage was the one listed as *Actual* in Fig. 2? It seems the patient did not take any drug at all for the first 2 days and had anginal attacks on days 2 and 3. He then took the drug for 3 days without angina, stopped taking the drug, and had an attack the next day. The same thing happened again after 1 week of full compliance without angina. Surely, if there were multiple records like this one and the placebo records did not show similar patterns, we would be

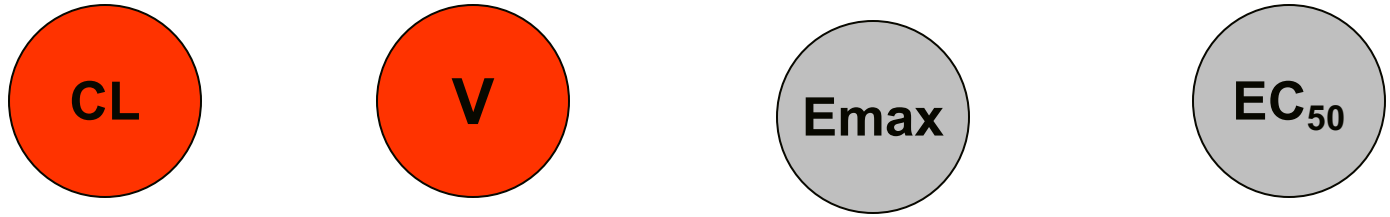
An approach around these difficulties

What do anaesthesiologists do?

