

principles of clinical pharmacology applied to analgesics in neonates and infants

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disclosure

**no relevant financial relationships to disclose
(off-label use will be discussed)**

European Medicines Agency + FAGG declaration in the public domain

limited size, extensive variability

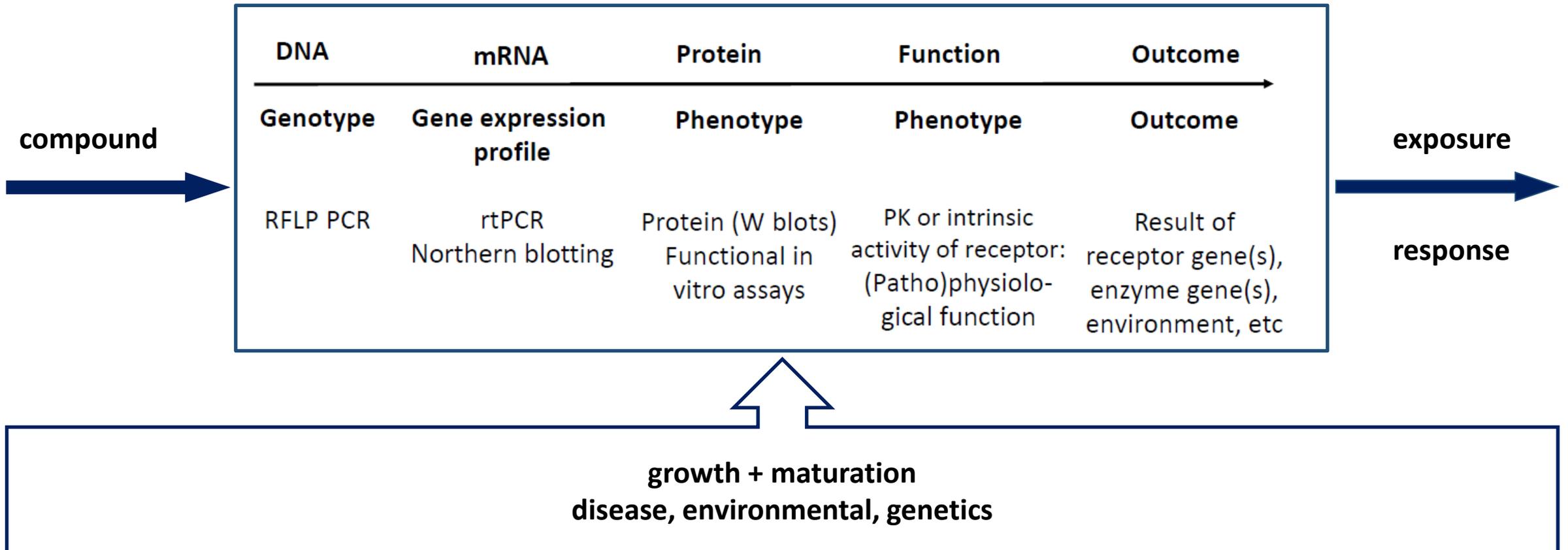
neonatal and infant physiology

" Pediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but...it has its own independent range and horizon..."

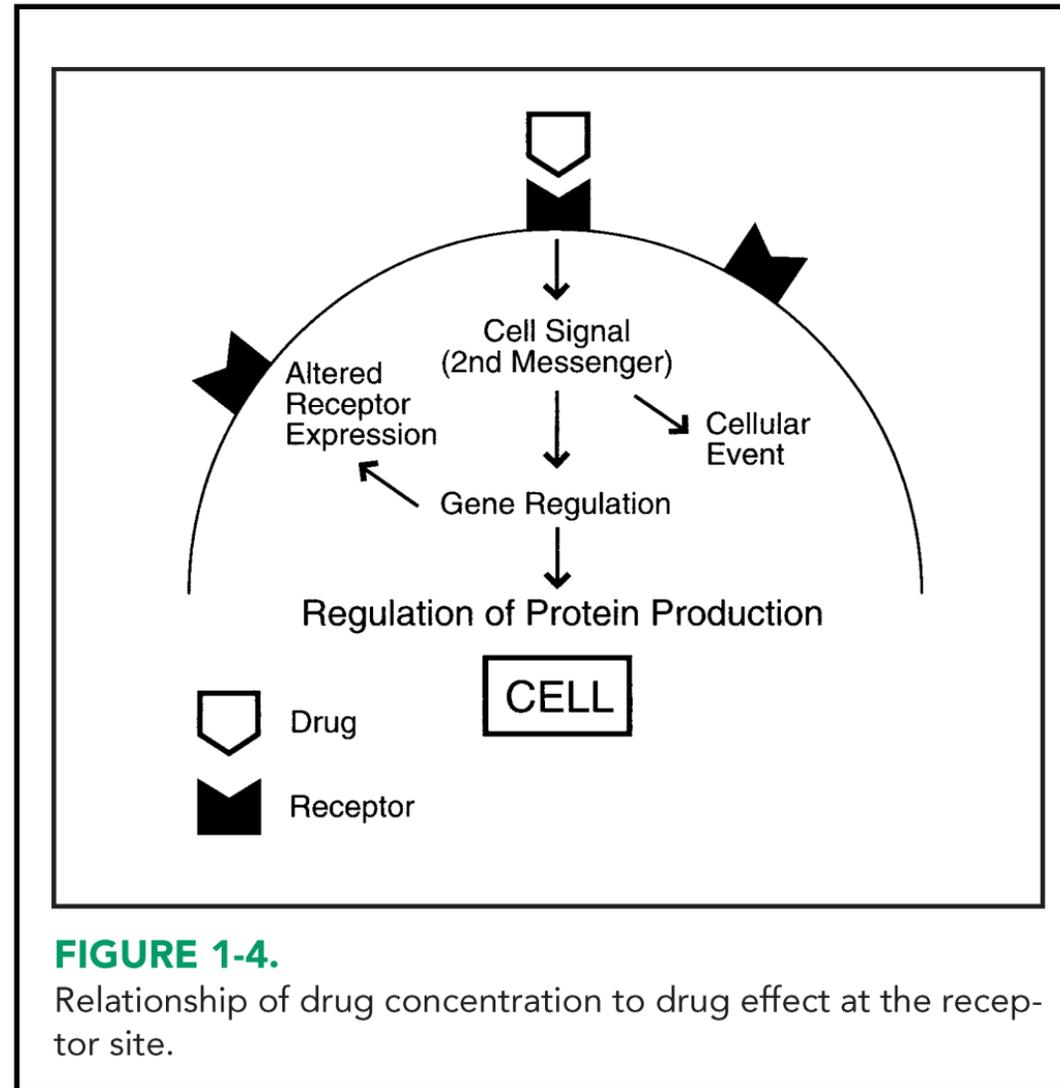
Dr. Abraham Jacobi, 1889

a child is not (just) a small adult
a newborn is not (just) a small child
a micro-preemie is not (just) a small preterm

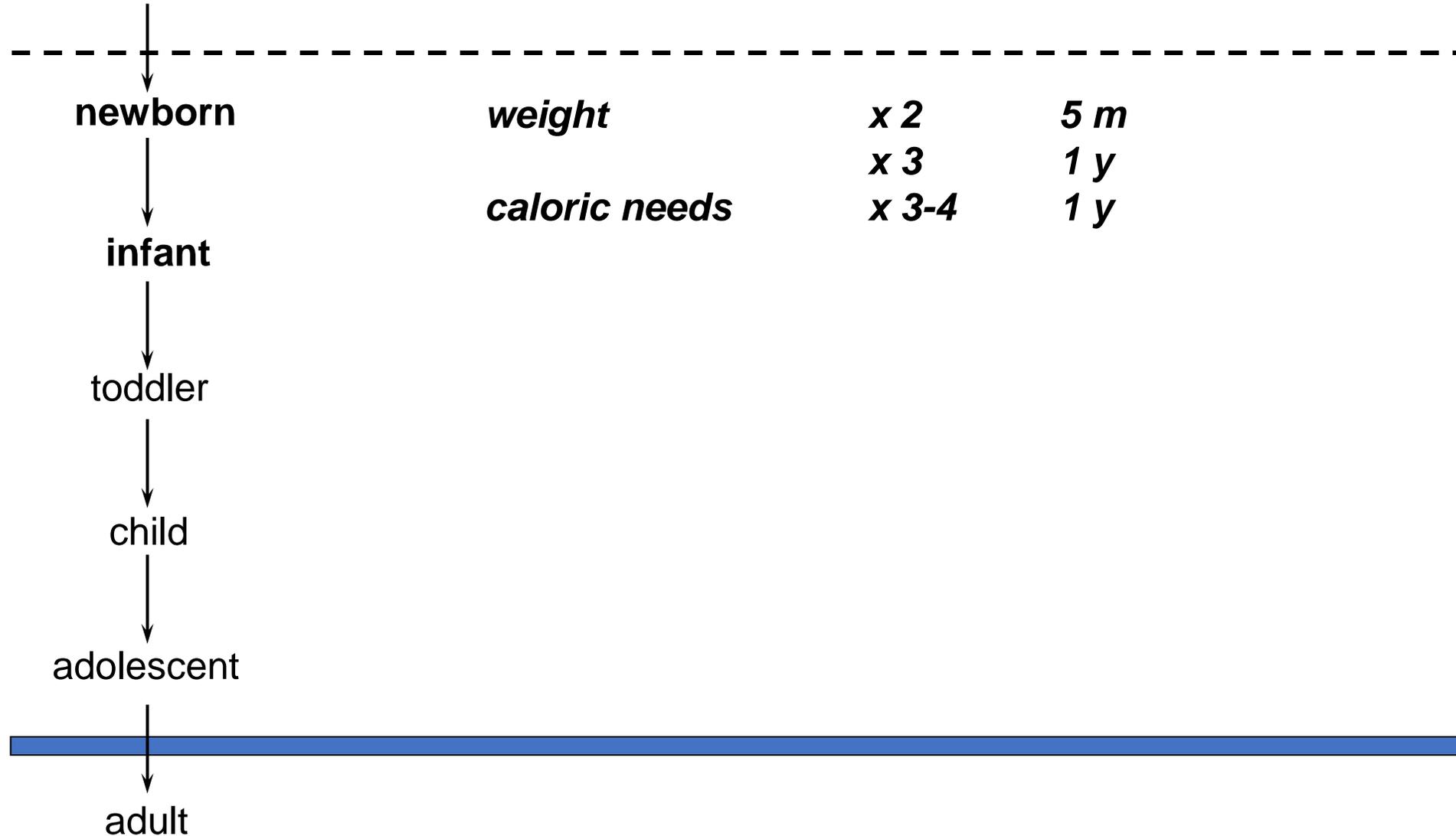
developmental pharmacokinetics and -dynamics



developmental pharmacokinetics and -dynamics



developmental pharmacokinetics and -dynamics



suggestion 1



suggestion 2



suggestion 2



Venipuncture Is More Effective and Less Painful Than Heel Lancing for Blood Tests in Neonates

Björn A. Larsson, MD*; Gunnilla Tannfeldt, RN*; Hugo Lagercrantz, MD, PhD†; and
Gunnar L. Olsson, MD, PhD*

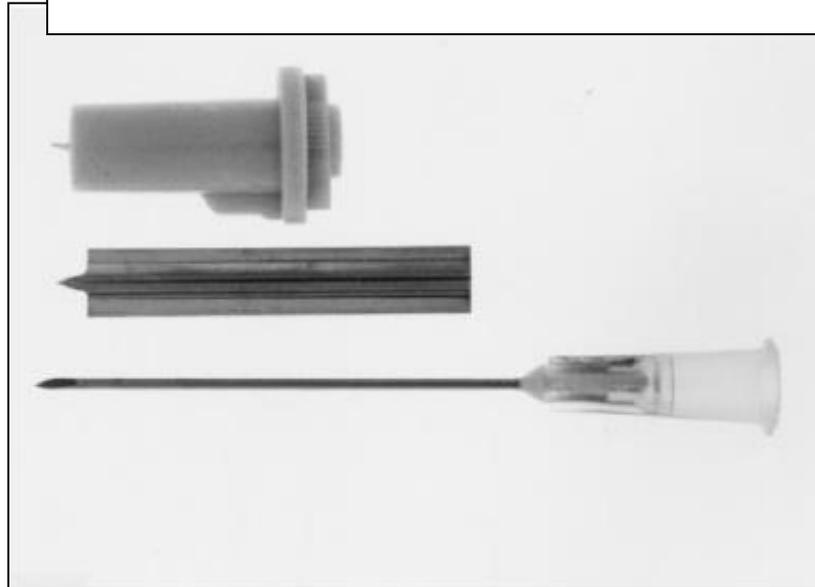


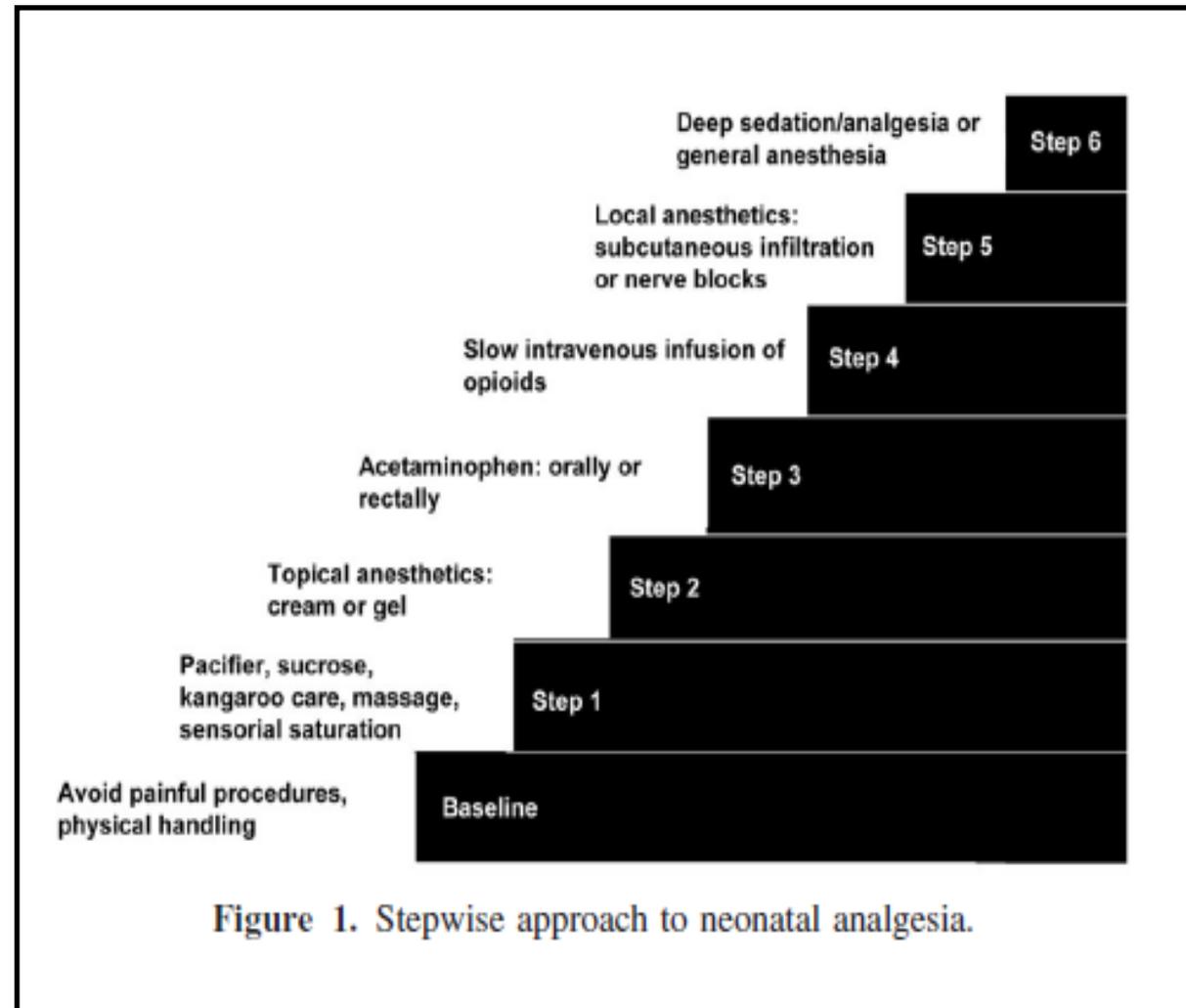
Fig 1. Three devices used for the PKU test. From the top: the CCS Minilancet used in the SL group, the Microlance used in the LL group, and the Microlance needle (0.9 × 40 mm) used in the VP group.



