Procedural sedation and analgesia in the very young

practical pharmacology

PROSA2022

Erasmus MC Rotterdam, the Netherlands

KU Leuven, Belgium

karel.allegaert@uzleuven.be
k.allegaert@erasmusmc.nl

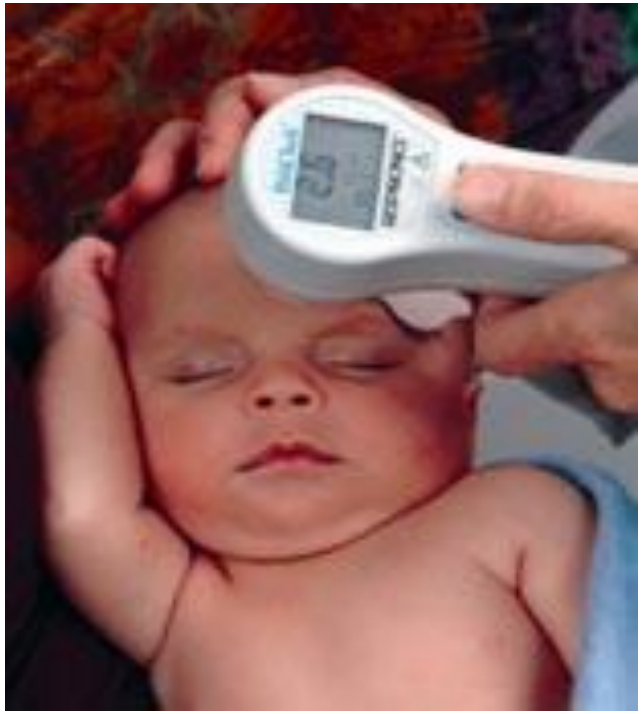
disclosure

No, I have no relevant financial relationships to disclose (off-label use will be discussed)

but

suggestion 1

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*

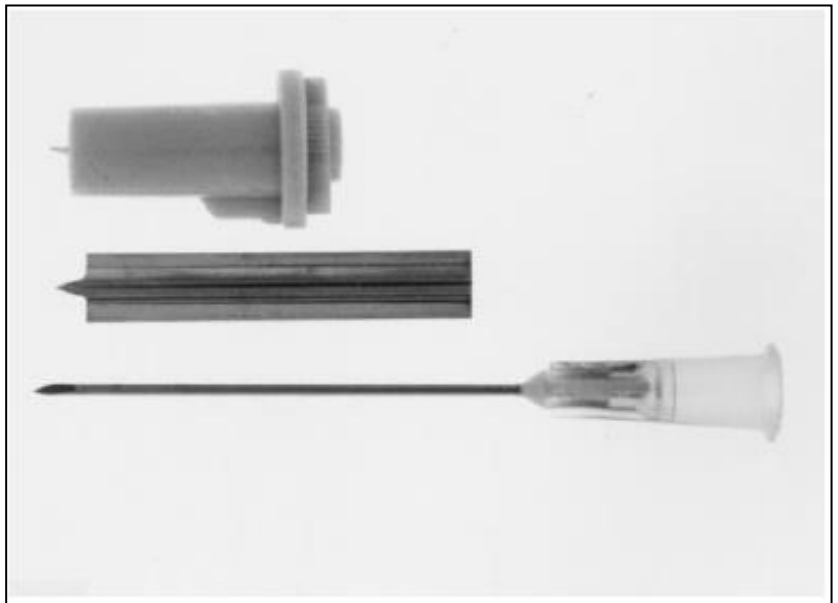


Fig 1. Three devices used for the PKU test. From the top: the CCS Minilancet used in the SL group, the Microlance used in the LL group, and the Microlance needle (0.9 × 40 mm) used in the VP group.