Clinical Pharmacology

Pharmacokinetics

Pharmacodynamics



Concentration

Dose

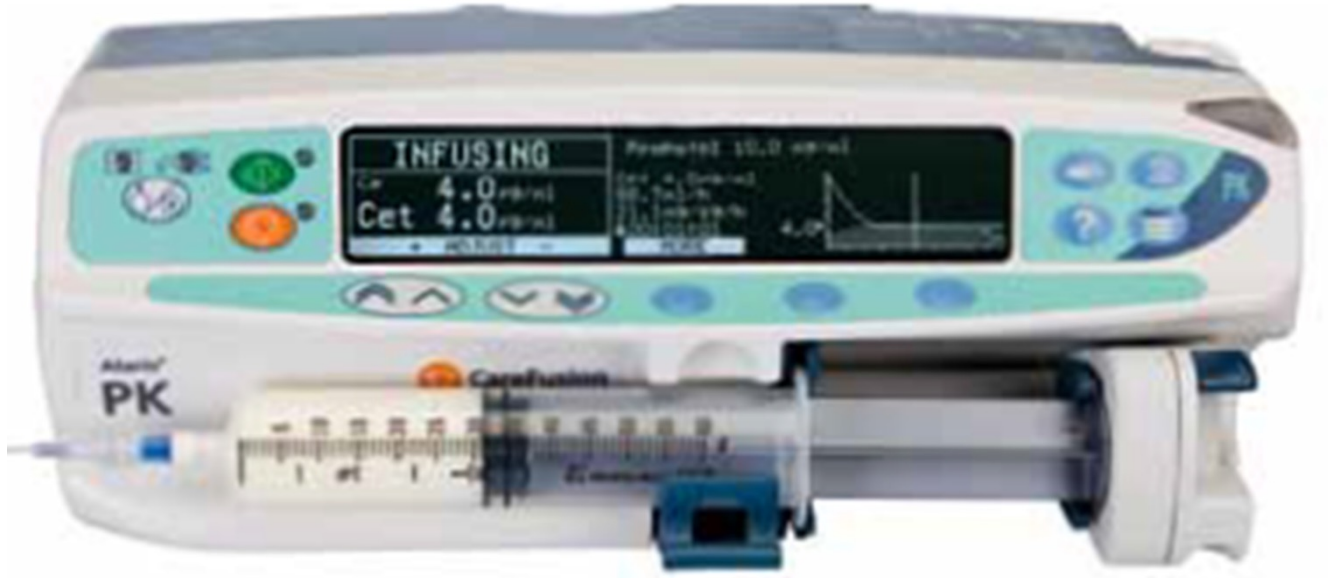
Effect

$$C = Dose/V \cdot e^{-CL/V \cdot t}$$

$$Effect = \frac{E\max \cdot C^N}{EC_{50}^N + C^N}$$

Holford 2009

Example: What dose propofol in infants

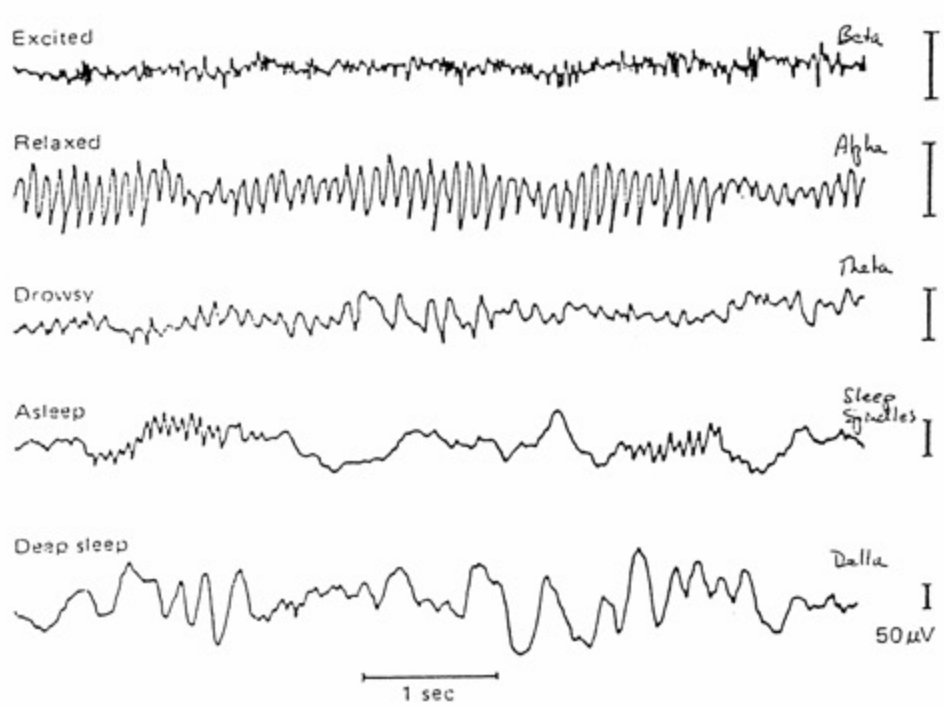


- PKPD parameters incorporated into pump

ANAESTHESIA IS NOT…

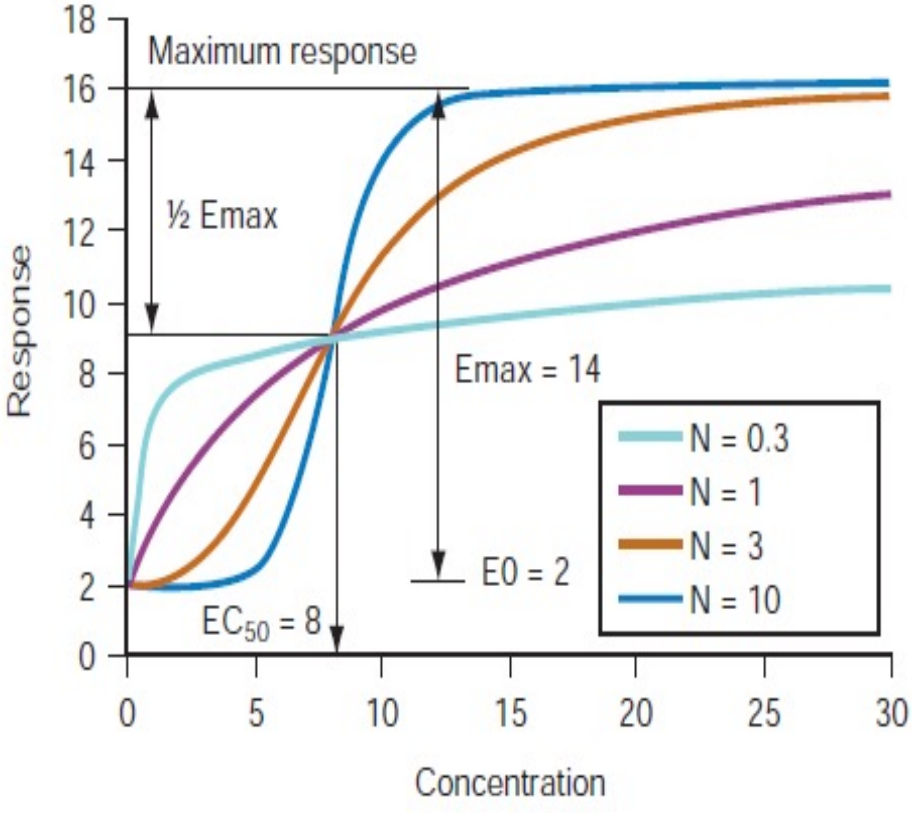
the half-asleep watching the half-wake being half-murdered by the half-witted

Malcolm Fisher

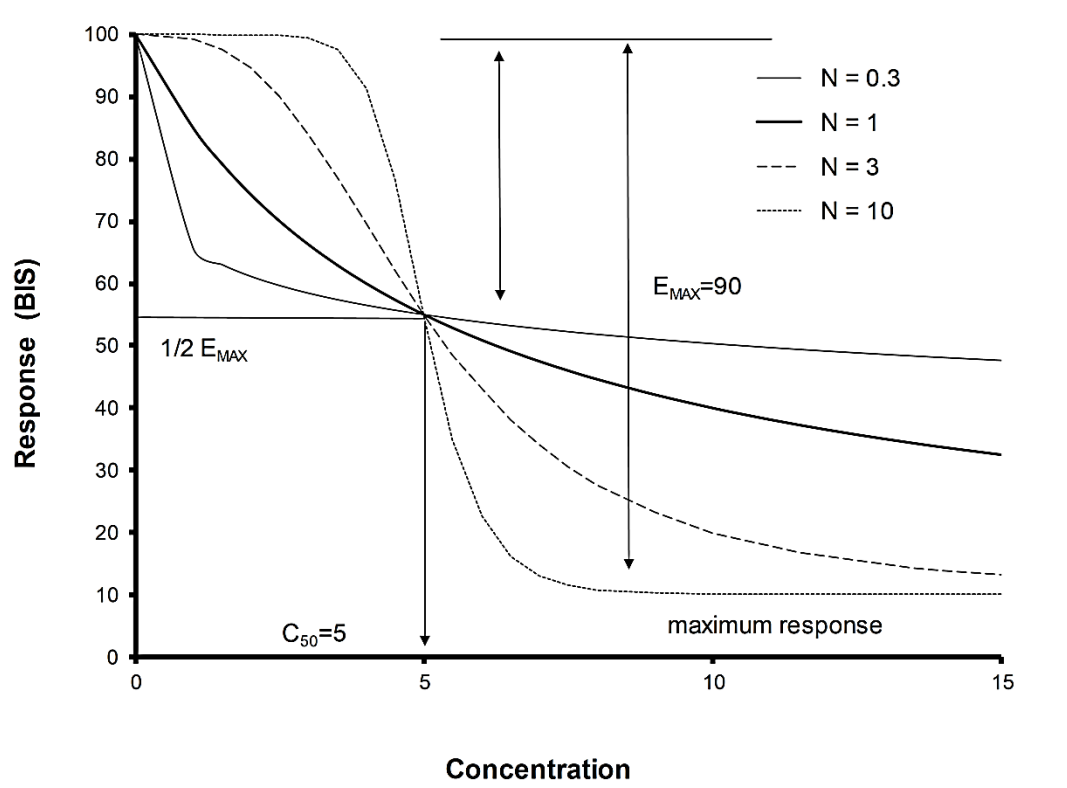


Emax Model Upside Down

Most Drugs



Bispectral Index

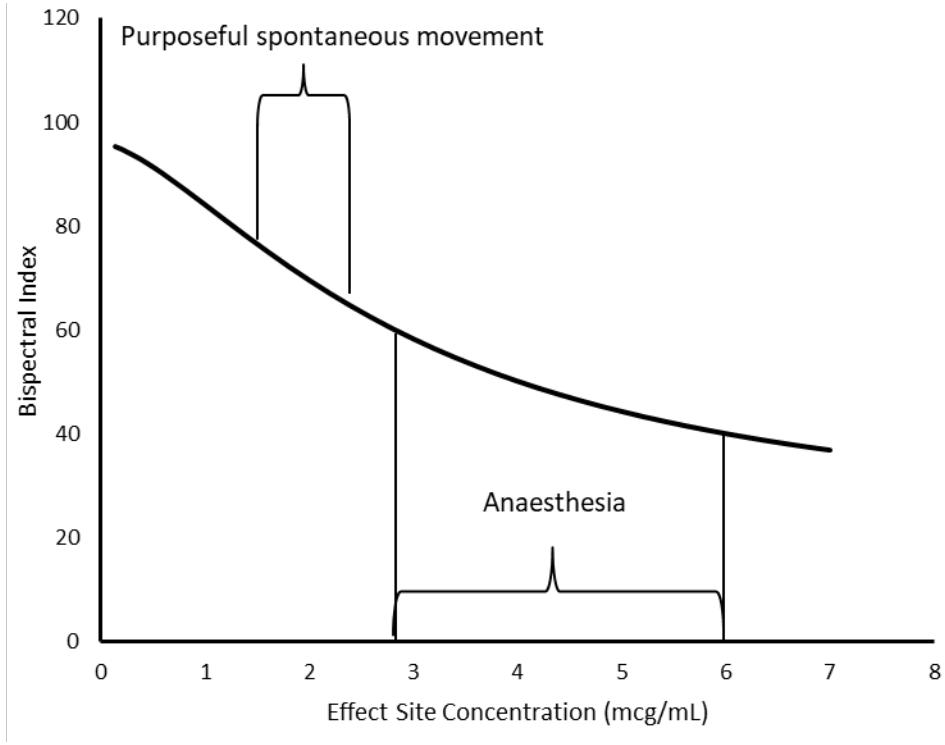


$$Effect = E0 + {}^{E_{MAX} \times Ce^N}/_{(C_{50}^N + Ce^N)}$$

$$Bispectral\ Index = BIS_0 - {}^{E_{MAX} \times Ce^N}/_{(C_{50}^N + Ce^N)}$$

Target Concentration (PD)

	Estimate	95%CI	Sh %	CV (%)
BIS_0	94	86.8, 94.6	48.1	5
E_{MAX}	0.81	0.70, 0.93	47.8	14.8
$C_{50,PROP}$ (mg/L)	2.99	2.45, 3.66	47.1	35.4
$T_{1/2}keo_{,PROP}$ (min)	2.38	4.21, 14.6	45.9	67.6
Hill	1.55	1.31, 2.37	44.6	44.5
Additive residual Error (BIS units)	5.9	5.1, 6.8	-	η_{RUV} 0.363