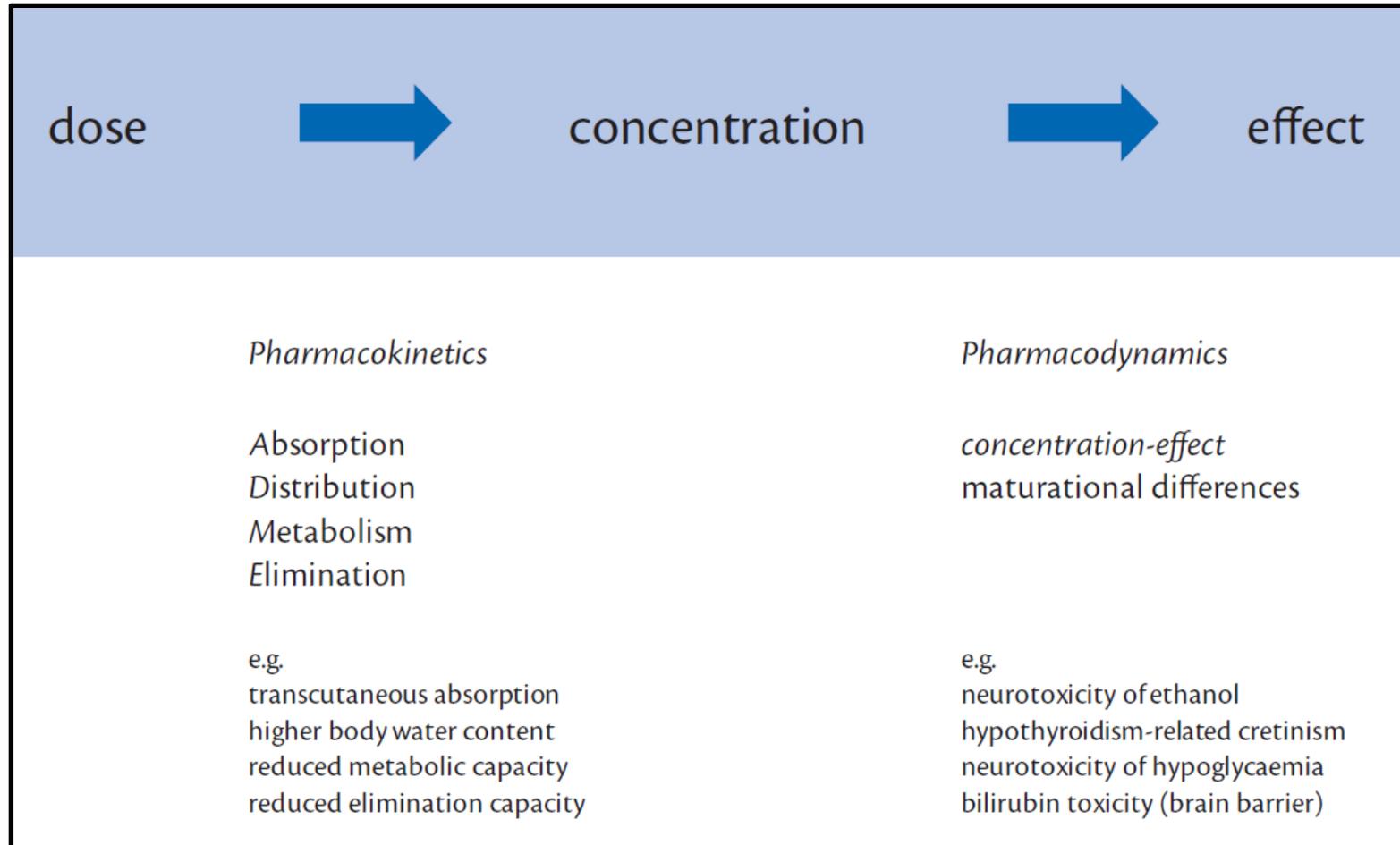
suggestion 3



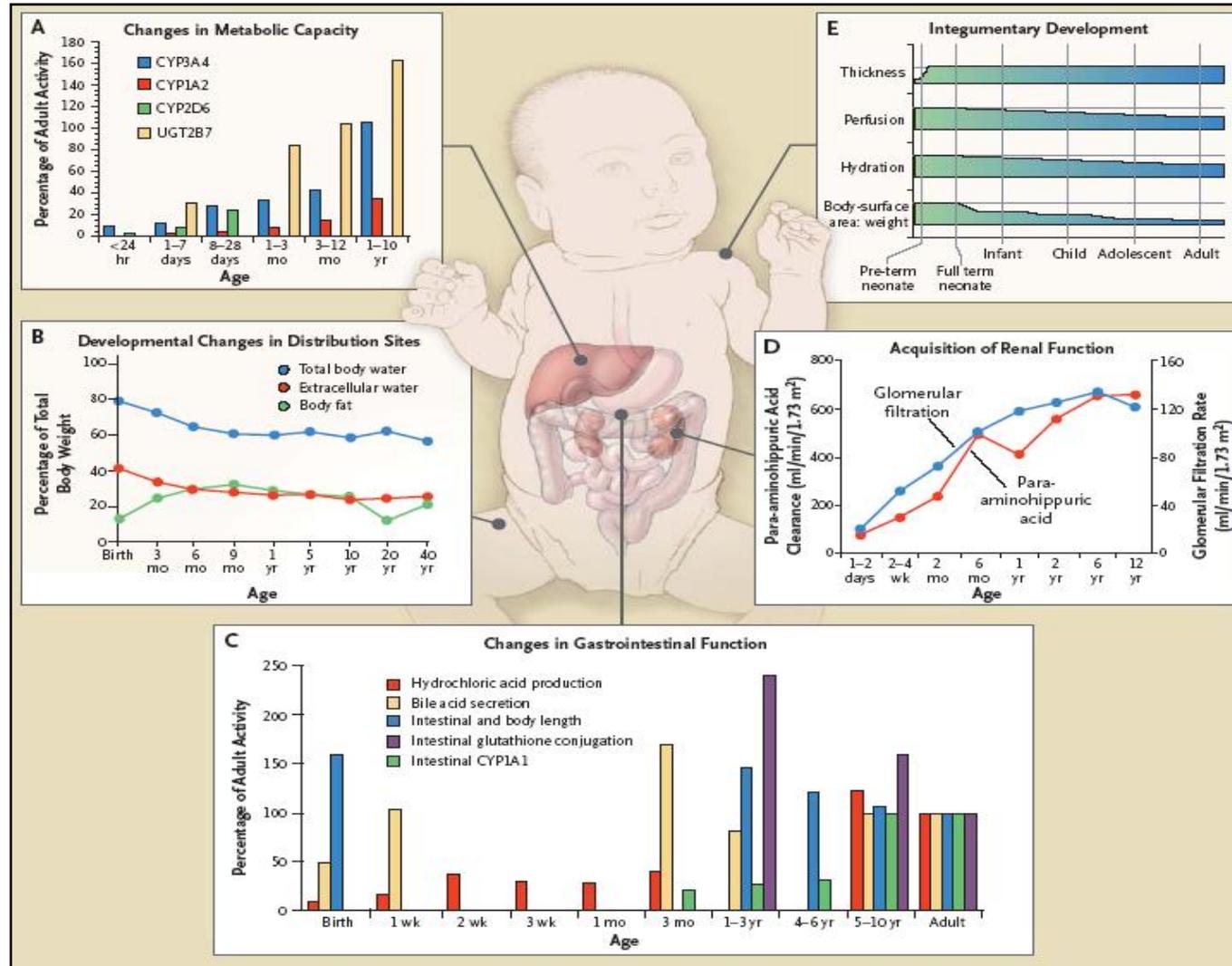
the formulary/toolbox available



the framework (clin pharm) to work with: PK/PD



the patient to aim for: a moving target (ADME)

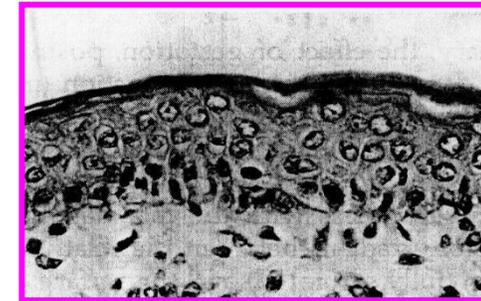
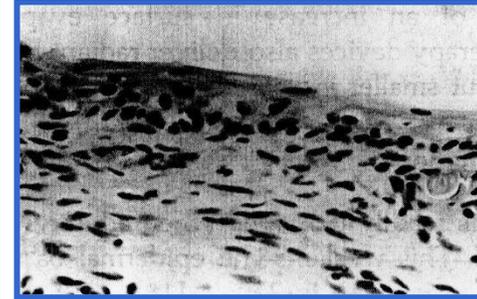
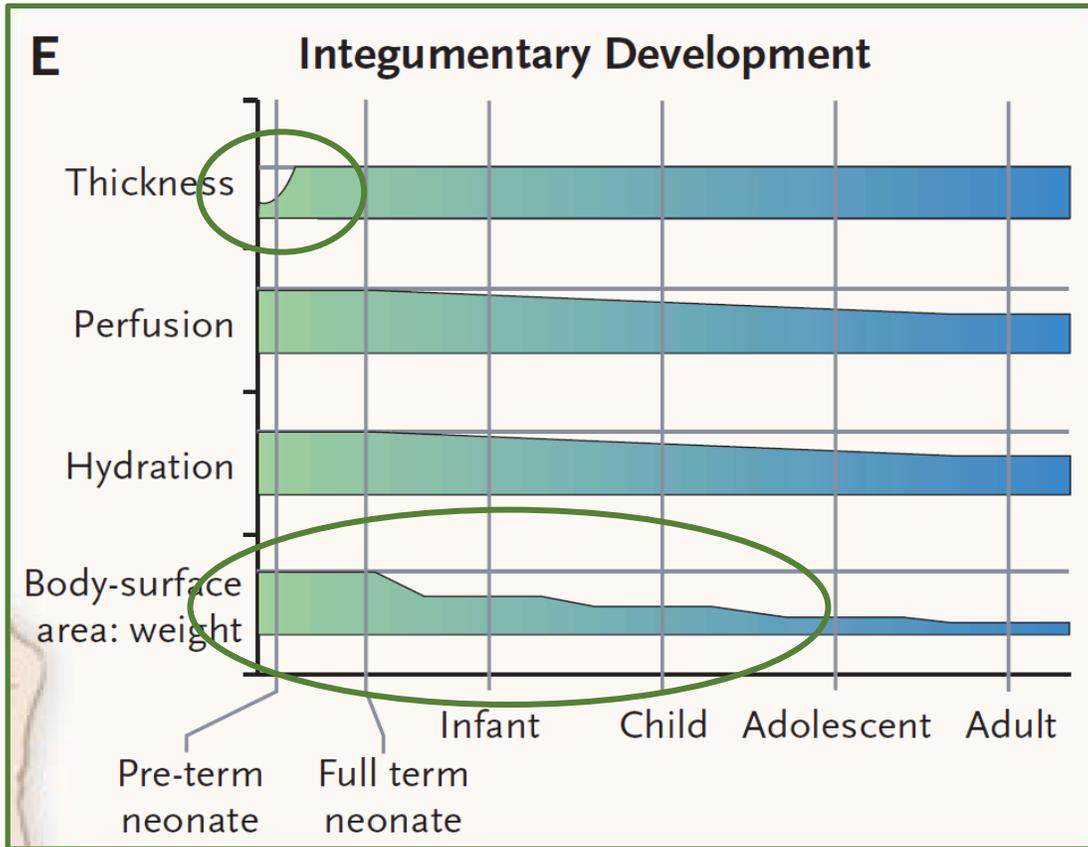


neonatal pharmacokinetics: ADME

maturational and non-maturational covariates



absorption, skin: $BSA > permeability$



higher BSA/kg in young children: risk for inadvertent absorption

absorption, skin: BSA > permeability

Cyanosis in a premature infant induced by topical anesthesia

Methemoglobinemia is a rare cause of cyanosis in pediatric patients and it is characterized by increased quantities of hemoglobin in which the iron of heme is oxidized to the ferric (Fe^{3+}) form. The condition may arise as a result of a genetic defect in red blood cell metabolism or hemoglobin structure, or it may be acquired following exposure to various oxidant drugs or toxins.



Preterm neonates are exposed to a range of painful procedures and topical anesthetics as EMLA are used routinely for pain management. Because premature neonates are low weight and consequently they are easily overdosed, routinely use of EMLA should be carefully evaluated.

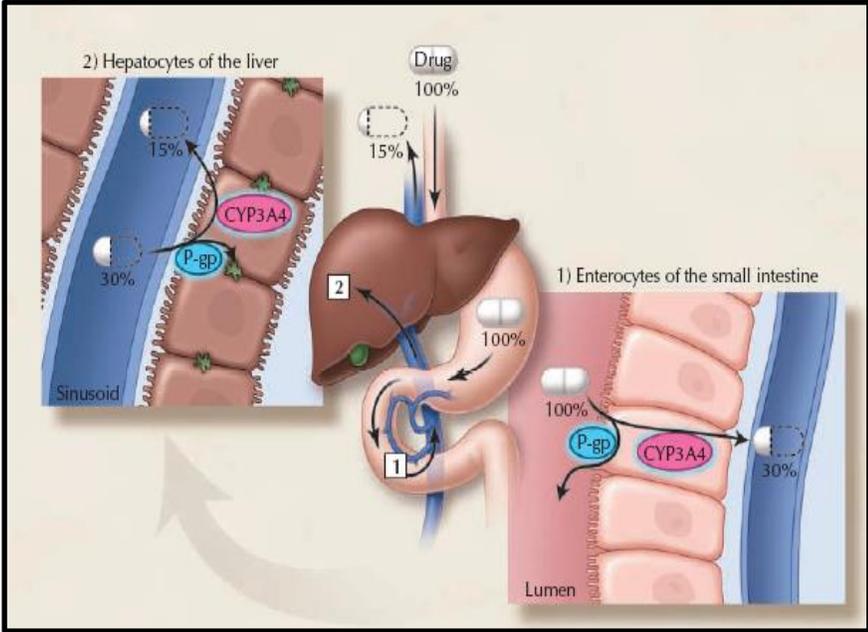
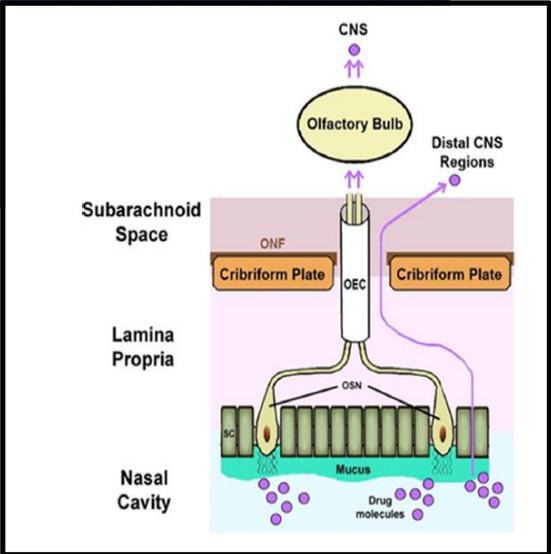


absorption, skin: BSA > permeability

Table 15.3 Reported papers on the analgesic effects of tetracaine/amethocaine in neonates (type of procedure highlighted)

Reference	Study design and results
Shah et al. [88]	Randomized, double-blind, placebo-controlled trial, <i>intramuscular injection</i> (vitamin K) in 110 term neonates, topical amethocaine gel 4 %. There were no differences in crying duration, in pain score and only the latency to cry was somewhat longer in the treated group. Topical amethocaine gel 4 % was ineffective in reducing pain intramuscular injection of vitamin K in full-term neonates
Jain A et al. [89]	Randomized, double-blind, placebo-controlled trial in 40 (pre)term neonates during <i>venipuncture</i> . Topical amethocaine provided effective pain relief (crying, neonatal facial coding system) during venipuncture in the newborn when used as single technique for analgesia
Lemyre et al. [90]	Randomized, double-blind, placebo-controlled trial in 142 preterm (from 24 weeks onward) infants during <i>venipuncture</i> . Tetracaine did not significantly decrease procedural pain in infants undergoing a venipuncture, when used in combination with routine sucrose administration
Lemyre et al. [91]	Randomized, double-blind, placebo-controlled trial in 54 preterm neonates on the add-on effect of tetracaine gel in addition to sucrose to treat procedural pain related to <i>peripherally inserted central catheter (PICC) placement</i> . Tetracaine 4 % when applied for 30 min was not beneficial in decreasing procedural pain associated with a PICC in very small infants
Jain et al. [92]	Randomized, double-blind, placebo-controlled trial in 60 (pre)term neonates during <i>heel prick blood sampling</i> . Topical amethocaine gel does not have a clinically important effect on the pain of heel prick blood sampling. Its use for this purpose cannot therefore be recommended

absorption, skin: BSA > permeability



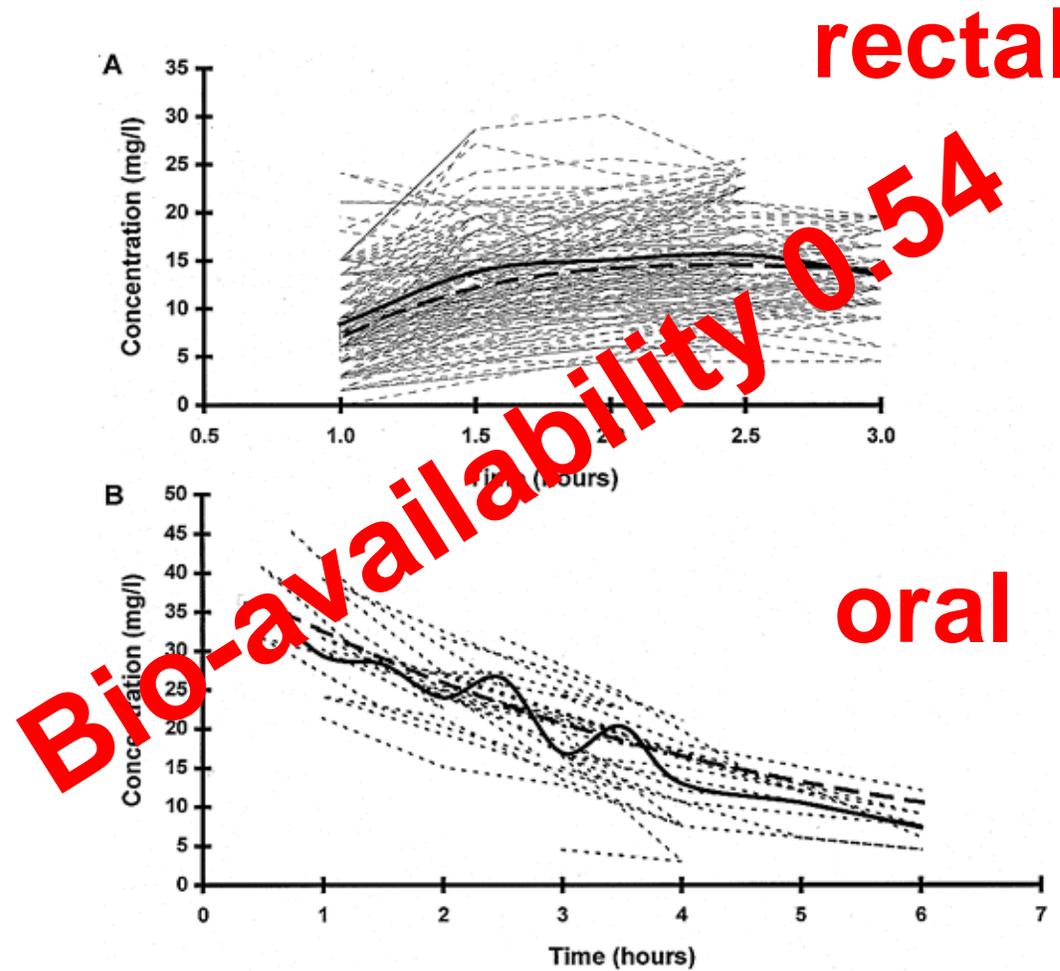
Intranasal dexmedetomidine, as midazolam-sparing drug, for MRI in preterm neonates