suggestion 3

PROSA2022

the formulary/toolbox available

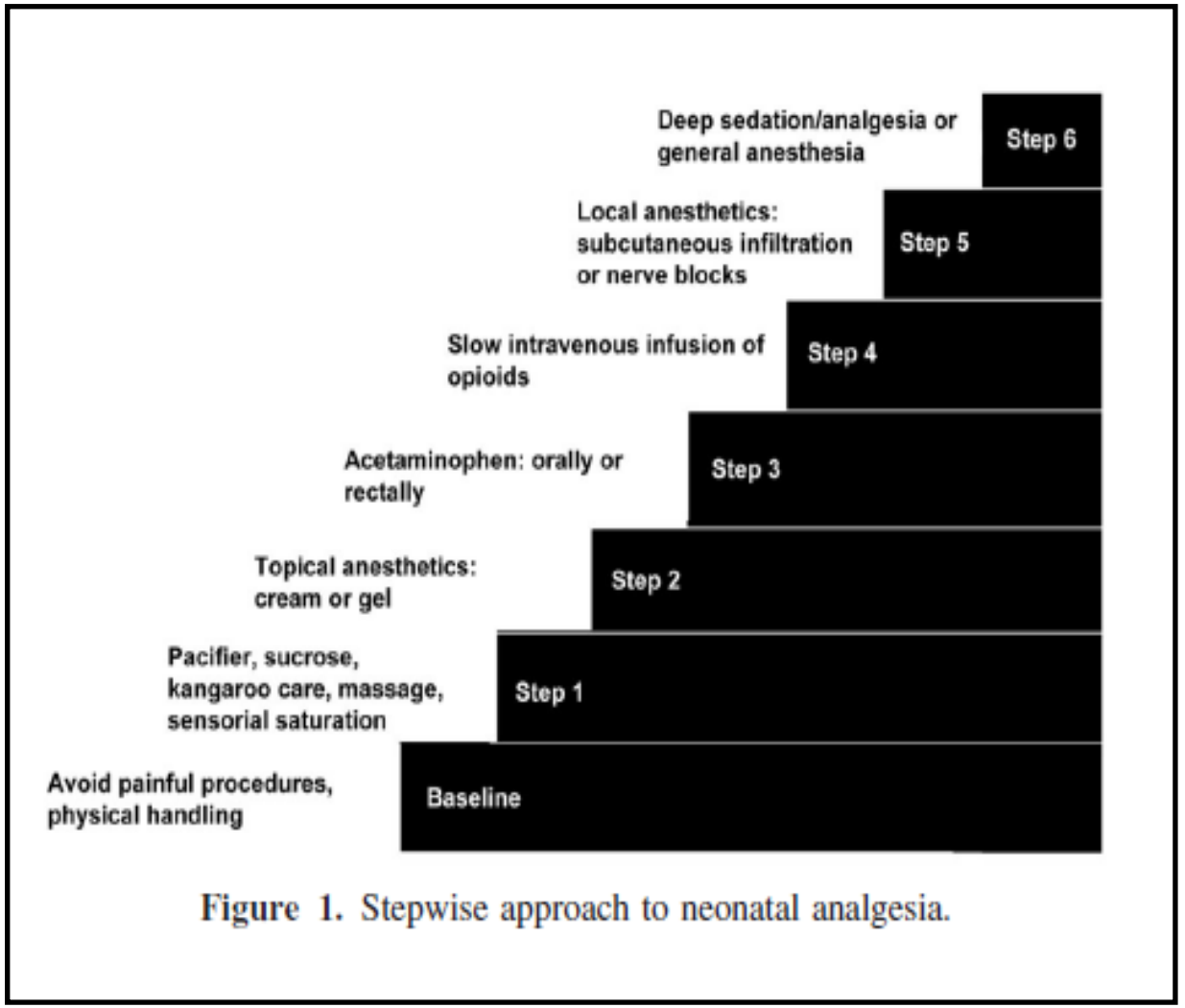
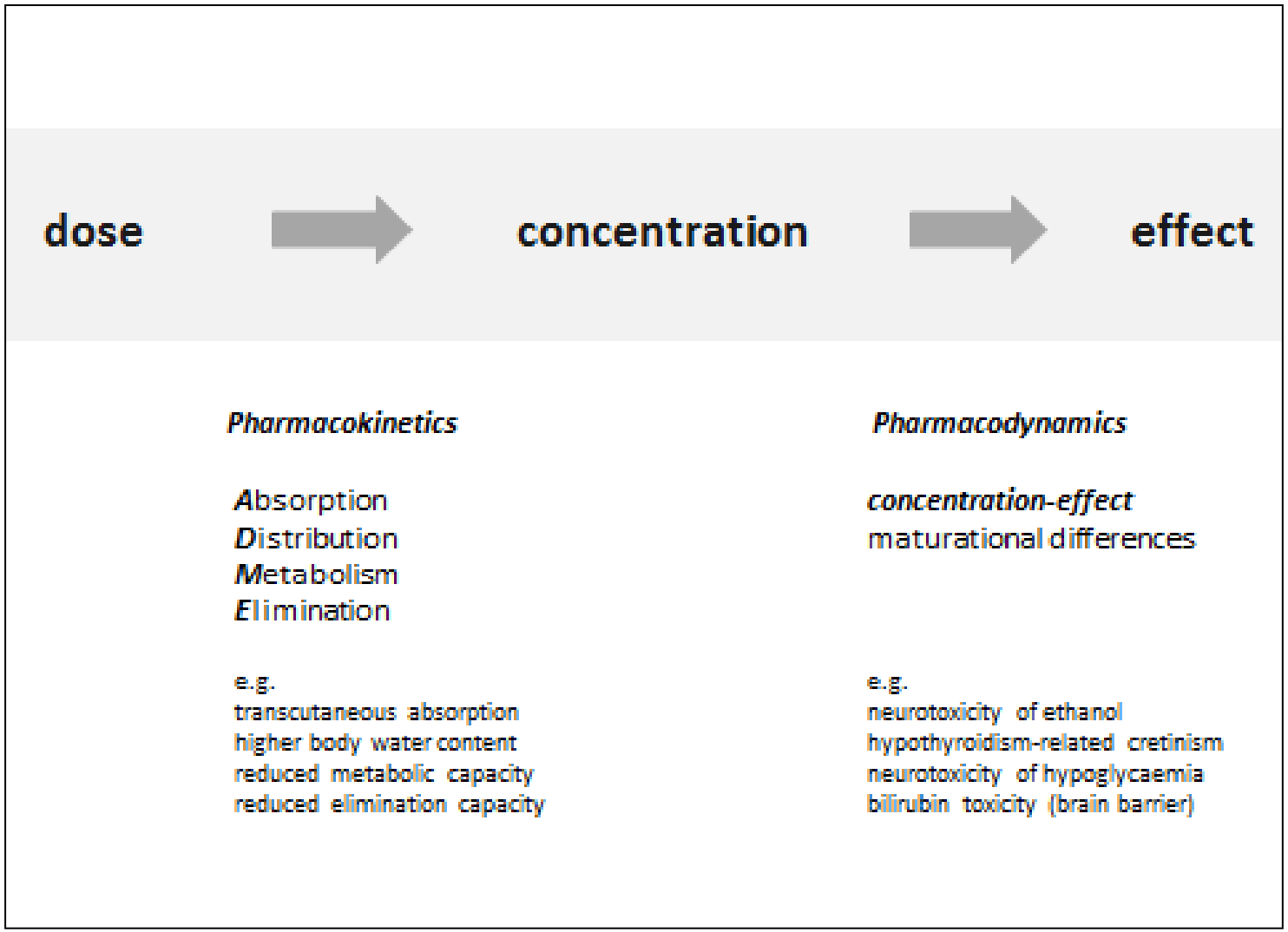