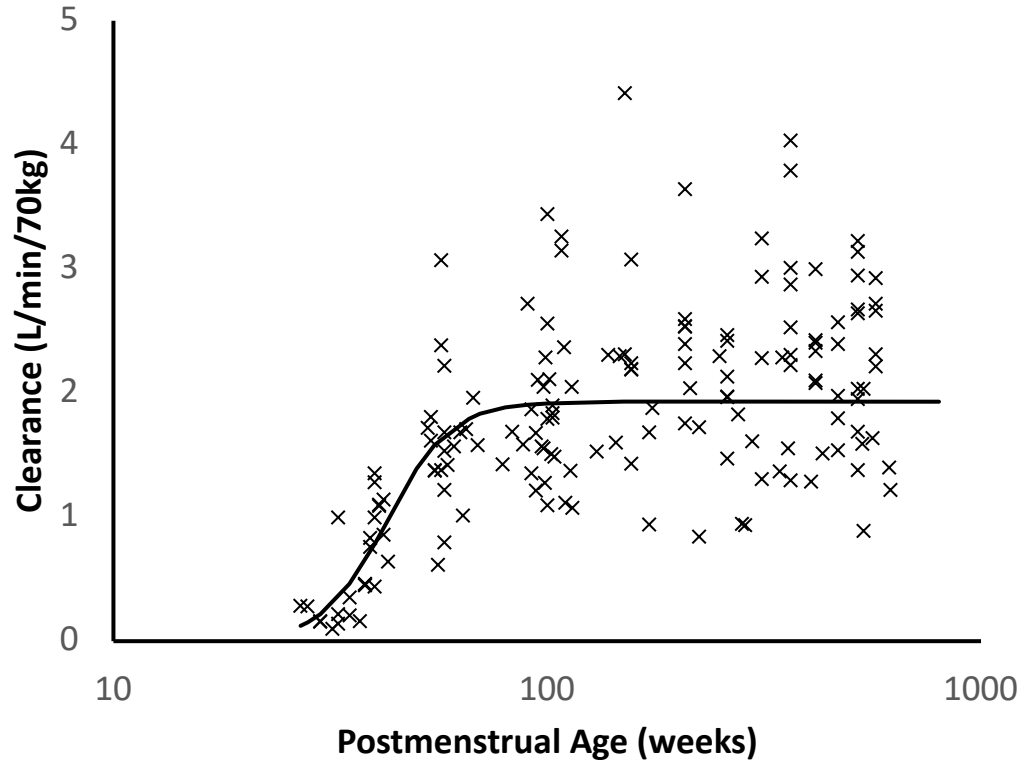


Target Effect BIS=50
Target concentration 3 mg/L

Fuentes Pediatric Anesth 2018

Propofol Clearance Variability (PK)

	Estimate	95%CI	Sh %	PPV (%)
V1 (L/70 kg)	18.5	5.2, 23.8	8.5	41.1
V2 (L/70kg)	41.1	29.2, 58.1	9.7	23.3
V3 (L/70 kg)	230	178, 390	14.5	50.3
CL (L/min/70 kg)	1.93	1.74, 2.19	2.9	40.7
Q2 (L/min/70kg)	3.82	3.24, 7.64	11.1	47.4
Q3 (L/min/70 kg)	0.837	1.09, 1.65	6.2	69.6
TM50	42.6		-	-
Hill	5.88			-
Additive residual Error (μg.mL^{-1})	0.012	0.0002, 0.0184		η_{RUV} 0.56
Proportional Residual Error (%)	16.9	12.5, 28.3		



$$MF = \frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}}$$

$$CL_{GRP} = CL_{STD} \cdot \left(\frac{WT}{WT_{STD}}\right)^{3/4} \cdot MF$$

Morse J. Pediatric Anesth 2019

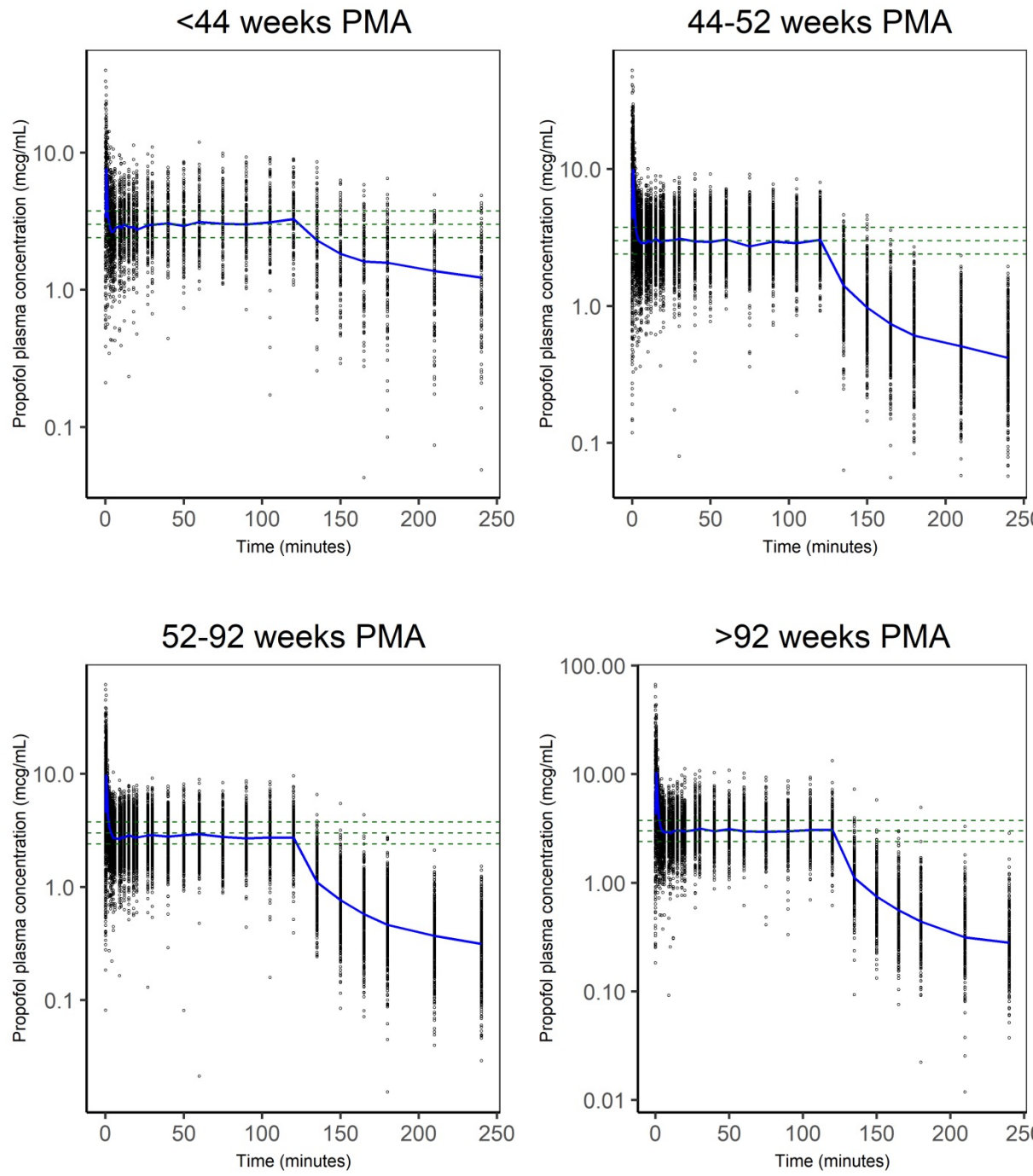
Propofol Dosing Regimen

Age	Induction dose (mg/kg)	0-15 min	15-30 min	30-60 min	60 – 120 min
Target plasma concentration 3 µg.mL^{-1}					
27-44 PMA weeks	2	9	7	6	5
44-52 PMA weeks	2.5	11	10	9	8
3-12 months	2.5	12	11	10	9
1-3 years	2.5	13	12	11	10