TABLE 1 Number of patients in the historical and dexmedetomidine group according to number of midazolam doses needed to achieve sedation for MRI at equivalent age

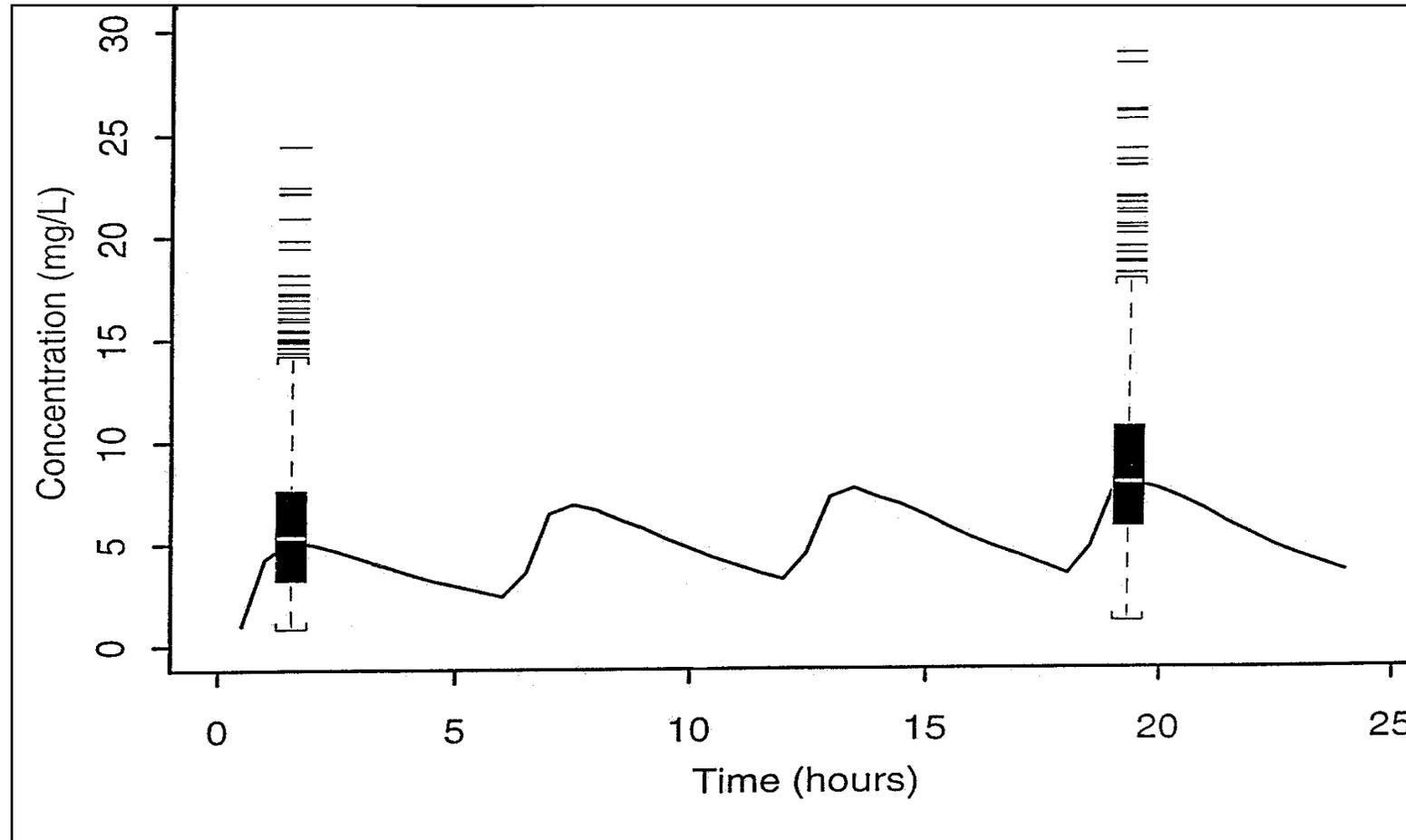
Number of doses of midazolam	Historical midazolam group (n = 40), number (%)	Dexmedetomidine group (n = 53), number (%)
0	0	27 (51)
1	12 (30)	25 (47)
2	14 (35)	1 (2)
3	14 (35)	0

3 microgr/kg intranasal, single dose

absorption, rectal to oral paracetamol (ENT, children)



absorption, rectal to oral paracetamol (ENT, children)



Neonatal formulary¹²

Oral	Loading dose	24 mg/kg
	Maintenance	12 mg/kg/dose q4h in ≥ 32 wk PMA, q8h in < 32 wk
Rectal	Loading dose	36 mg/kg
	Maintenance	24 mg/kg, q8h in term neonates No advice in preterm neonates
Intravenous	Loading dose	20 mg/kg, irrespective of age
	Maintenance	15 mg/kg, q6h in term cases 12.5 mg/kg, 31–36 wk PMA 10 mg/kg, ≤ 30 wk PMA

Dutch formulary¹³

Oral	Loading dose	Not sufficiently supported by clinical evidence
	Maintenance	60 mg/kg/d, > 32 wk PMA 30 mg/kg/d, 28–32 wk PMA
Rectal	Loading dose	30 mg/kg, < 32 wk PMA
	Maintenance	20 mg/kg, 28–32 wk PMA 20 mg/kg, q8h in term neonates 20 mg/kg, q12h in preterm neonates
Intravenous	Loading dose	Off label in preterm neonates 20 mg/kg, irrespective of age
	Maintenance	10 mg/kg, max 40 mg/kg/d, in term cases 10 mg/kg, max 30 mg/kg/d, 31– 36 wk PMA 10 mg/kg, max 20 mg/kg/d, < 31 wk PMA

PMA = postmenstrual age (in weeks).

distribution

body composition, (non)maturational covariates

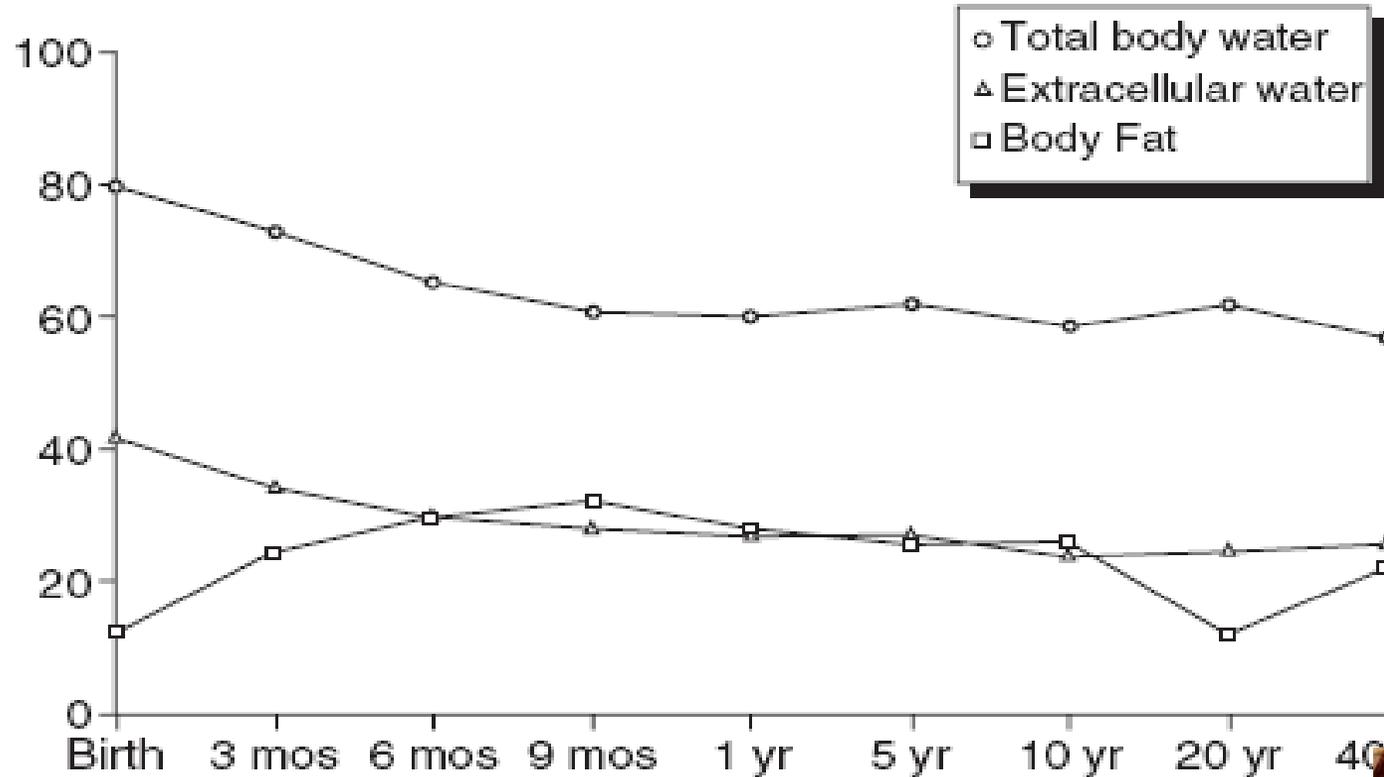
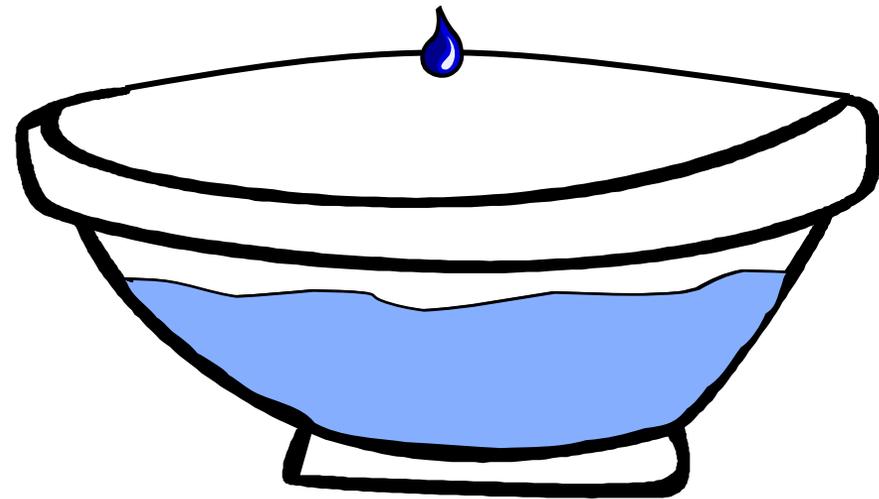


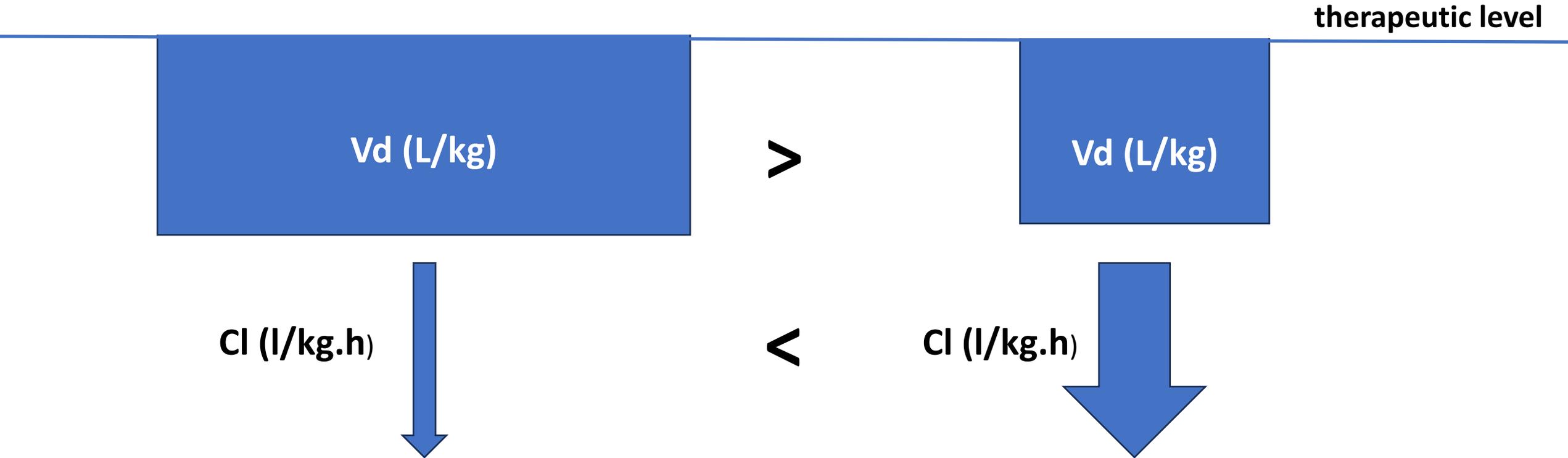
Fig. 1. Changes occurring in percentages of body fat and water stores along the continuum of age [16].



distribution volume adult versus newborn



distribution volume and clearance newborn versus adult



distribution volume: relevance

Table 2 Dose suggestions for systemic analgesics in the surgical term neonate are formulated based on the currently available evidence on pharmacokinetics or dynamics of these analgesics in neonates (iv= intravenous) [4, 5, 10, 12]

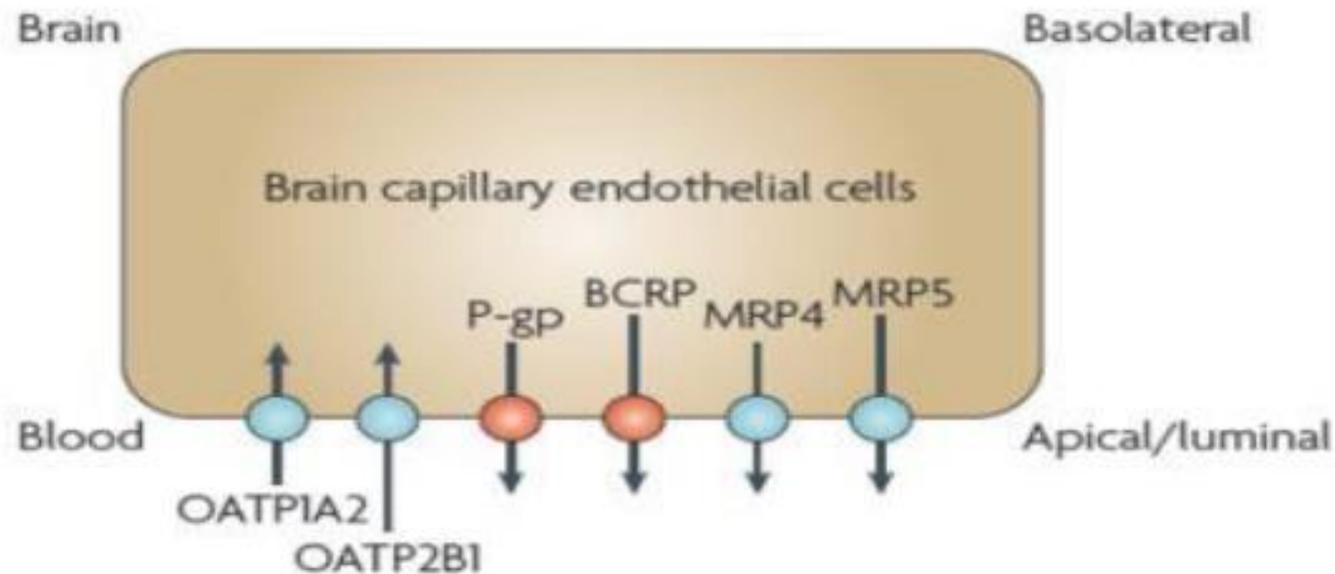
	Route	Loading dose	Maintenance dose
Morphine	iv	50–100 µg/kg	10–30 µg/kg/h
Fentanyl	iv	1–3 µg/kg	1–5 µg/kg/h
Tramadol	iv	2 mg/kg/30 min	6–8 mg/kg/day
Paracetamol	Oral	20 mg/kg	4 × 10 mg/kg/day
	Rectal	40 mg/kg	4 × 20 mg/kg/day
	iv	20 mg/kg	4 × 10 mg/kg/day

distribution volume: relevance (CNS compartment)

The ontogeny of P-glycoprotein in the developing human blood–brain barrier: implication for opioid toxicity in neonates

Jessica Lam^{1,2}, Stephanie Baello³, Majid Iqbal², Lauren E. Kelly⁴, Patrick T. Shannon⁵, David Chitayat^{6,7}, Stephen G. Matthews³ and Gideon Koren^{1,2,4}