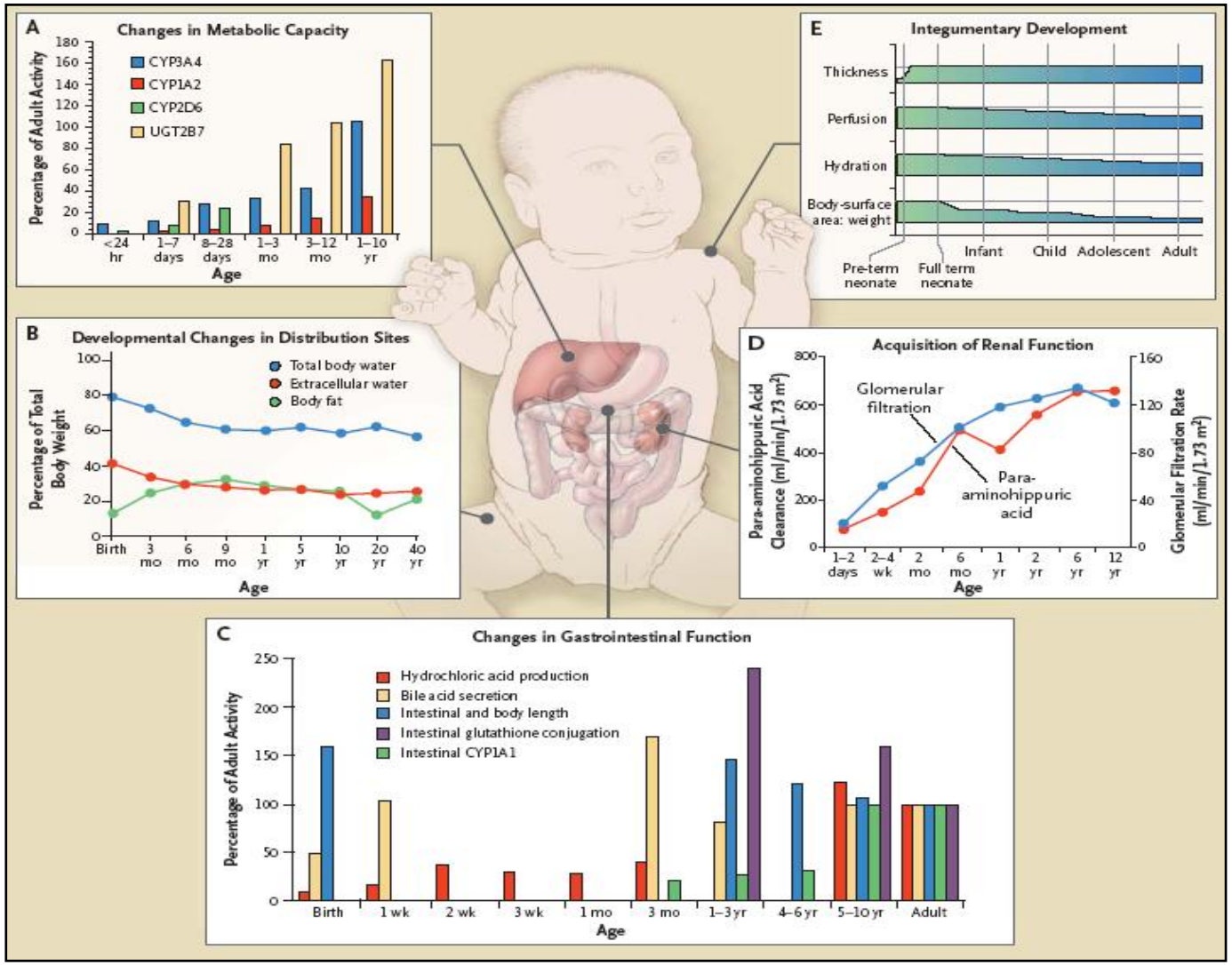