Morse J. Pediatr Anesth 2019

Simulation of 1000 individuals reveals unexplained variability

Half of the predictions were in the range 80-125% of the target concentration between 5 and 90 minutes of infusion duration



Anderson BJ. Pediatr Anesth 2019

Target Concentration Strategy

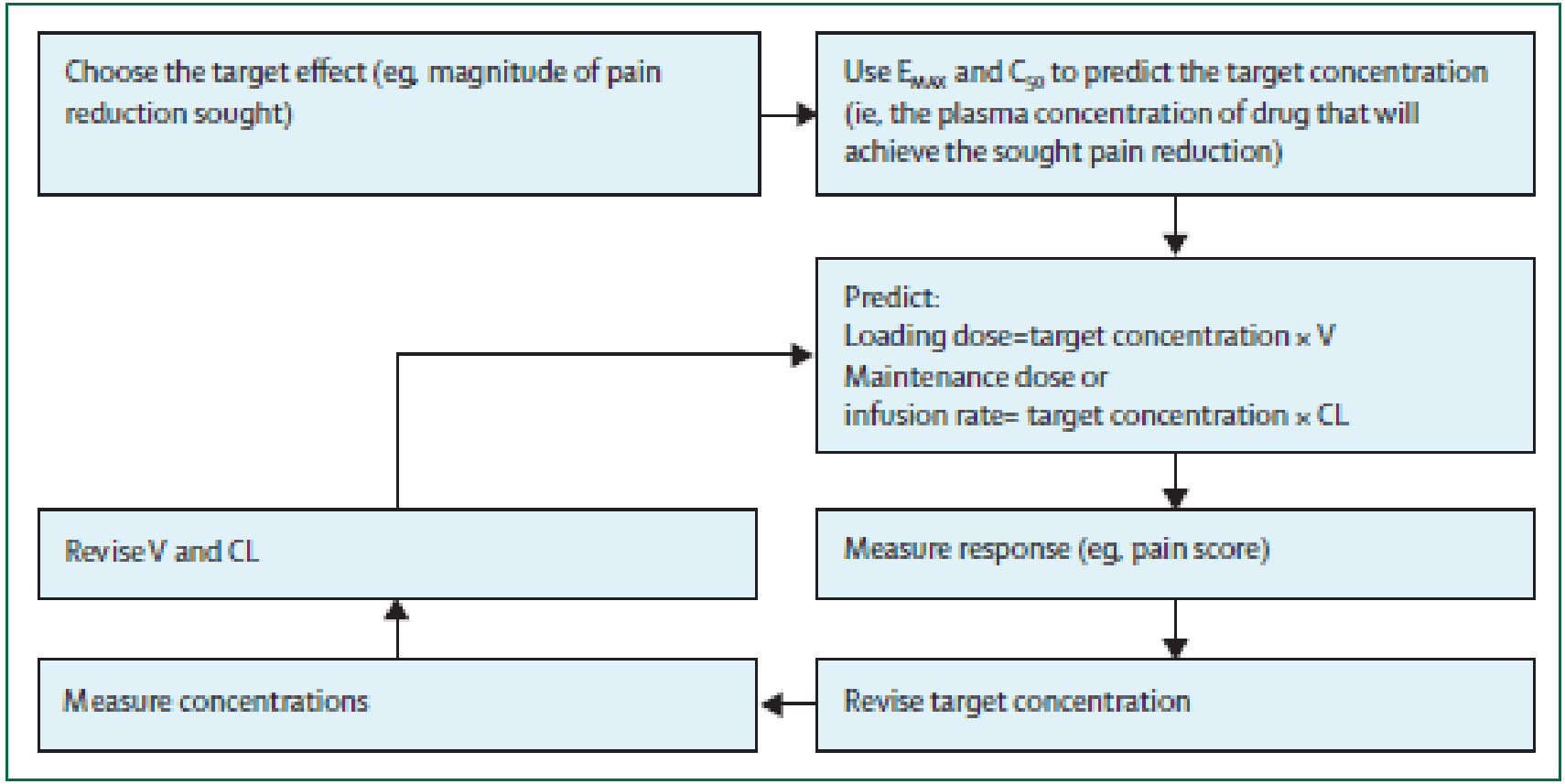


Figure 6: Strategy to determine the correct dose of pharmacological treatment

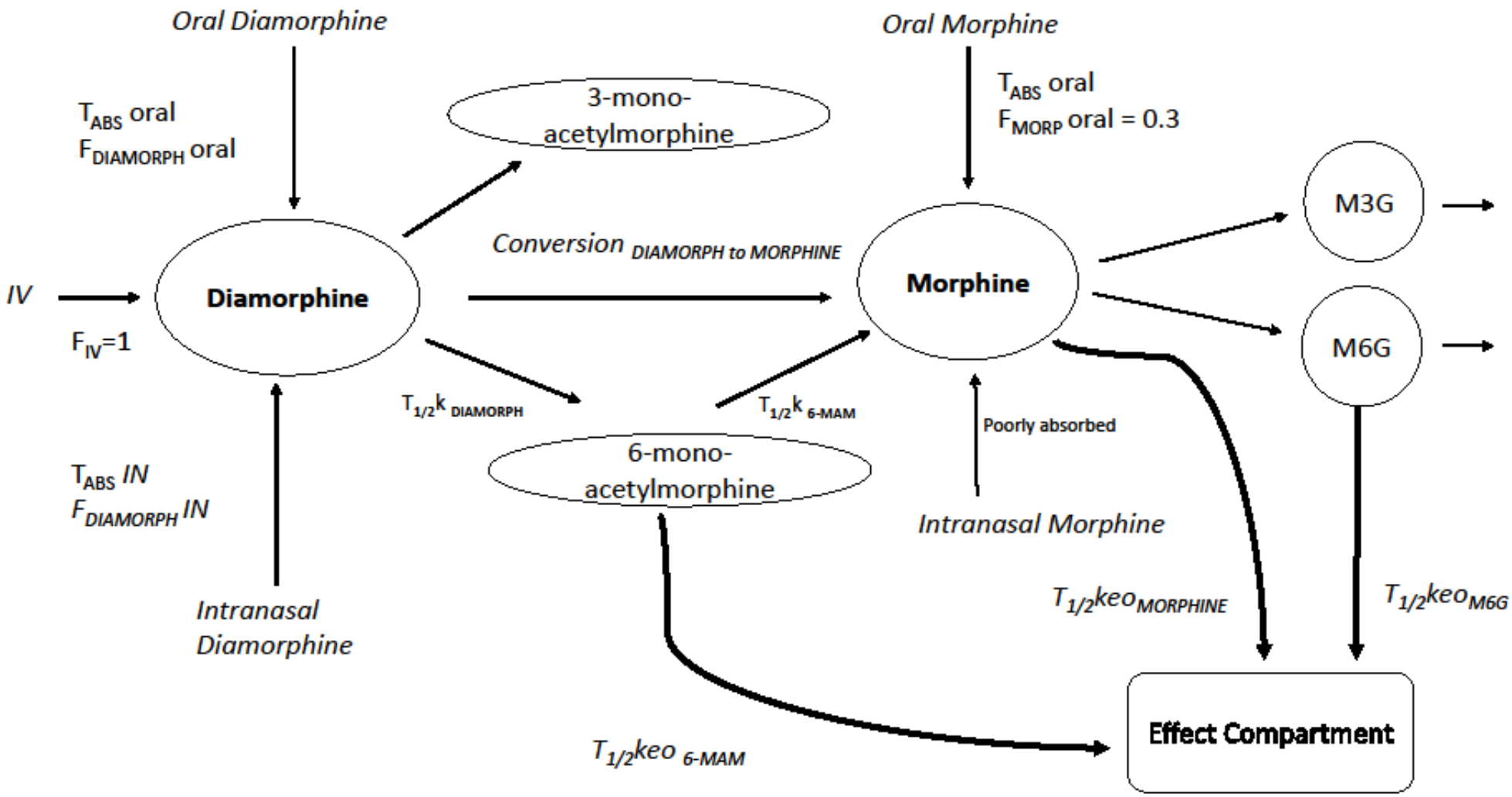
C_{50}=concentration at 50% of maximum response. CL=clearance. E_{MAX}=maximum effect. V=volume of distribution.