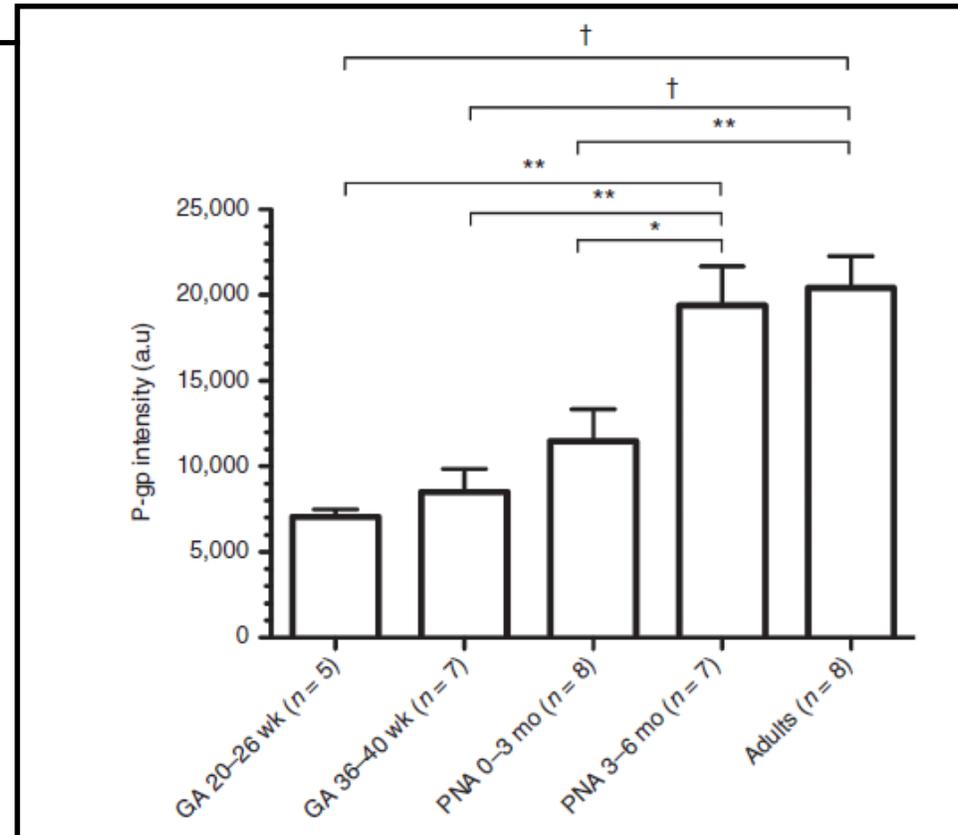
d Blood–brain barrier



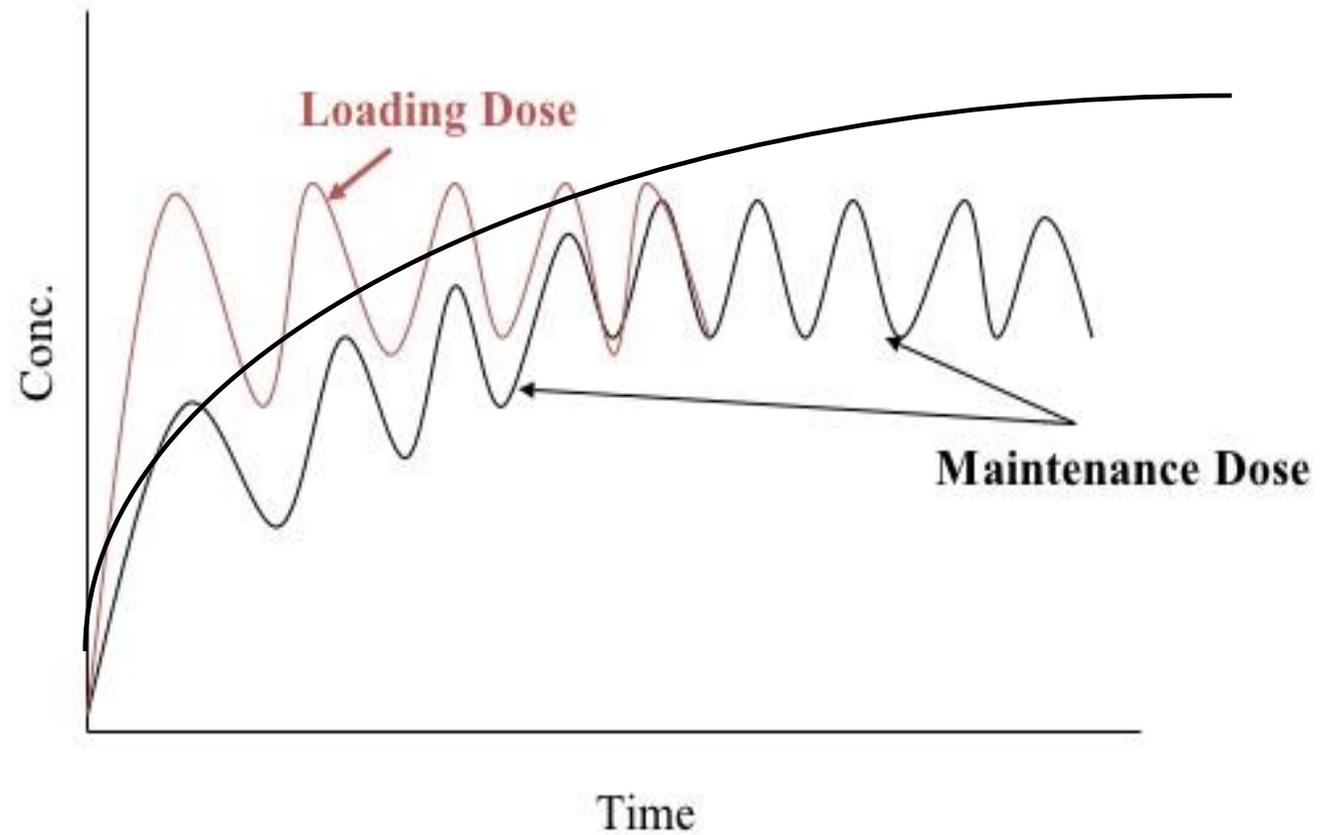
distribution volume: relevance (CNS compartment)

The ontogeny of P-glycoprotein in the developing human blood–brain barrier: implication for opioid toxicity in neonates

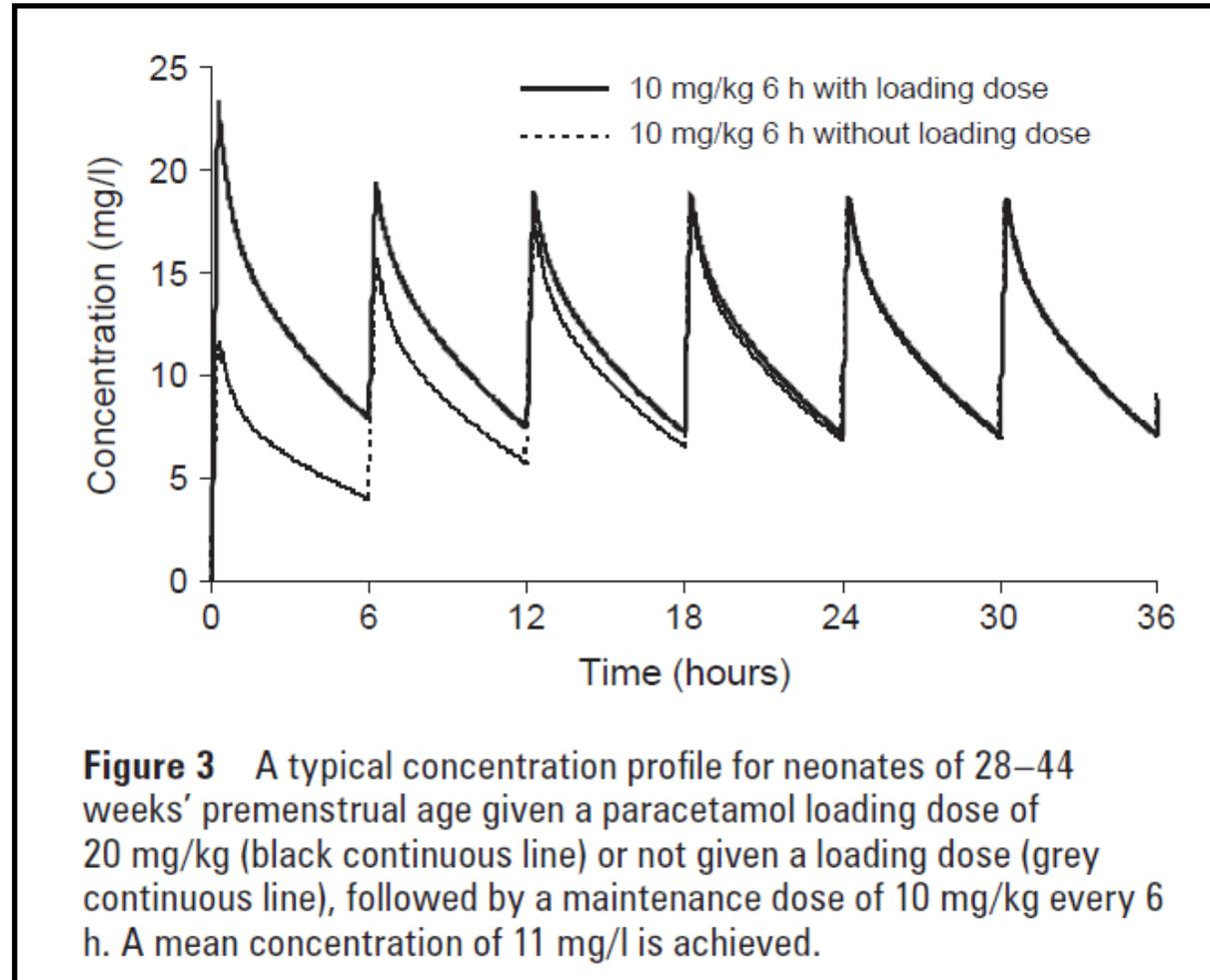
Jessica Lam^{1,2}, Stephanie Baello³, Majid Iqbal², Lauren E. Kelly⁴, Patrick T. Shannon⁵, David Chitayat^{6,7}, Stephen G. Matthews³ and Gideon Koren^{1,2,4}



distribution volume: relevance (continuous)

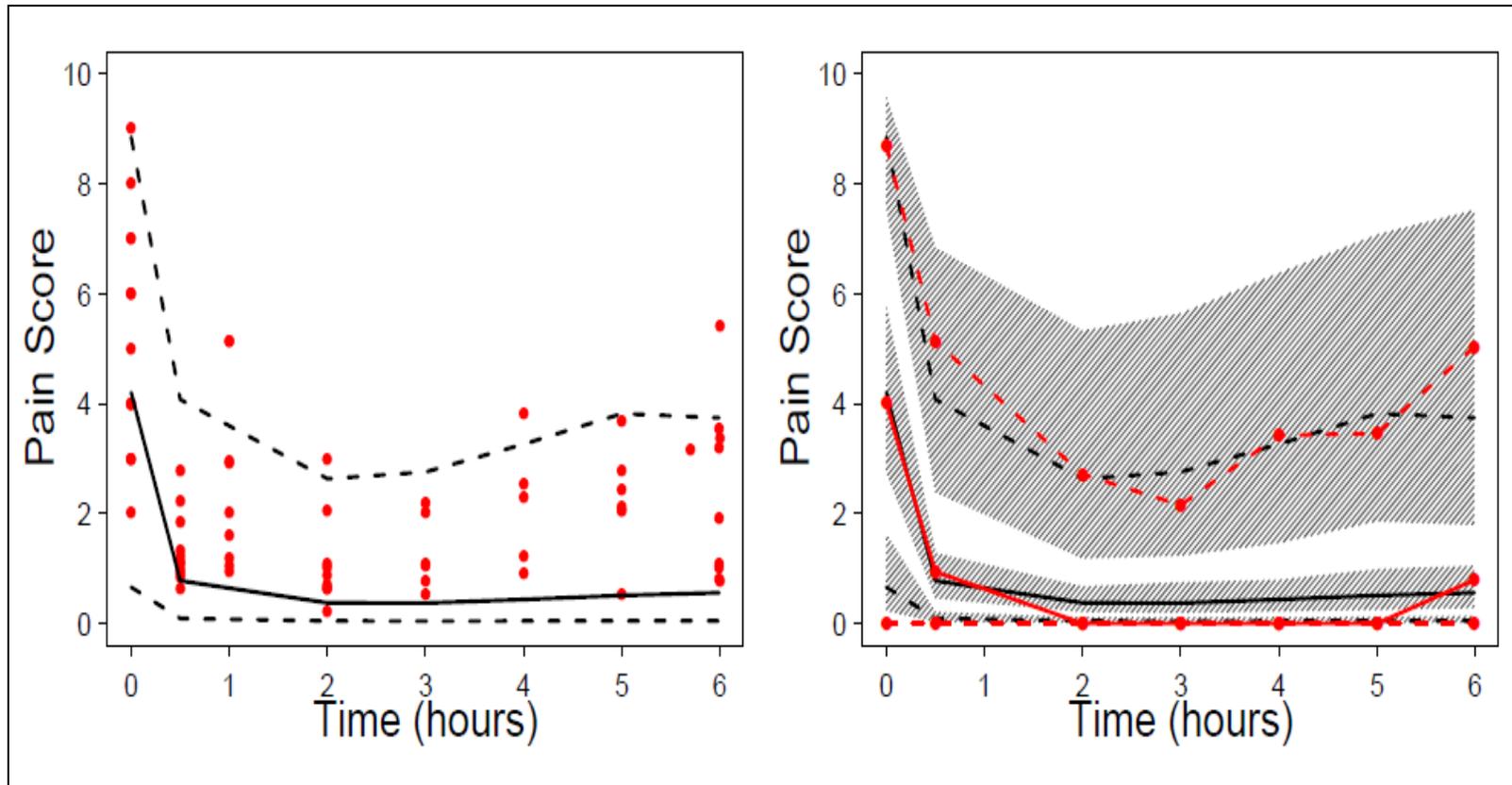


distribution volume: relevance (intermittent)



distribution volume: relevance

'minor' pain syndromes



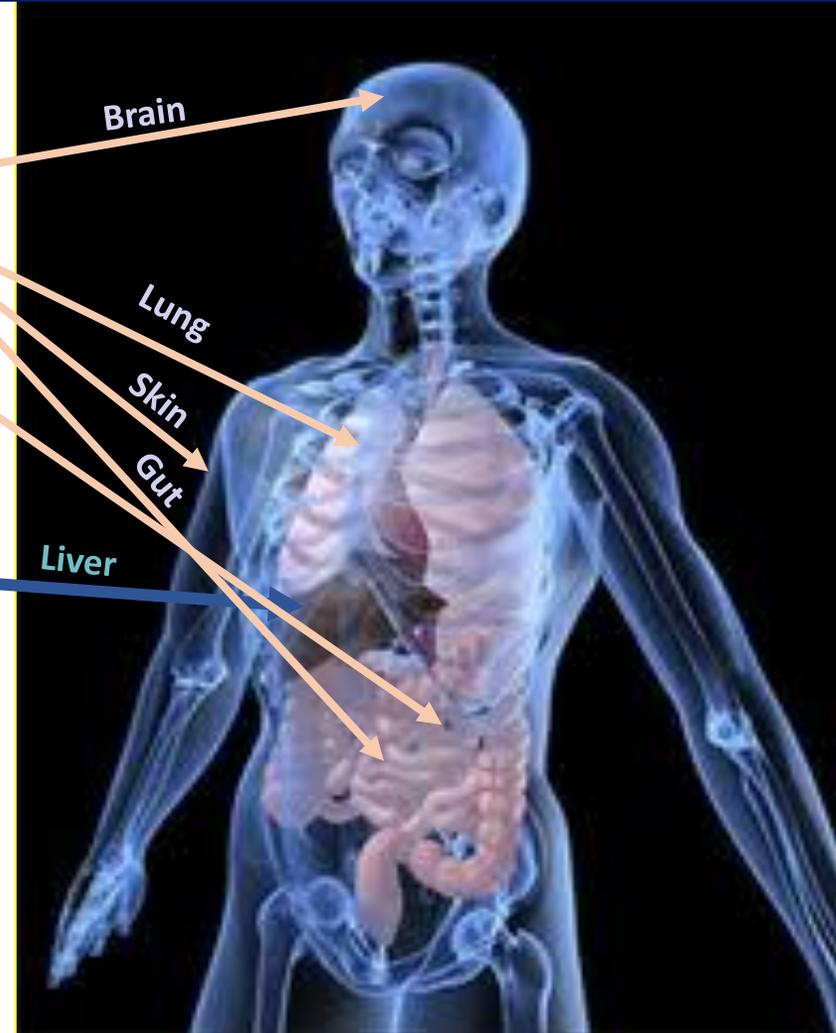
after procedural pain (heel prick), uniform negative

Reference	Study design and pain model	Paracetamol dosing	Results
Shah et al. Arch Dis Child Fetal Neonatal Ed 1998	Double blind placebo controlled trial 75 term neonates, heel prick. Facial action pain scores and cry score.	Single oral paracetamol 20 mg/kg or placebo, 60 to 90 min before prick.	No differences in facial action pain scores, nor in cry score.
Bonetto et al. Arch Argent Pediatr 2008	Prospective randomized trial 76 term neonates, heel prick pain scores (NIPS, neonatal infant pain score >4)	Placebo, dextrose (25%) EMLA or oral paracetamol (20 mg/kg, 60 min)	NIPS <4 similar between placebo, paracetamol or ELMA (47, 42 and 63 %). Oral dextrose most effective (84% NIPS <4, NNT 2.7)
Badiee et al. Saudi Med J 2009	Randomized placebo controlled trial in 72 preterm (mean 32 weeks) neonates, heel prick PIPP (premature infant pain profile) score	Single (high dose) oral paracetamol (40 mg/kg) 90 minutes before prick.	PIPP scores placebo (9,7, SD 4.2) were similar to paracetamol (11.1, SD 3.8)