Eccleston C The Lancet Child and Adolescent Health Commission 2021

Application of principles to Opioids: Example, Diamorphine (Heroin) age < 2 years

- Use restricted to a few countries
- Paediatric dose acute and palliative care unknown
- Renewed interest in the drug, clinical trials advocated
- Metabolism complex, never described in children (PK)
  - Maturation
  - Size
  - Physiological functions (renal system clears some metabolites)
- Effect attributed to metabolite, morphine (PD)
  - Other metabolites also have effect
  - No concentration-response relationship for morphine
  - Drug interactions
  - Pharmacogenomics

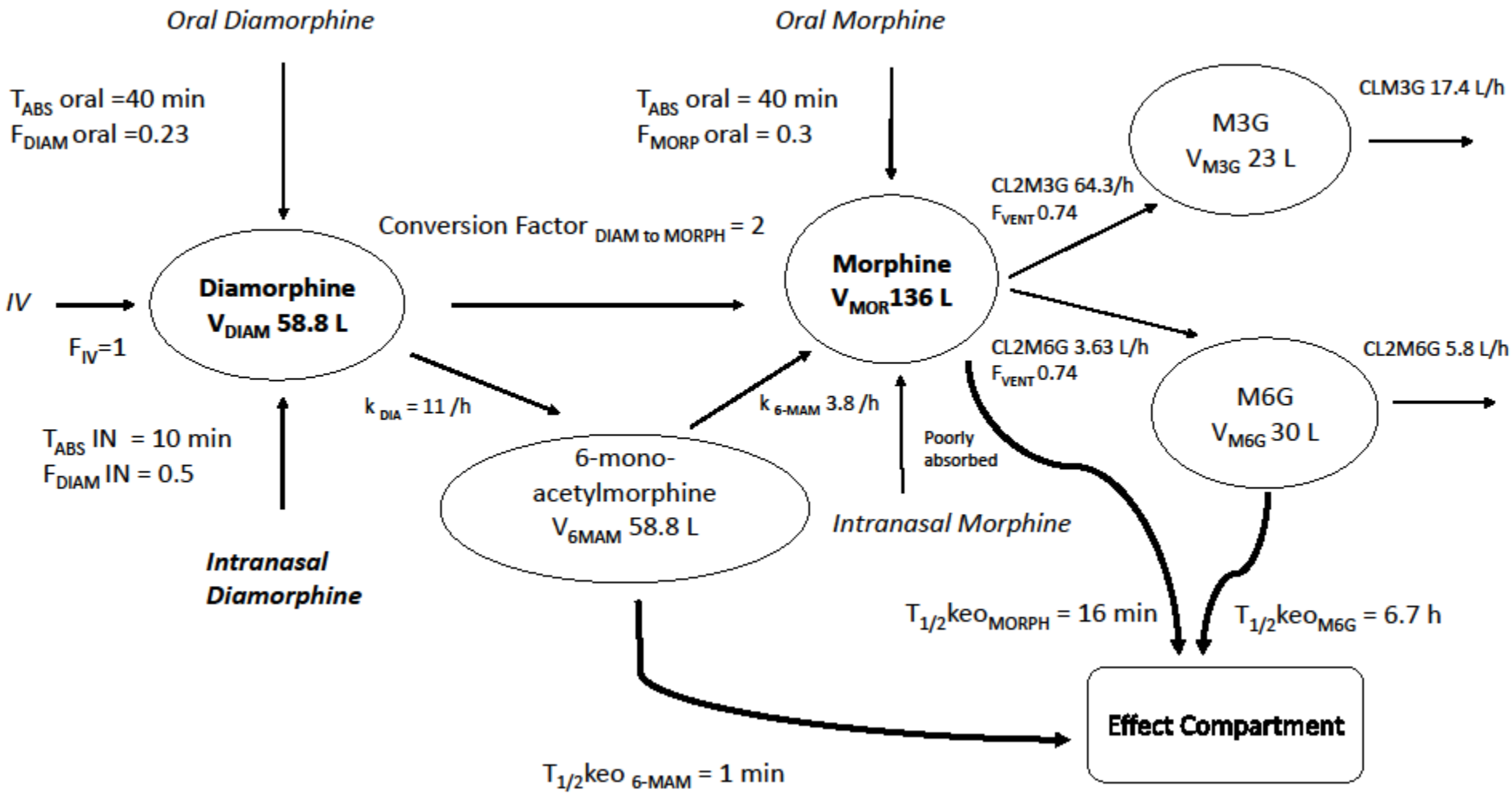
Diamorphine Metabolism



Diamorphine Pharmacokinetics

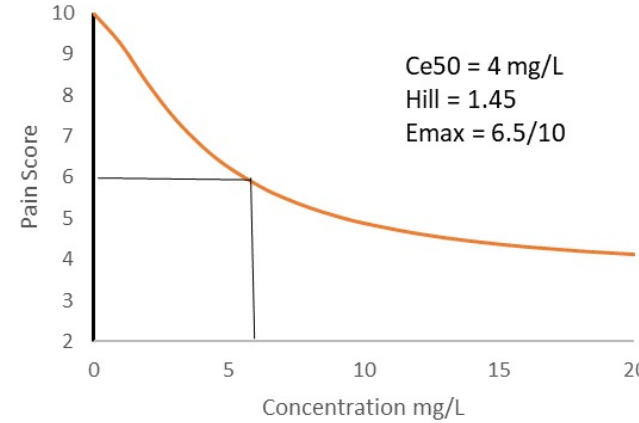
- Adult rate constants known
- Pediatric morphine PK described
- Formulation bioavailability assumed
- PK maturation models known (premature neonate to adult)
  - Premature neonatal data (Barrett 1991-6, ventilation)
- Renal function maturation known
- Size factors assumed (allometry)
- PBPK modelling supportive

Diamorphine Metabolism



Diamorphine Pharmacodynamics

- Link parameters known ($T_{1/2}$keo)
- No Concentration-response
  - unlike NSAIDs, tramadol, acetaminophen
- Maturation receptors poorly defined
- Metabolite interactions (6-MAM, M6G)



Hannam JA,Pediatr Anesth 2018

Anderson BJ. Pediatr Anesth 2019

BUT

Target concentration defined

morphine 10 mcg/L

respiratory concentration-response same neonates-adults

Target Concentration Strategy

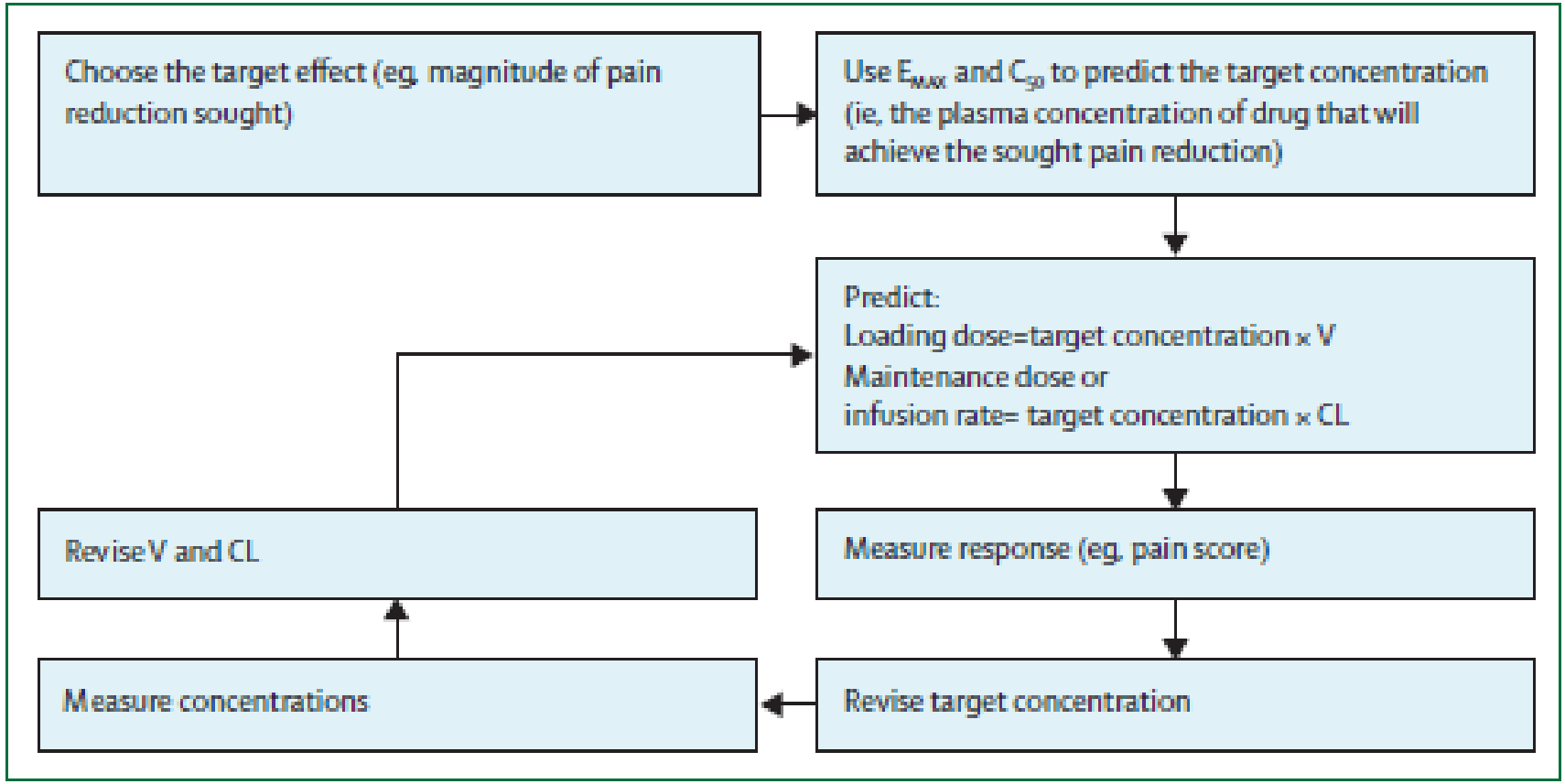


Figure 6: Strategy to determine the correct dose of pharmacological treatment

C_{50}=concentration at 50% of maximum response. CL=clearance. E_{MAX}=maximum effect. V=volume of distribution.

Eccleston C The Lancet Child and Adolescent Health Commission 2021

Population Modelling

Quantify the exposure-response relationship
Provide clarity and insight
Enable extrapolation beyond the observed data
Provide scientific rationale to dose selection
A knowledge management tool to capture and integrate pooled data from studies
Drive decision making during drug development
Hypothesis generating – the learning phase of drug development
Give a mechanistic understanding of the drug effect - theory enrichment

Morse J. Curr Opin Anaesthesiology 2019

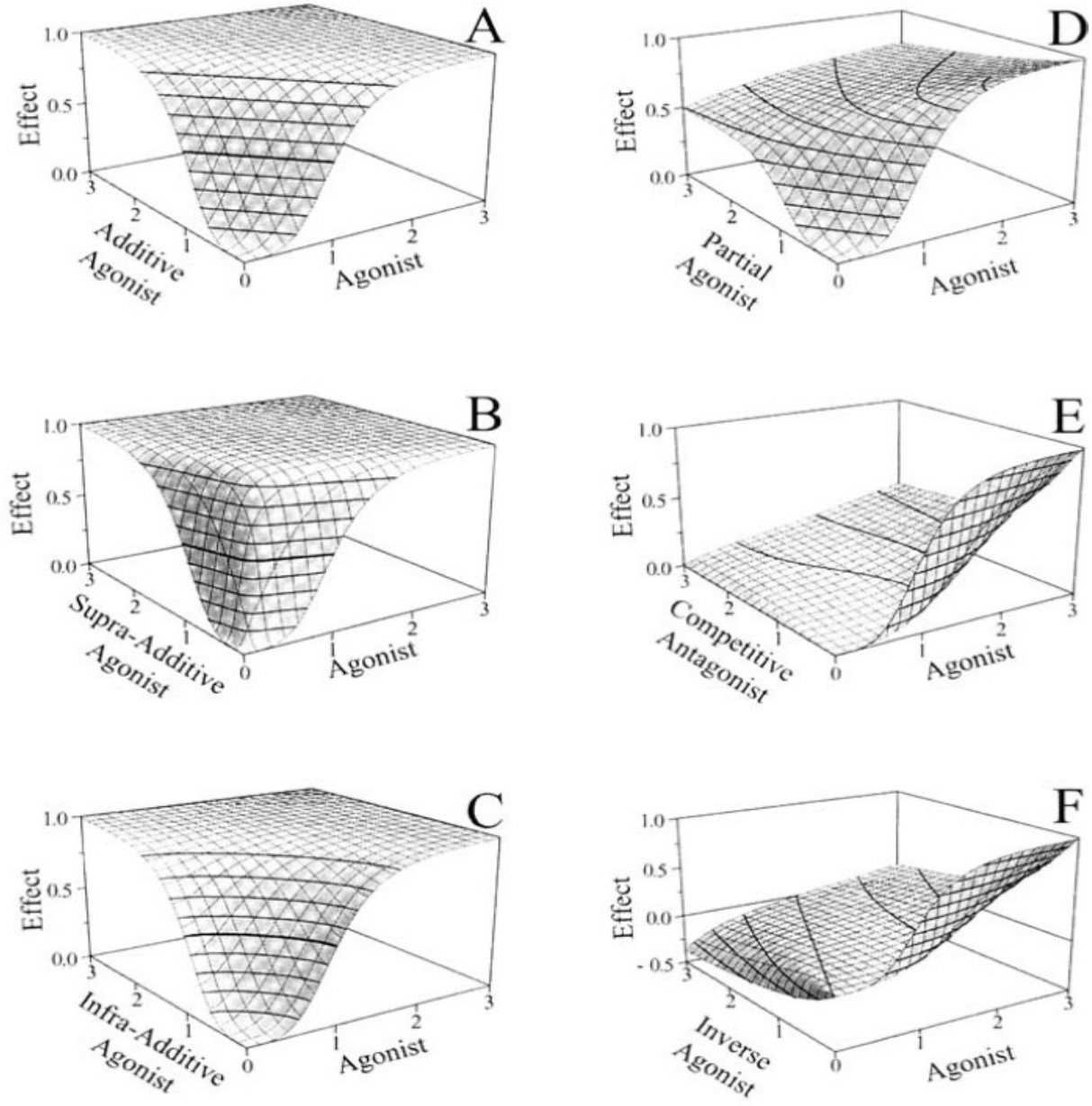
CLINICAL PHARMACOLOGY & THERAPEUTICS
VOLUME 61 NUMBER 3 MARCH 1997

COMMENTARY

Learning versus confirming in clinical drug development

Lewis B. Sheiner, MD *San Francisco, Calif.*

Drug Interactions: surface responses



Minto CF. Anesthesiology 2000; 92:1603-16

Opioid Drug Interactions

- Opioid drug interactions well described with anaesthesia agents
  - e.g., propofol-remifentanil
- Simple analgesic interactions in older children described
  - e.g., Hannam JA, Anderson BJ, Potts A. Acetaminophen, ibuprofen and tramadol analgesic interactions after adenotonsillectomy. Pediatr Anesth 2018; 28: 841-851