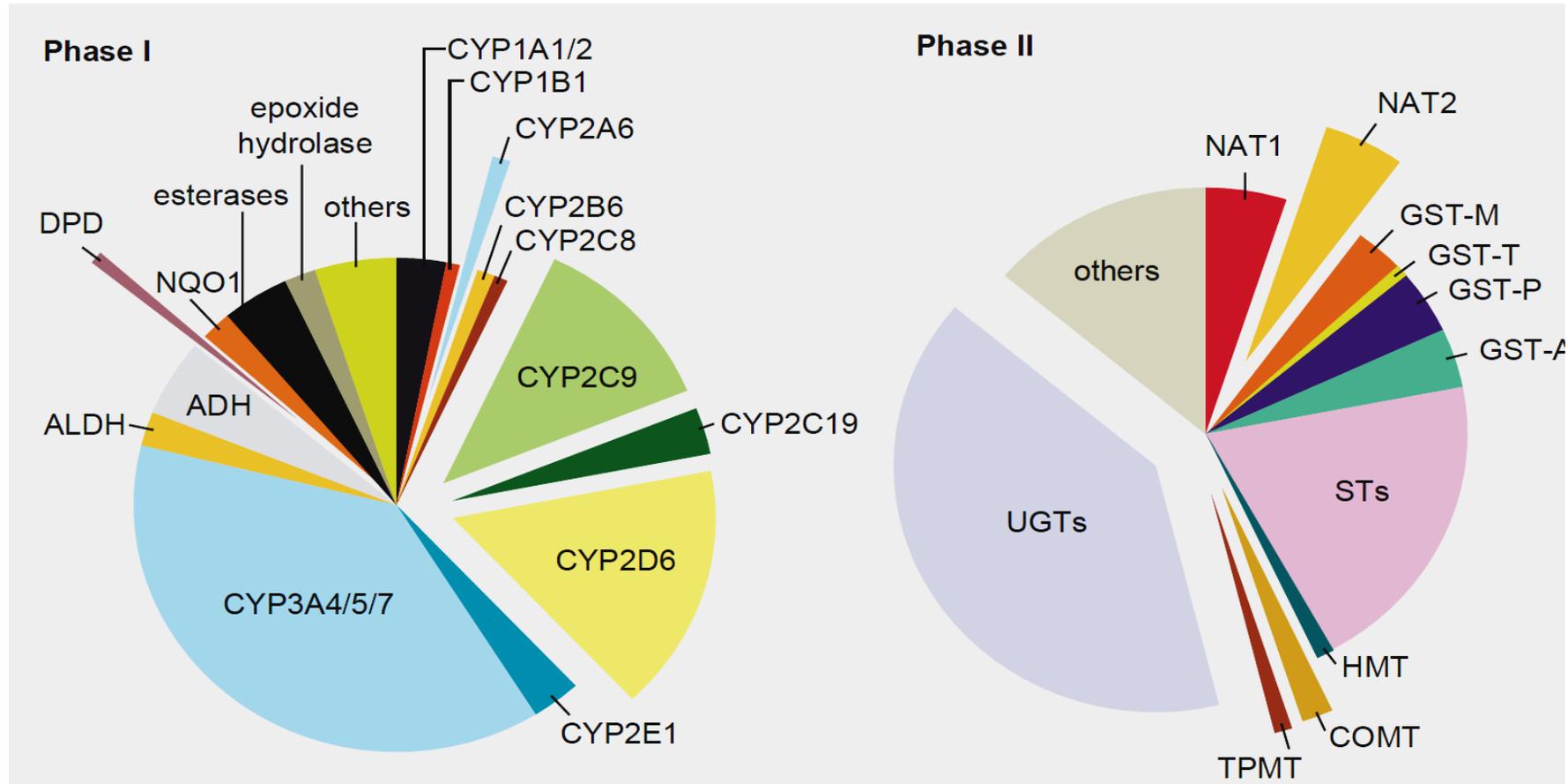
clearance: metabolism + excretion/elimination

Extrahepatic enzymes

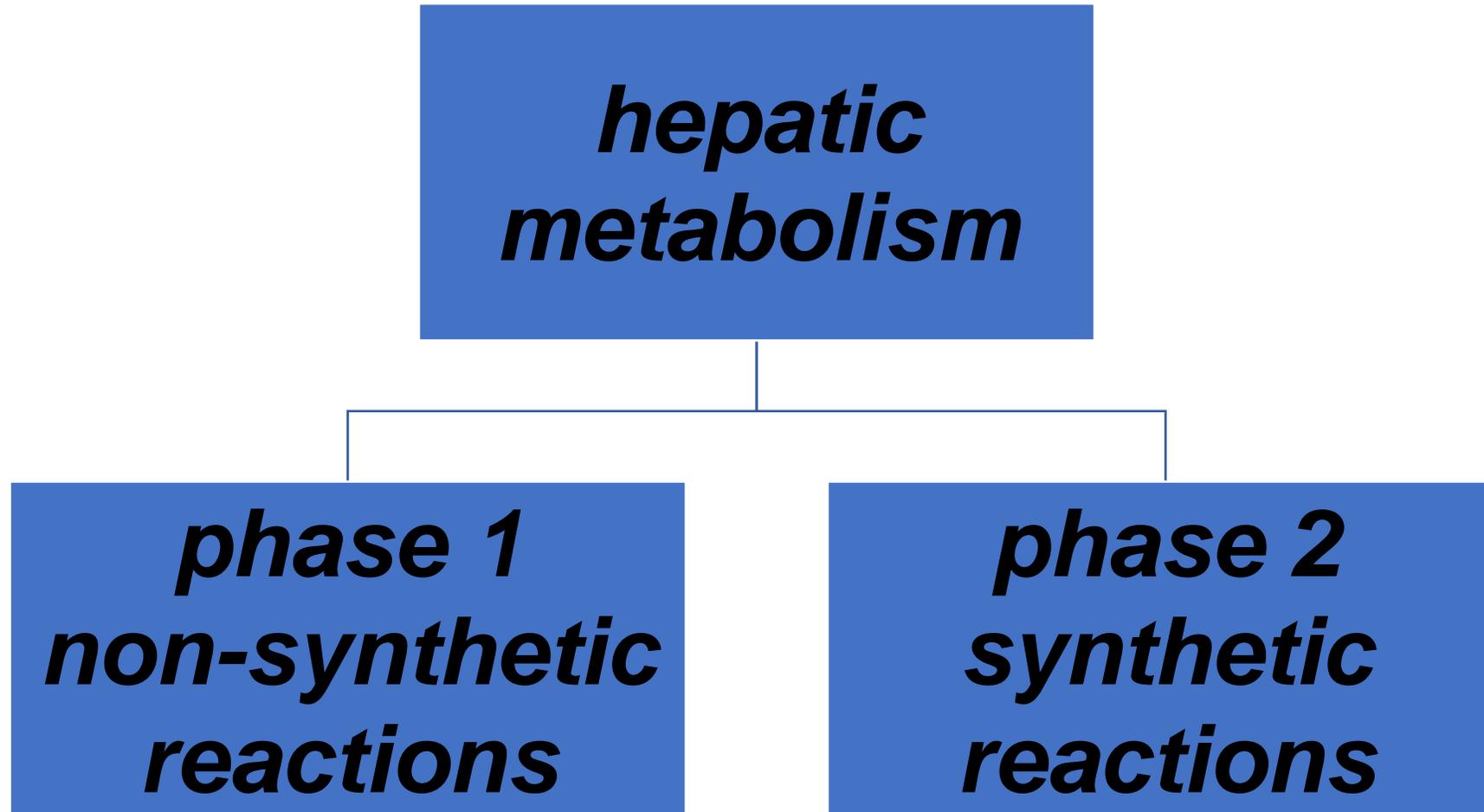
Hepatic enzymes



Phase I and phase II metabolism, enzymes



Phase I and phase II metabolism, enzymes



Phase I and phase II metabolism, enzymes

herbal medicine



disease



drugs



genetics

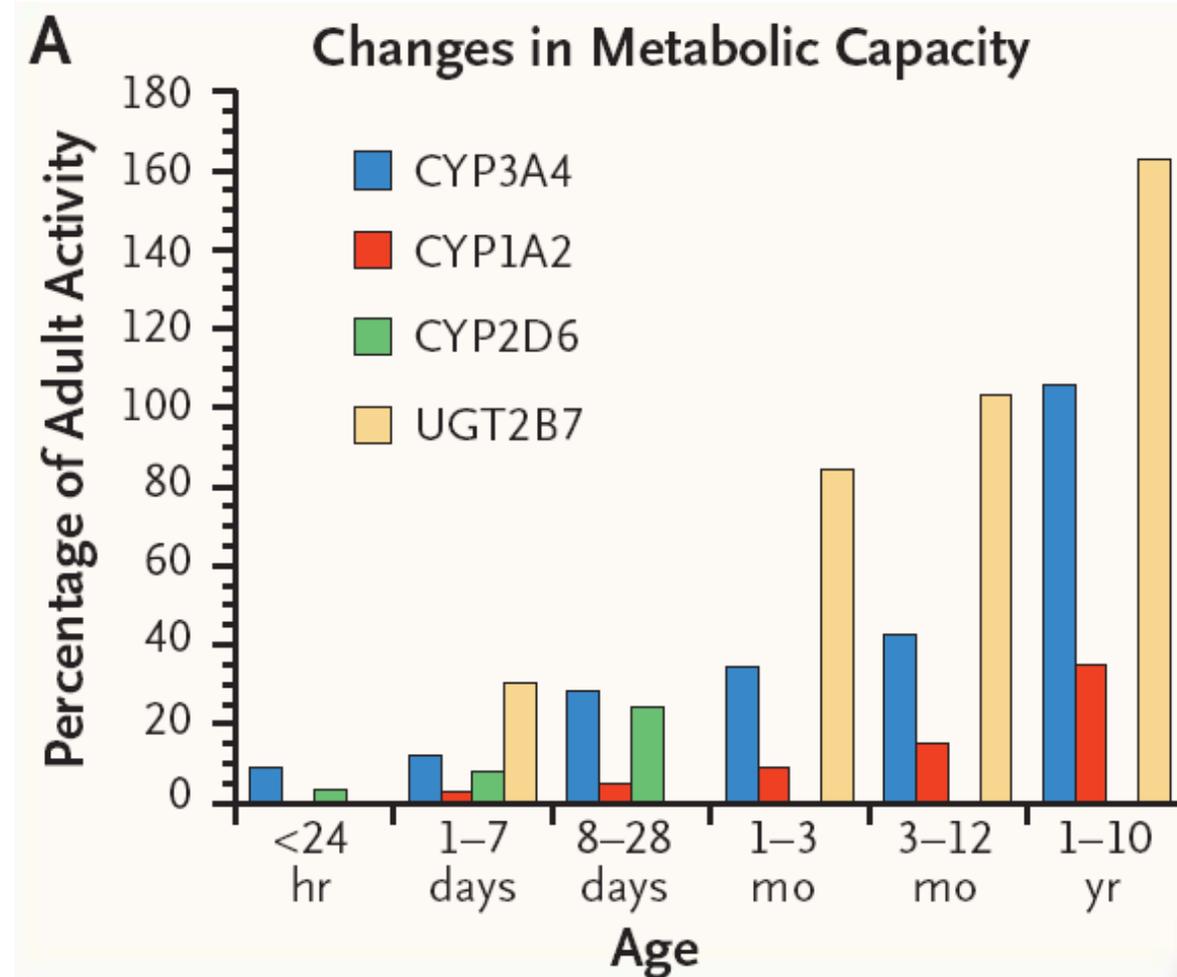


age

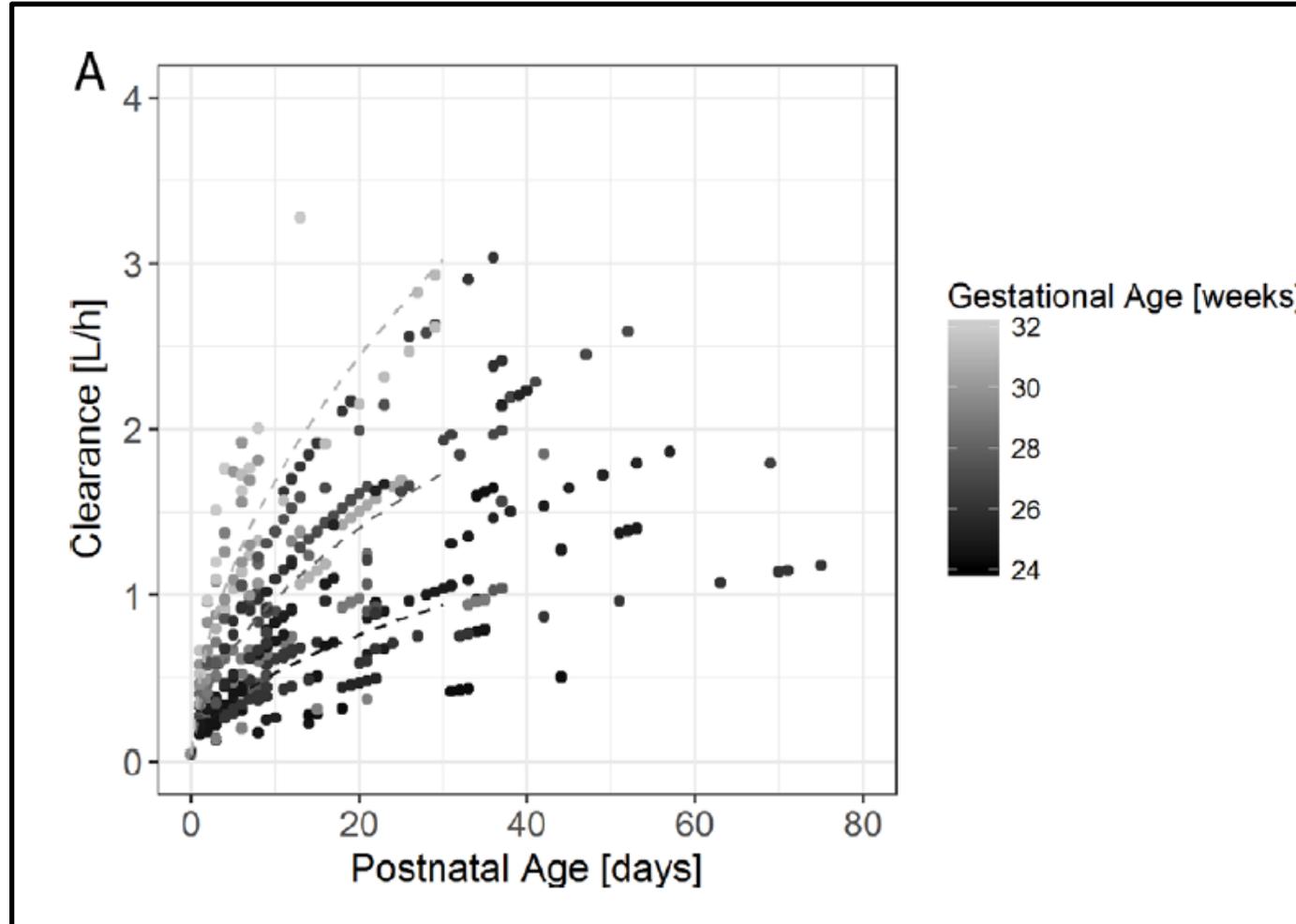


nutrition

Age related maturation is the common main driver, but...



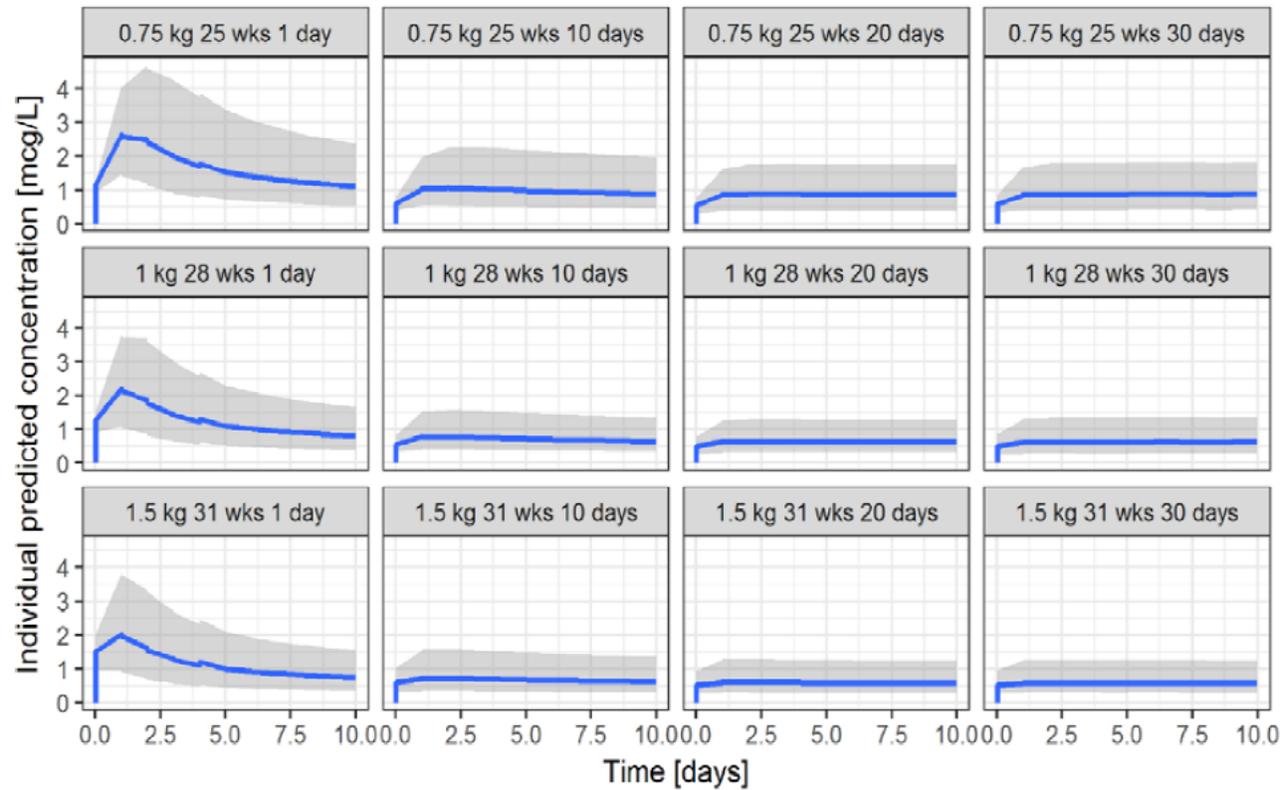
fentanyl clearance as a first illustration