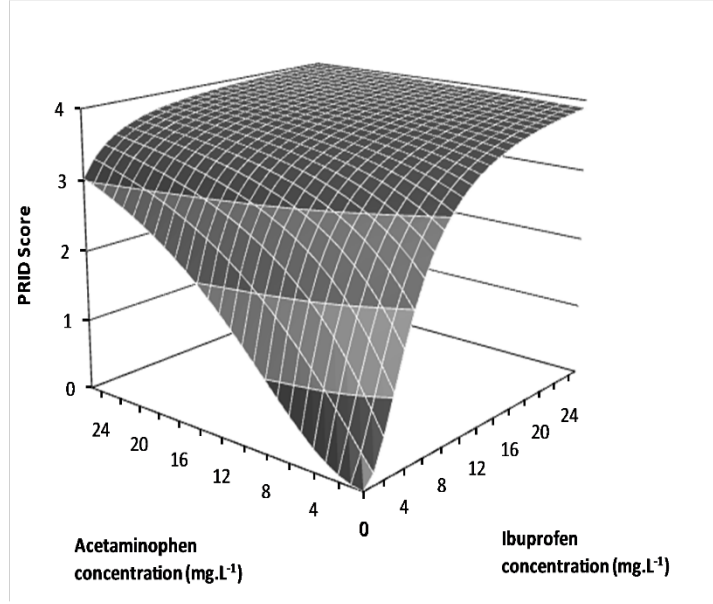
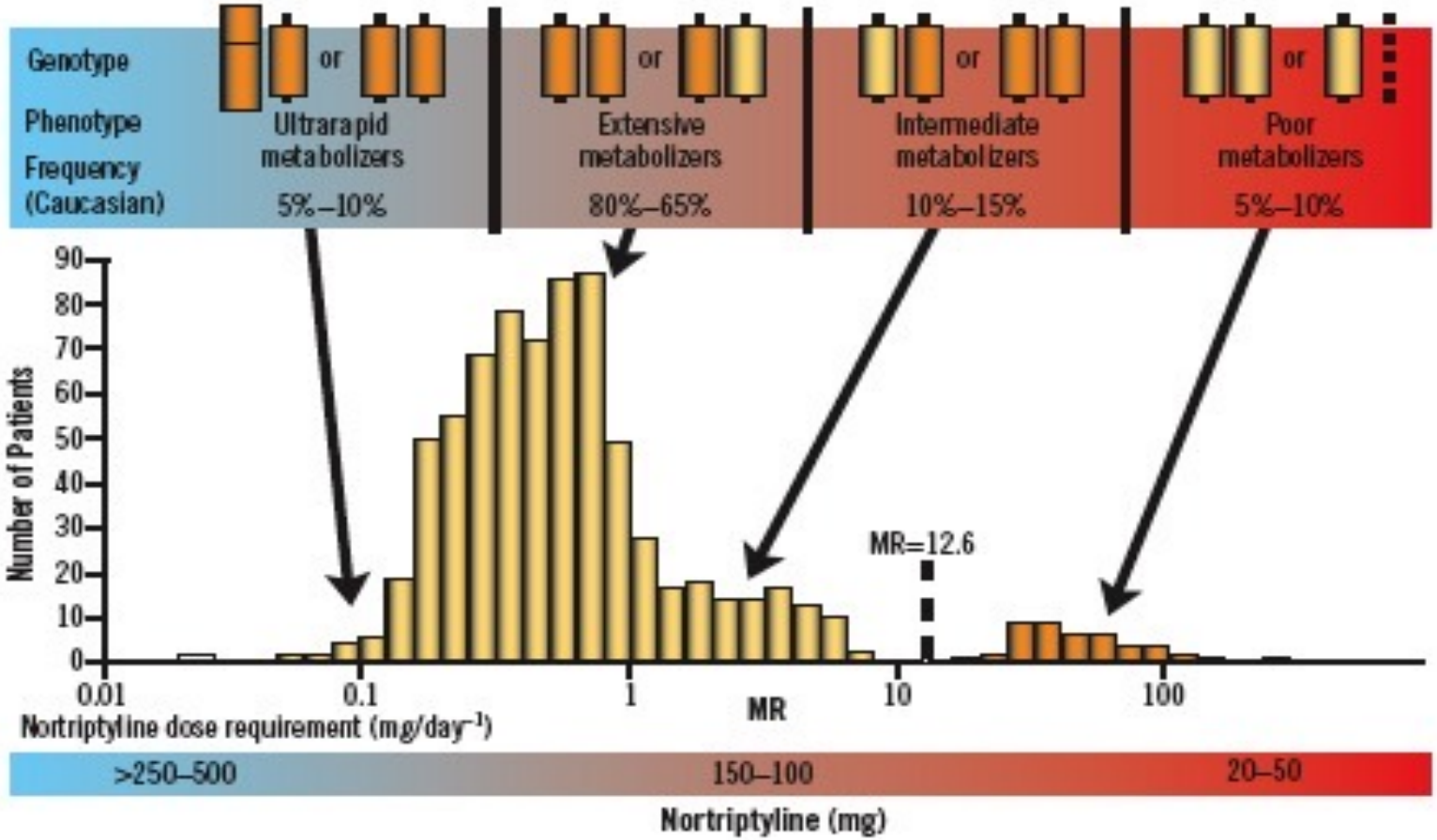