fentanyl clearance as a first illustration

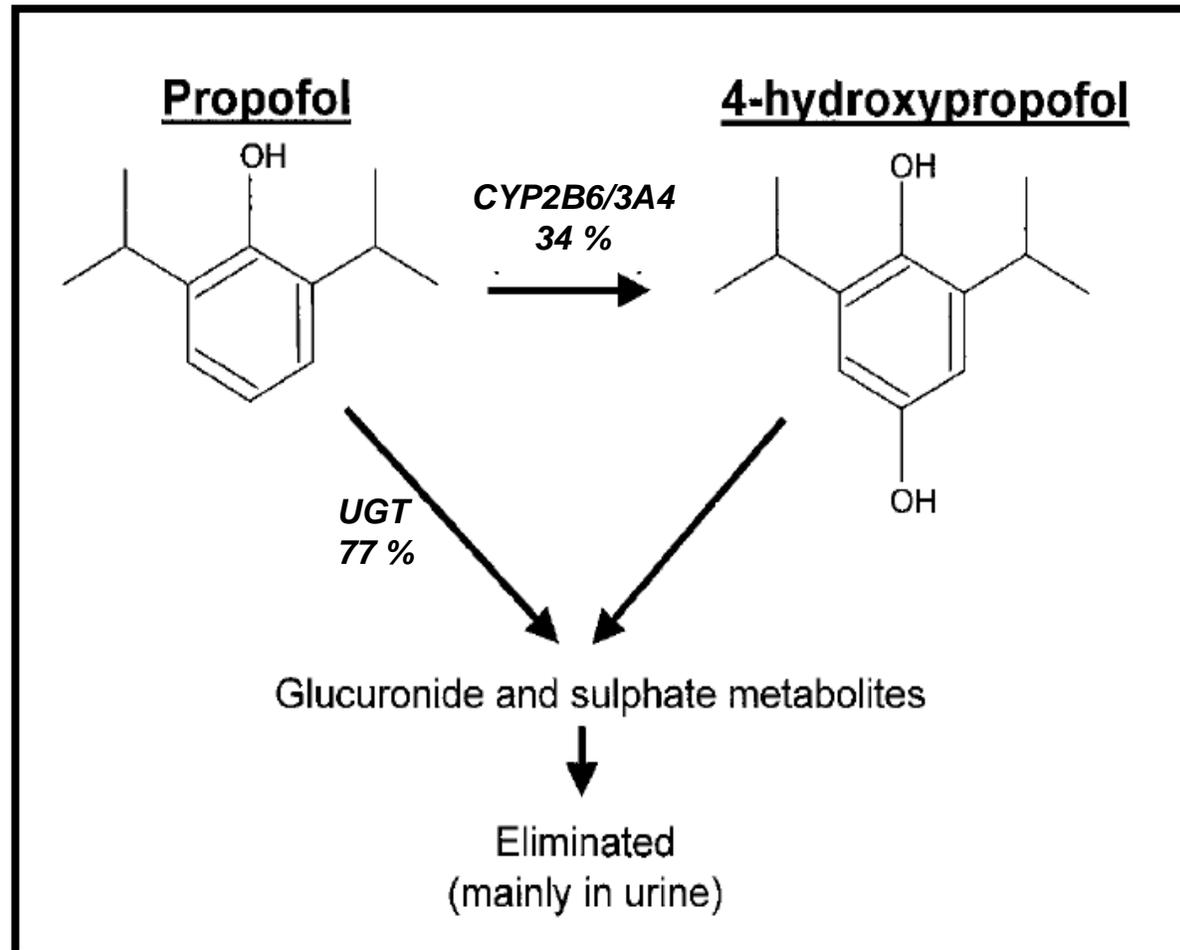
B

Continuous infusion of 1mcg/kg/h over 10 days

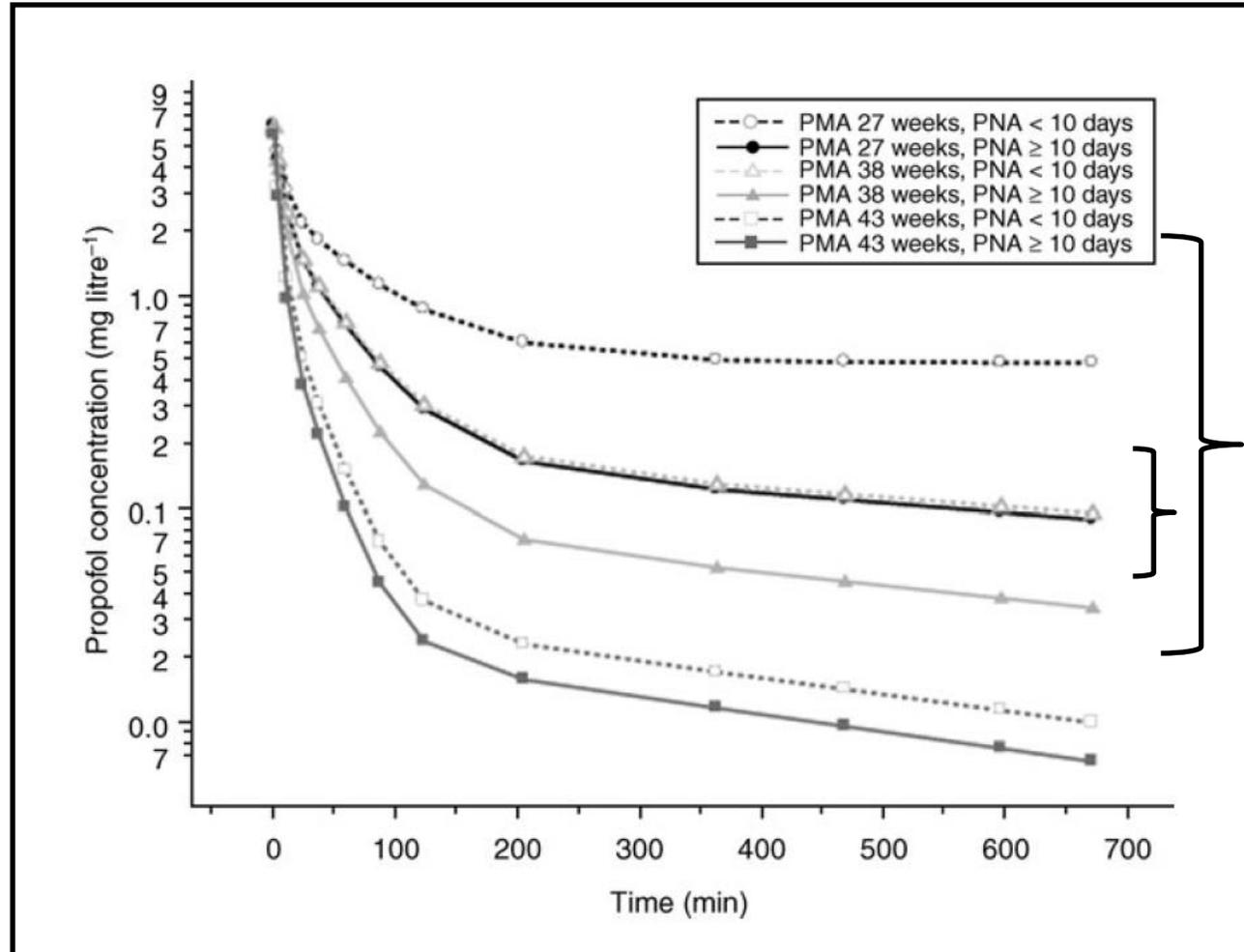


propofol clearance as second illustration

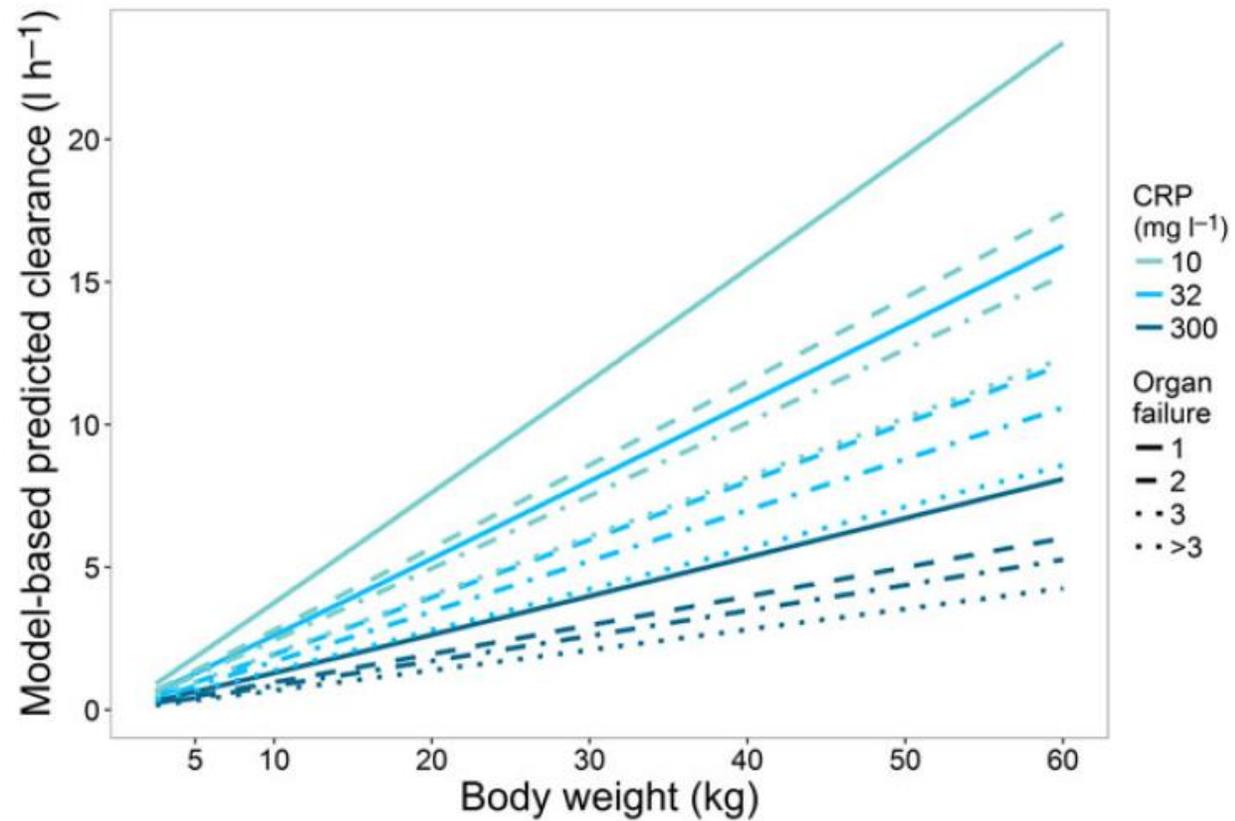
High capacity, low specificity : glucuronidation
Low capacity, high specificity: CYP2B6



propofol clearance as second illustration



midazolam clearance as final illustration: age and disease !



midazolam clearance as final illustration: age and disease, AKI !

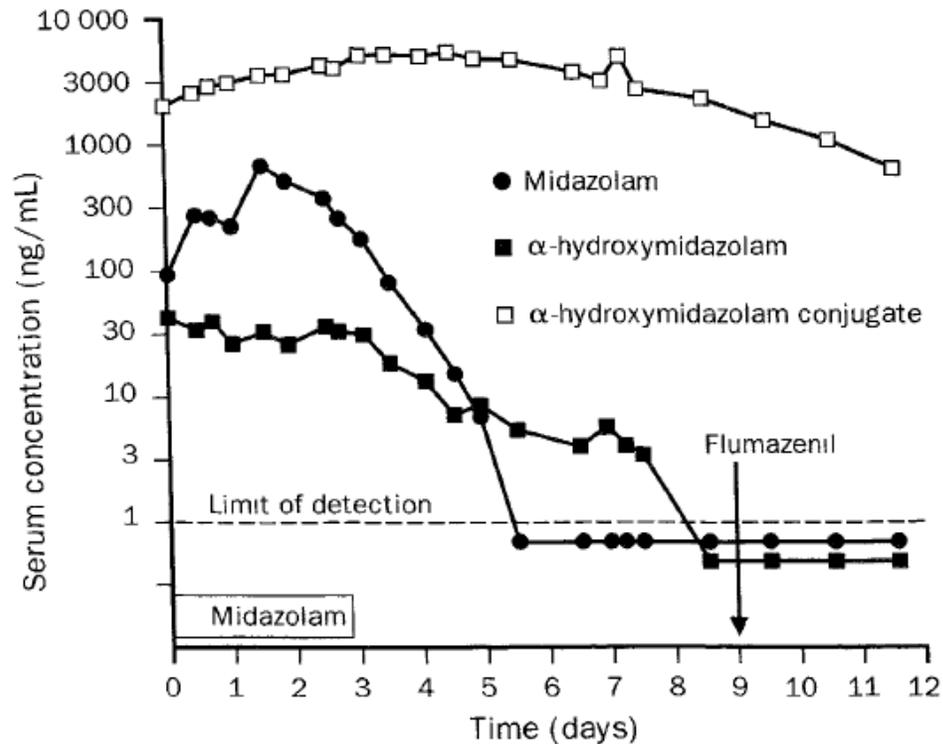


Figure 1: **Serum concentration time profile of midazolam and metabolites in patient 1.**

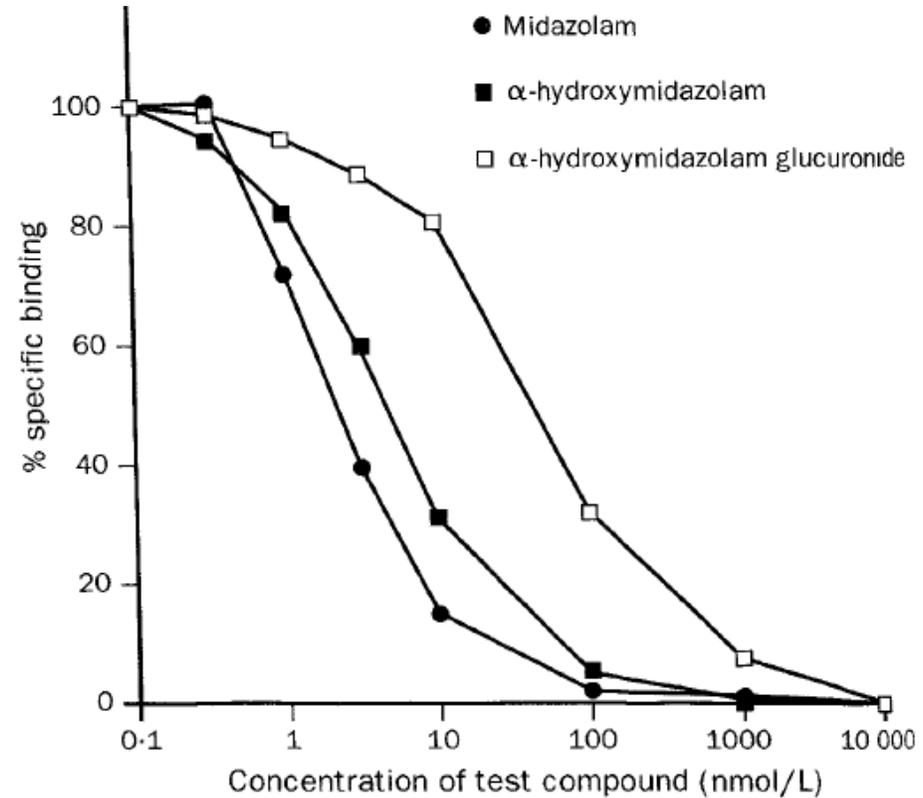
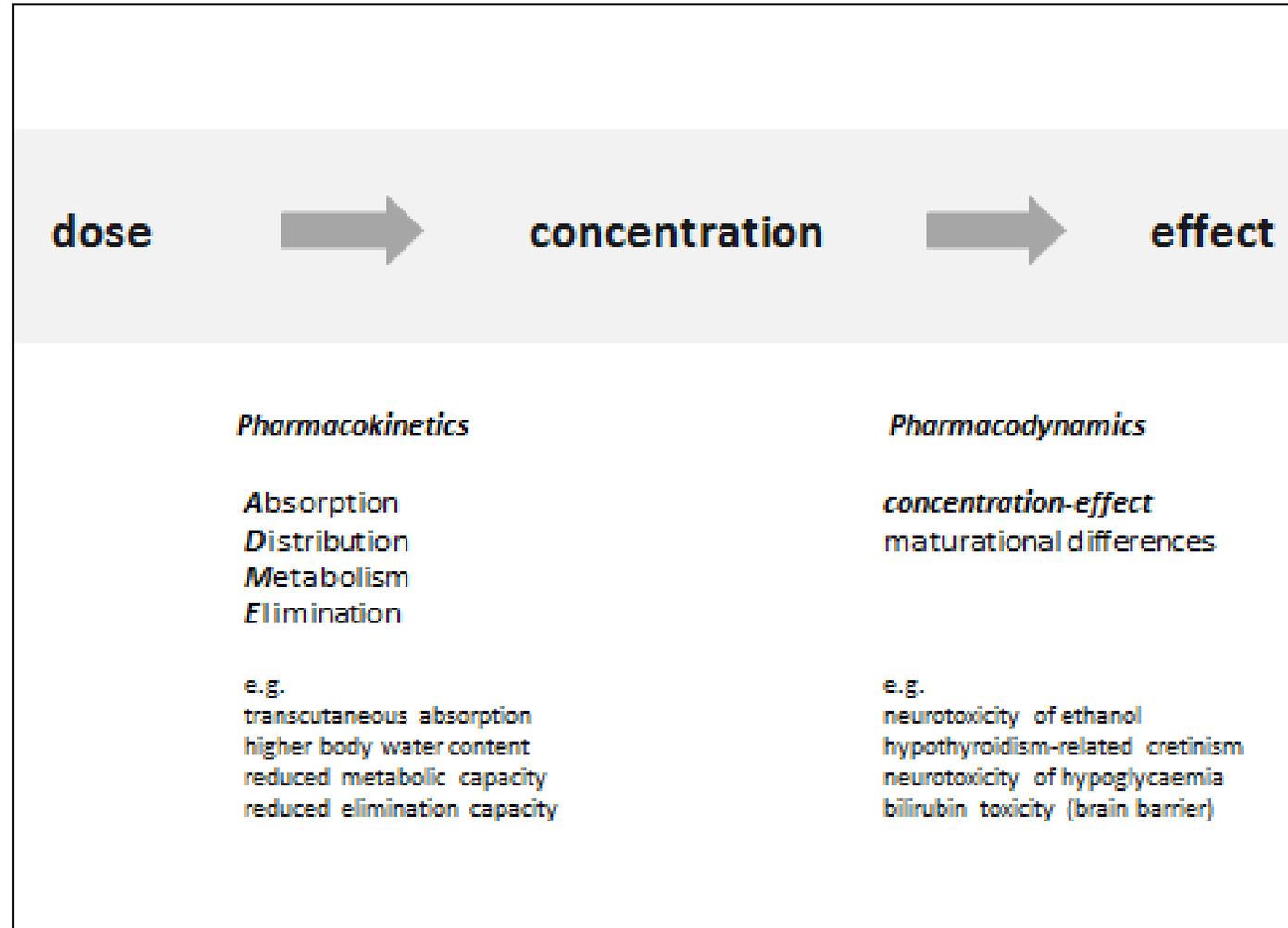


Figure 2: **Displacement of specific tritiated-flumazenil binding to rat cortical membranes by midazolam and metabolites.**

the framework (clin pharm) to work with: PD



Reasonable to assume (pediatric vs adult)
- Similar disease progression?
- Similar response to intervention?

No

Yes to both

Conduct PK studies
Conduct safety/efficacy trials

Reasonable to assume similar
CR in pediatrics and adults

No

No

Yes

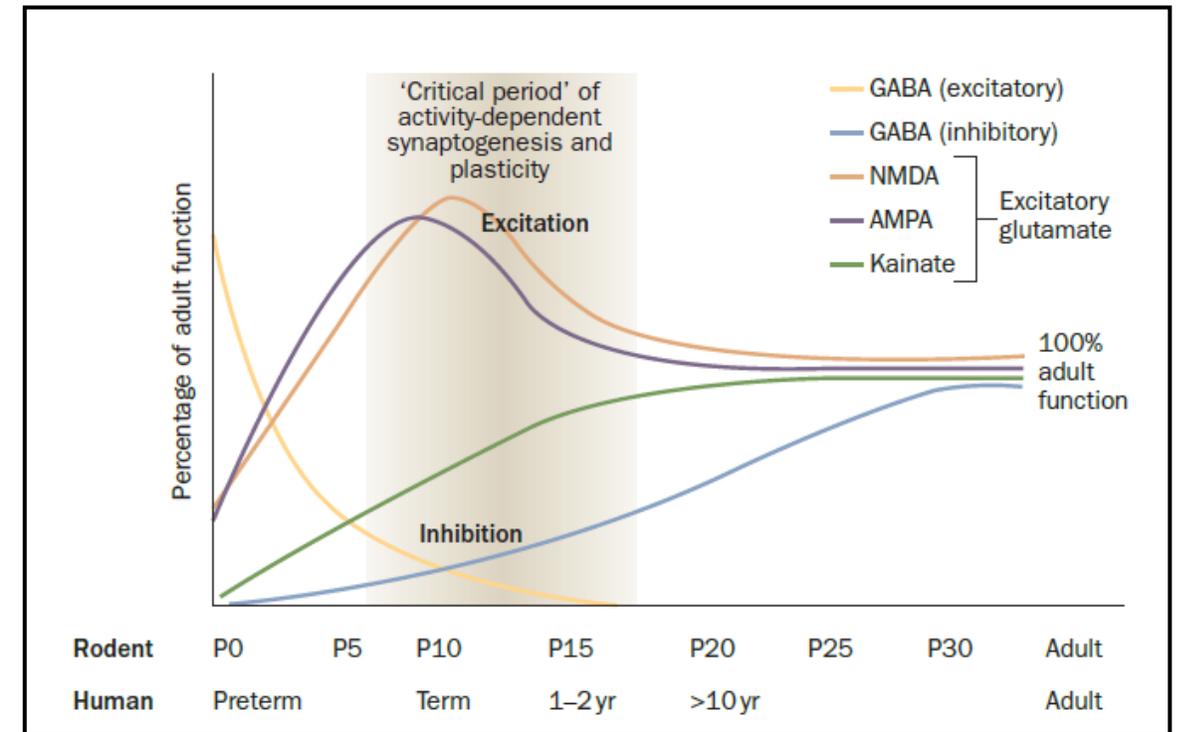
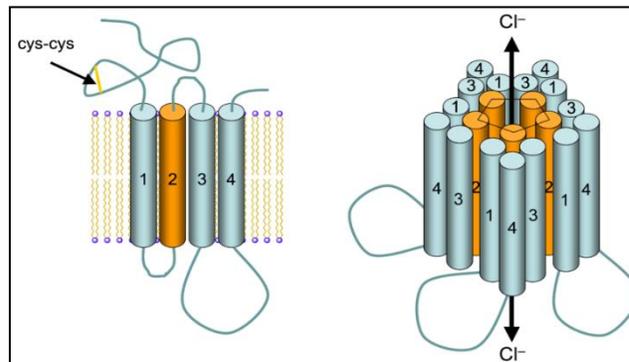
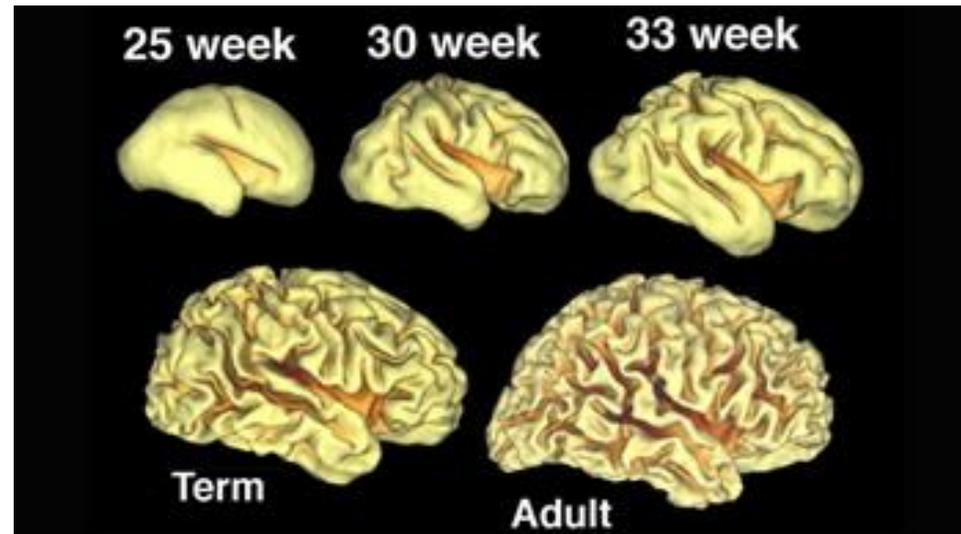
Is there a PD measurement
that can be used to
predict efficacy?

Conduct PK studies to
achieve levels similar to adults
Conduct safety trials

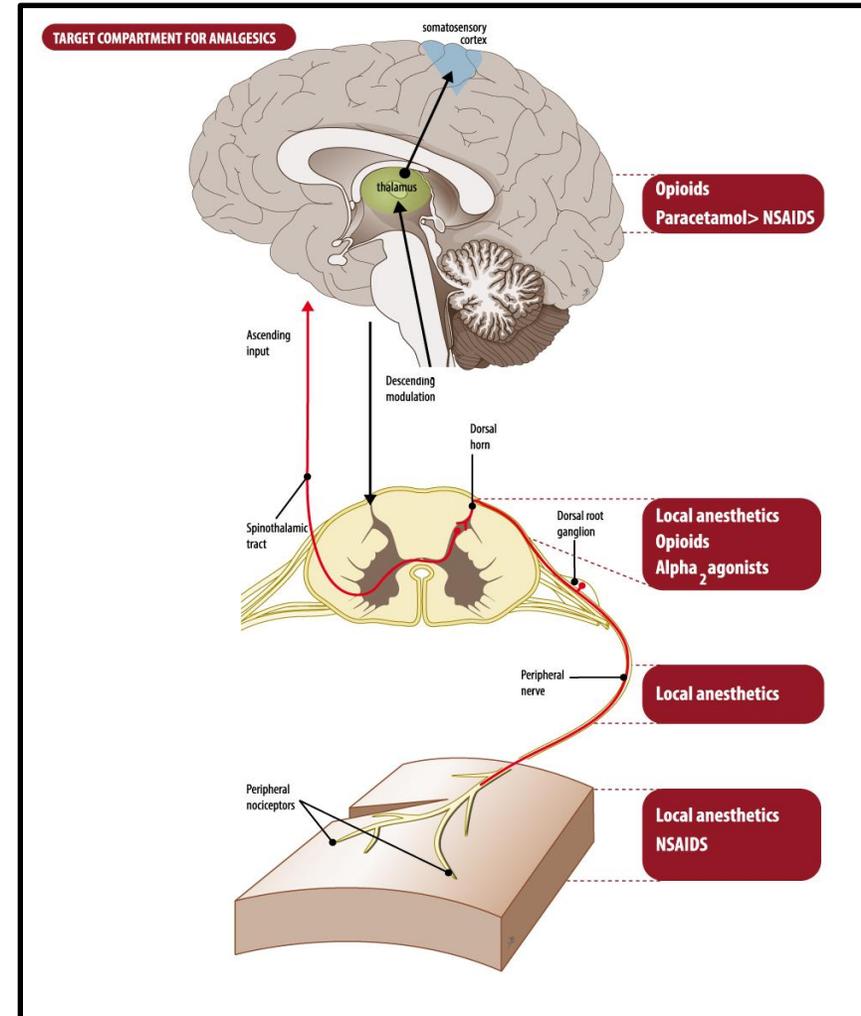
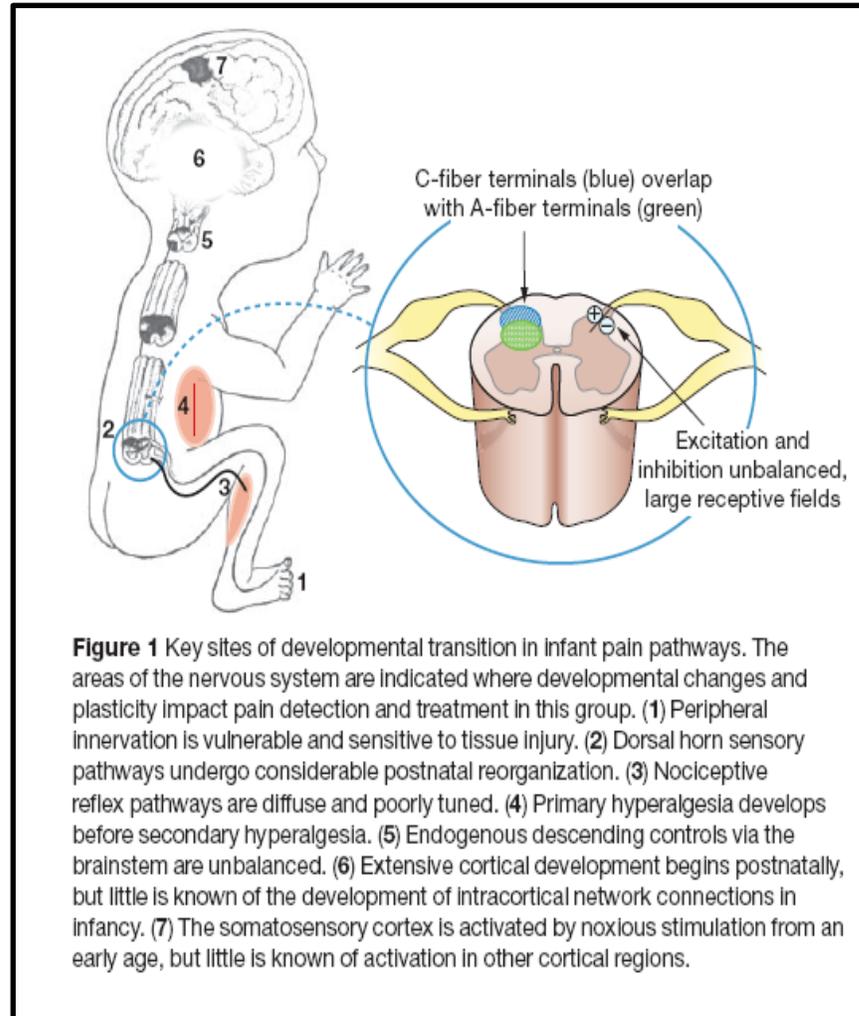
Yes

Conduct PK/PD studies to get CR for PD measurement
Conduct PK studies to achieve target concentrations based on CR
Conduct safety trials

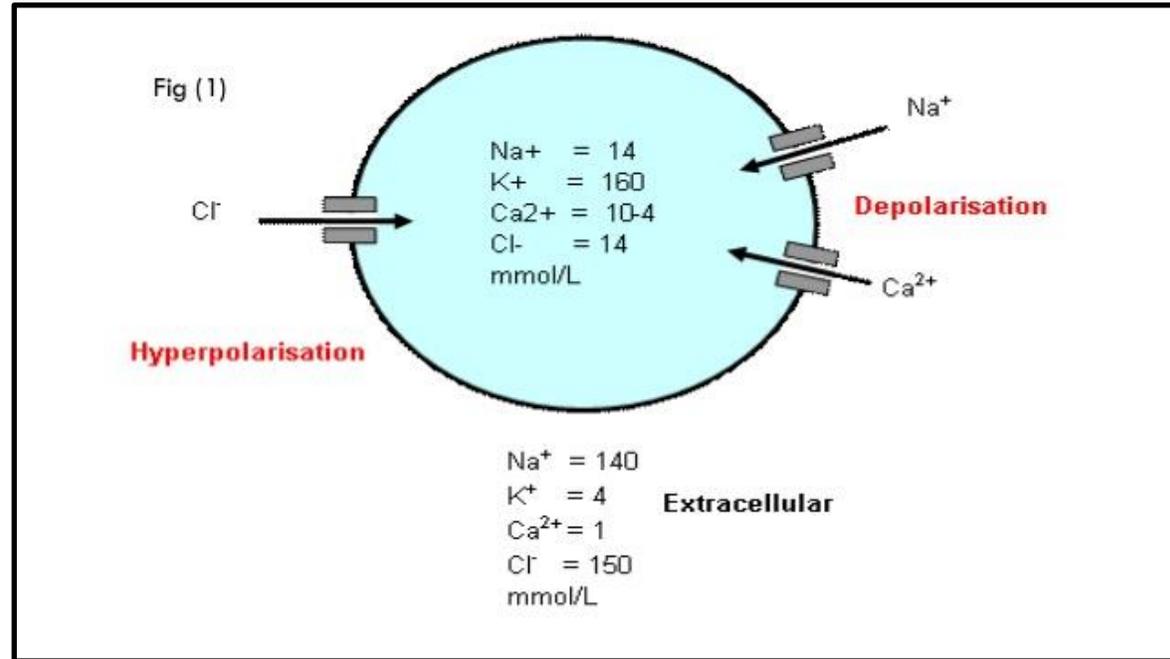
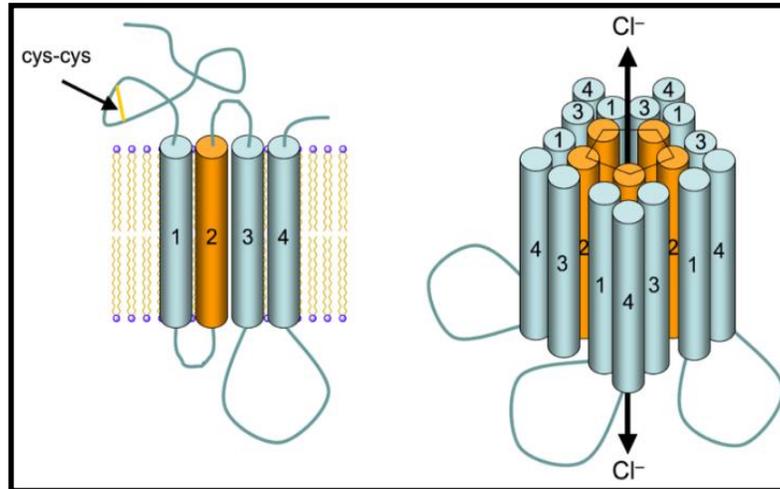
the framework (clin pharm) to work with: PD-target



the framework (clin pharm) to work with: PD-target



the framework (clin pharm) to work with: PD-target

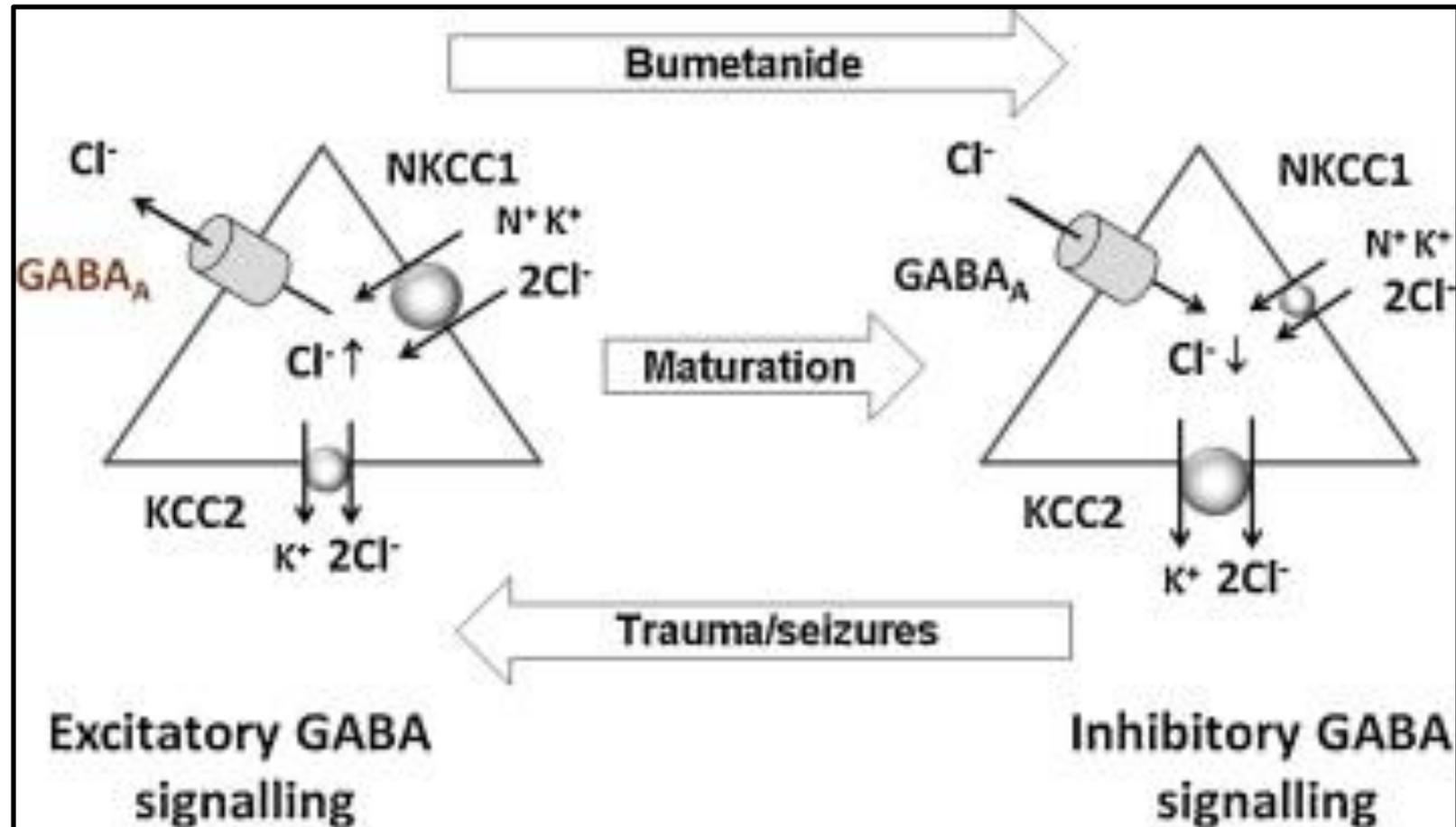


Open chloride receptor-channels induce hyperpolarisation by increasing intracellular chloride two types of receptors, GABA-a and GABA-b (G-protein coupled mechanism).