FIGURE 1

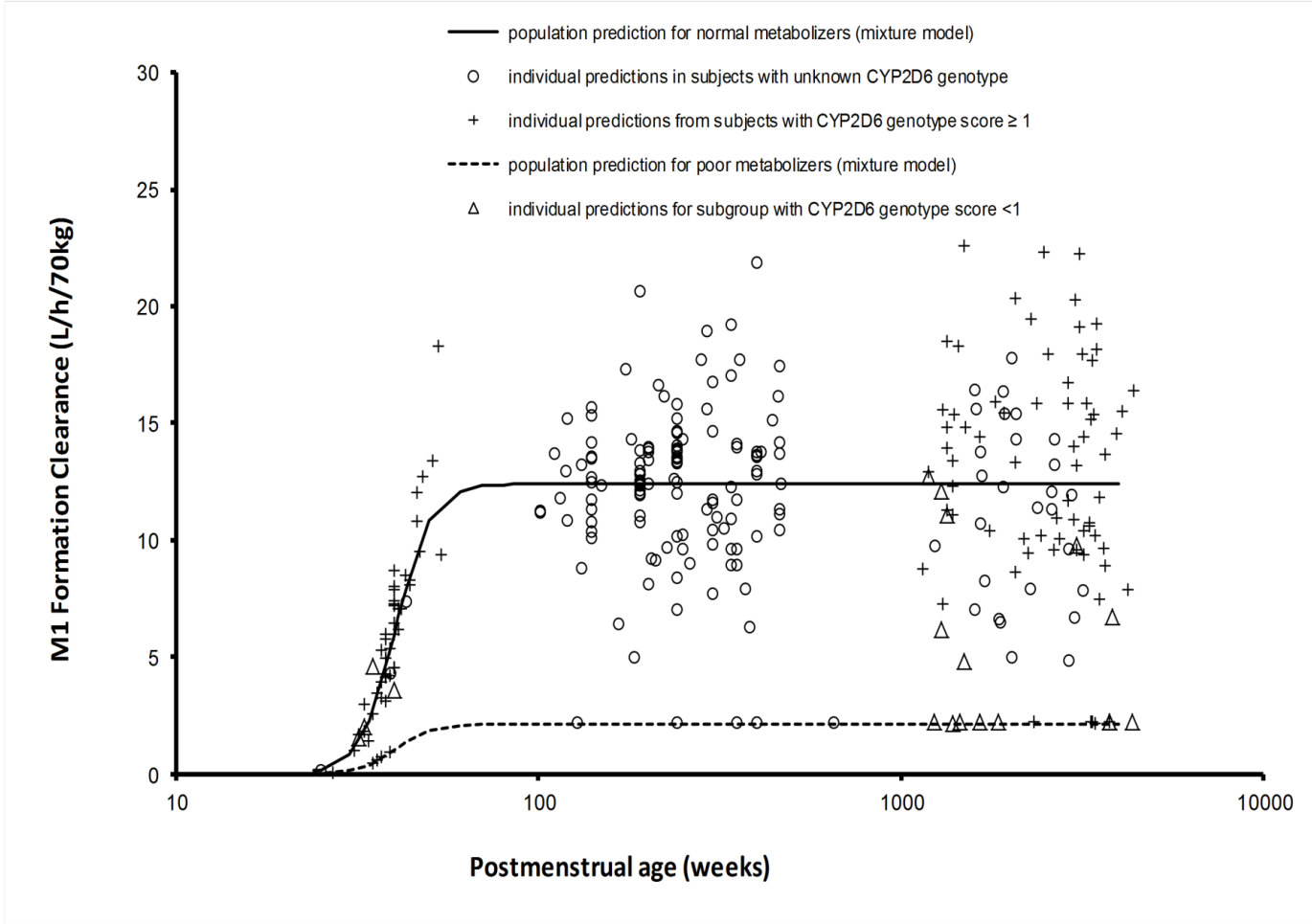
GENETICS OF CYP 2D6 METABOLIZING EFFECTS ON NORTRIPTYLINE



CYP=cytochrome P450; MR=metabolic ratio of parent debrisoquine ÷ metabolic OH-debrisoquine.

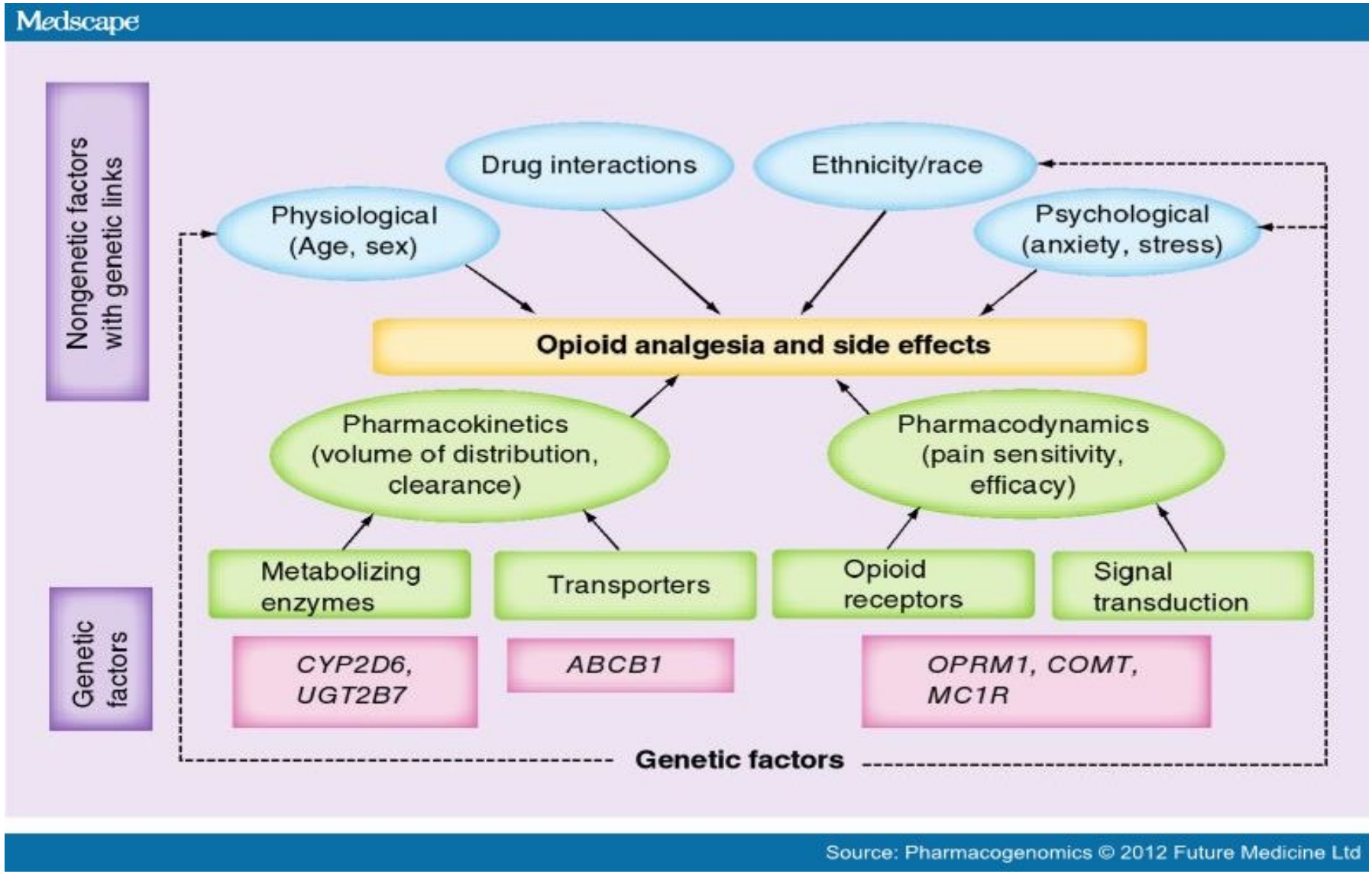
Preskorn SH, Flockhart D. *Primary Psychiatry.* Vol 16, No 12. 2009.

Impact of CYP2D6 on Tramadol Clearance



Holford SD et al. Parent-metabolite pharmacokinetic models for tramadol – tests of assumptions and predictions. J Pharm Clin Tox 2014;2(1):1023-34

Contributors to analgesic variability



The intellectual health of clinical drug evaluation

Lewis B. Sheiner, MD *San Francisco, Calif.*

Clin Pharm Ther 1991

"We have to trust the scientific judgement of the scientists . . . Statistics should be their handmaiden, not their jailer."

—D. Salsburg[1]

surely many tens, if not hundreds, of millions of dollars. Although proving unequivocally that the drug was effective, all those studies apparently did not reveal the minimum effective dose. This is not just an isolated in-

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THE END