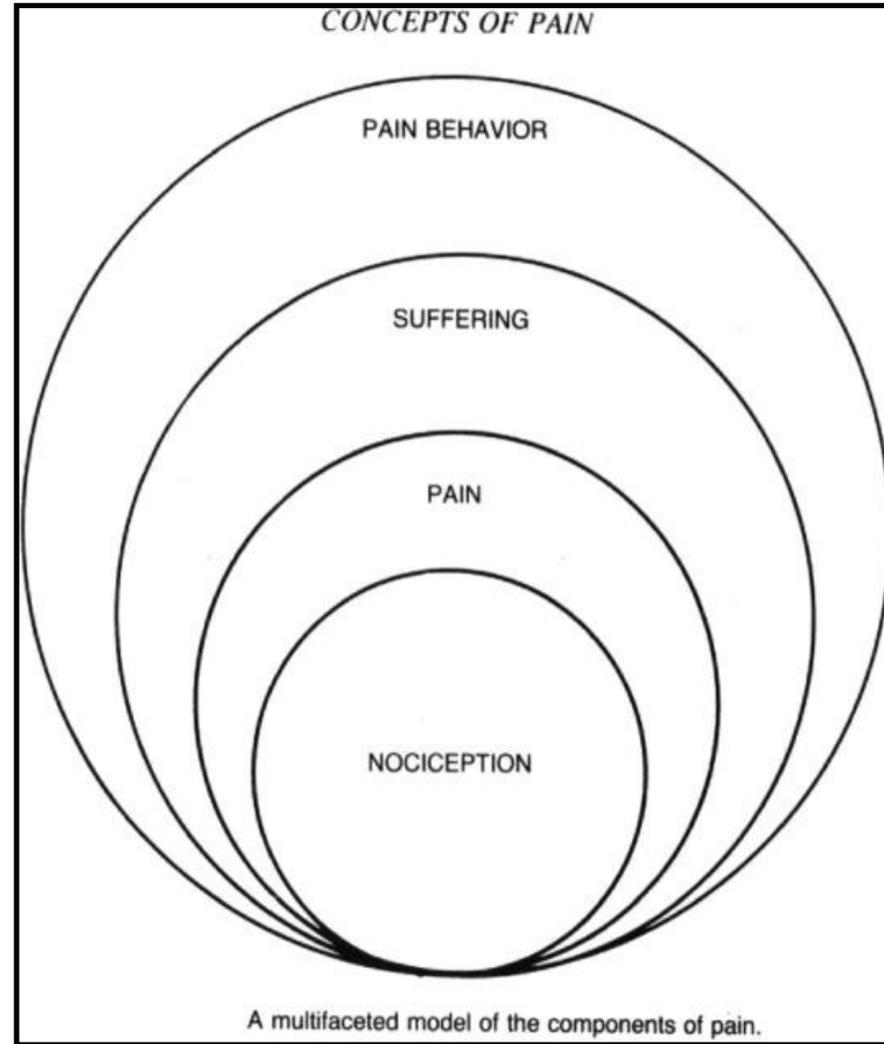
GABA release reduction and K efflux

Compounds of interest: benzodiazepines, propofol

the framework (clin pharm) to work with: PD-target



the framework (clin pharm) to work with: PD-assessment



the framework (clin pharm) to work with: PD-assessment (scores)

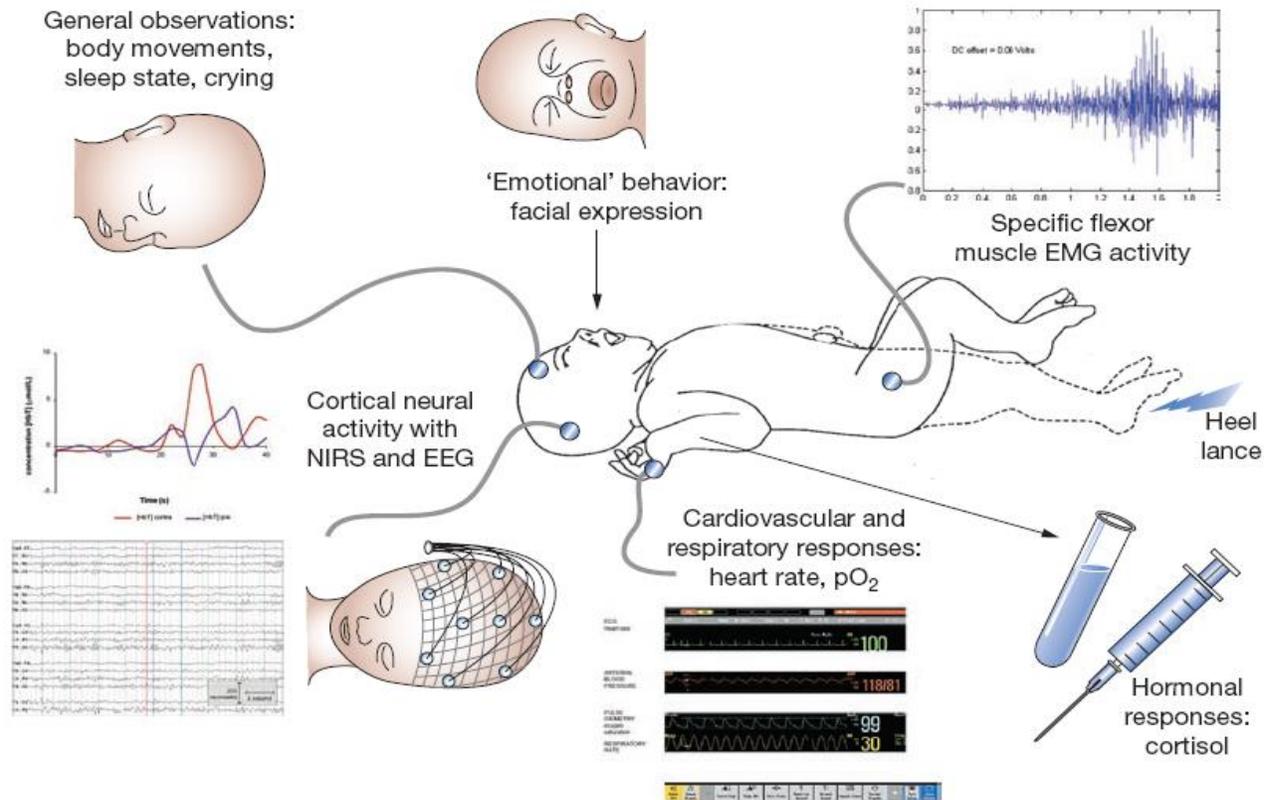


Figure 2 Methods of assessing infant pain. In the absence of language, infant pain is assessed by a number of different physiological methods. Some of these methods are integrated into current clinical pain assessment tools. The neurophysiological techniques EMG, EEG and NIRS are not used for routine pain assessment but are increasingly being used in research studies of infant pain. Abbreviations: EMG, electromyogram; NIRS, near-infrared spectroscopy; pO₂, partial pressure of oxygen.

the framework (clin pharm) to work with: PD-assessment

Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial



Rebecca Slater, Laura Cornelissen*, Lorenzo Fabrizi*, Debbie Patten, Jan Yoxen, Alan Worley, Stewart Boyd, Judith Meek†, Maria Fitzgerald†

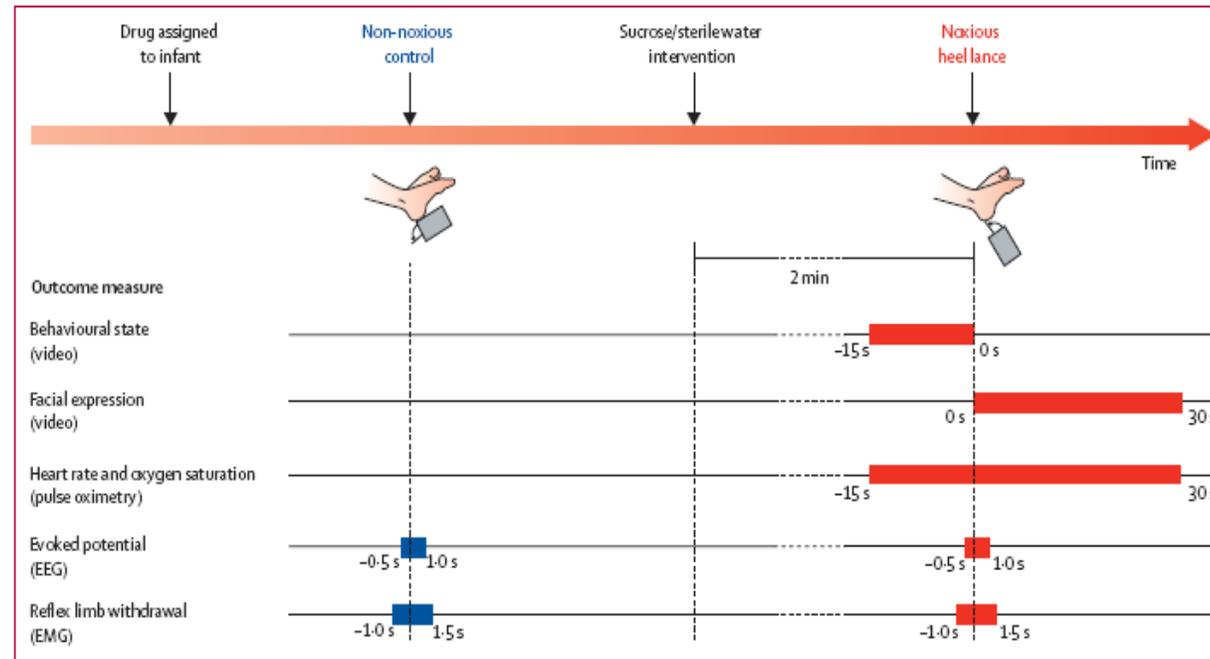


Figure 1: Experimental time line
EEG=electroencephalography. EMG=electromyography.

the framework (clin pharm) to work with: PD-assessment

Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial

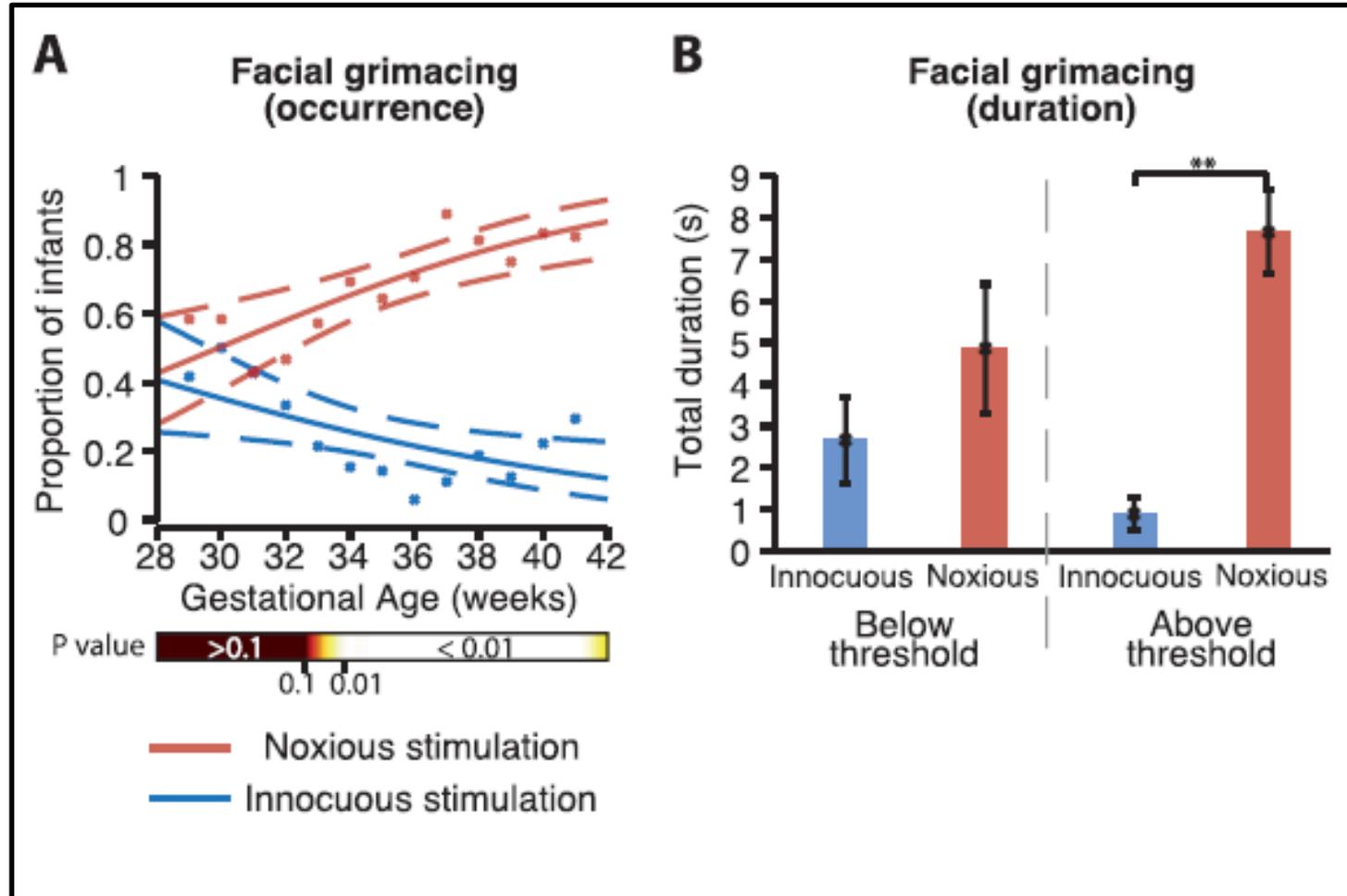


Rebecca Slater, Laura Cornelissen*, Lorenzo Fabrizi*, Debbie Patten, Jan Yoxen, Alan Worley, Stewart Boyd, Judith Meek†, Maria Fitzgerald†

	Sucrose (N=20)	Sterile water (N=24)	p value
Primary outcome			
Nociceptive-specific brain activity (mean weight)	0.10 (0.04-0.16)	0.08 (0.04-0.12)	0.46
Secondary outcomes			
Mean baseline heart rate (bpm)	132.6 (124.3-140.9)	131.8 (122.2-141.5)	0.90
Mean baseline oxygen saturation (%)	99.4% (98.8-100.1)	97.4% (95.0-99.8)	0.13
Baseline behavioural score (from PIPP)	1.3 (0.8-1.7)	1.3 (0.8-1.8)	0.91
PIPP score	5.8 (3.7-7.8)	8.5 (7.3-9.8)	0.02
Latency to change in facial expression (s)	3.8 (1.3-6.4)	3.5 (1.0-6.1)	0.86
Facial non-responders	7/20 (35%)	0/24 (0%)	<0.0001
Mean nociceptive reflex withdrawal activity (μ V)	36.11 (24.20-48.02)	30.82 (18.51-43.13)	0.49
Mean latency to nociceptive reflex withdrawal activity (ms)	363.3 (256.4-470.1)	413.5 (262.0-564.9)	0.56

Data are mean (95% CI) or n/N (%). bpm=beats per min. PIPP=premature infant pain profile.

the framework (clin pharm) to work with: PD-assessment





THINK
POSITIVE
😊

polymorphisms matter, but...

**Association of *OPRM1* and *COMT*
Single-Nucleotide Polymorphisms
With Hospital Length of Stay and Treatment
of Neonatal Abstinence Syndrome**

polymorphisms are not limited to drug metabolism