Figure 1. Stepwise approach to neonatal analgesia.

the framework (clin pharm) to work with: PK



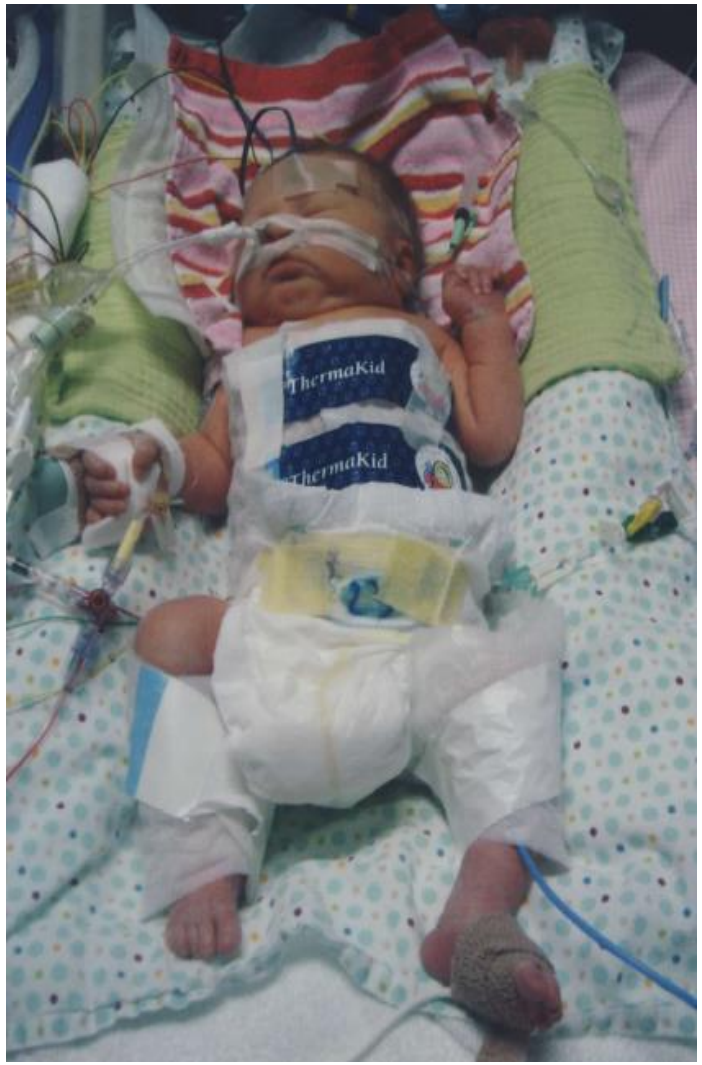
the patient to aim for: a moving target (ADME)

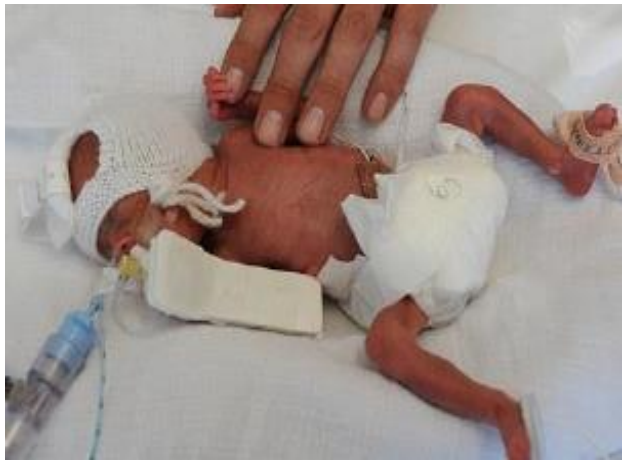


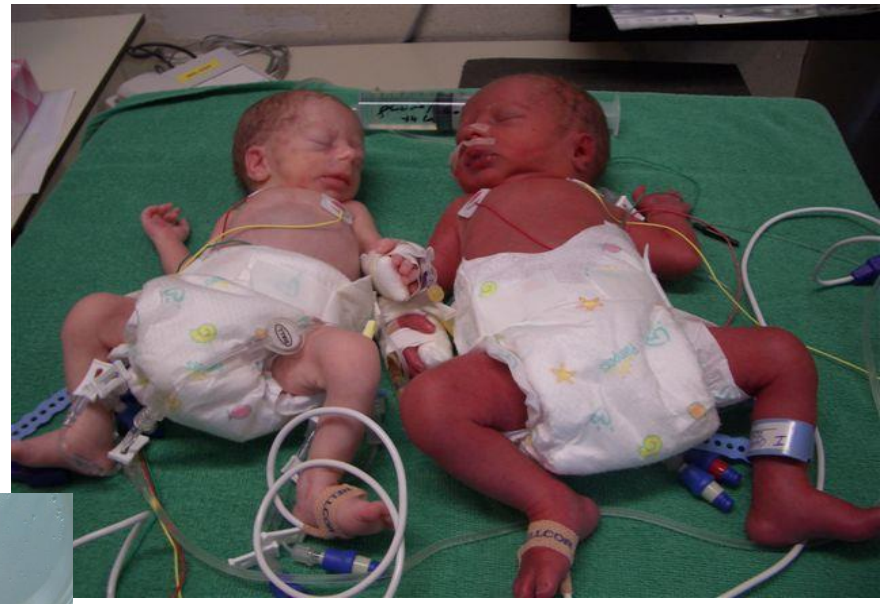
Kearns et al, NEJM 2003

PROSA2022

neonatal pharmacokinetics: ADME
maturational and non-maturational covariates

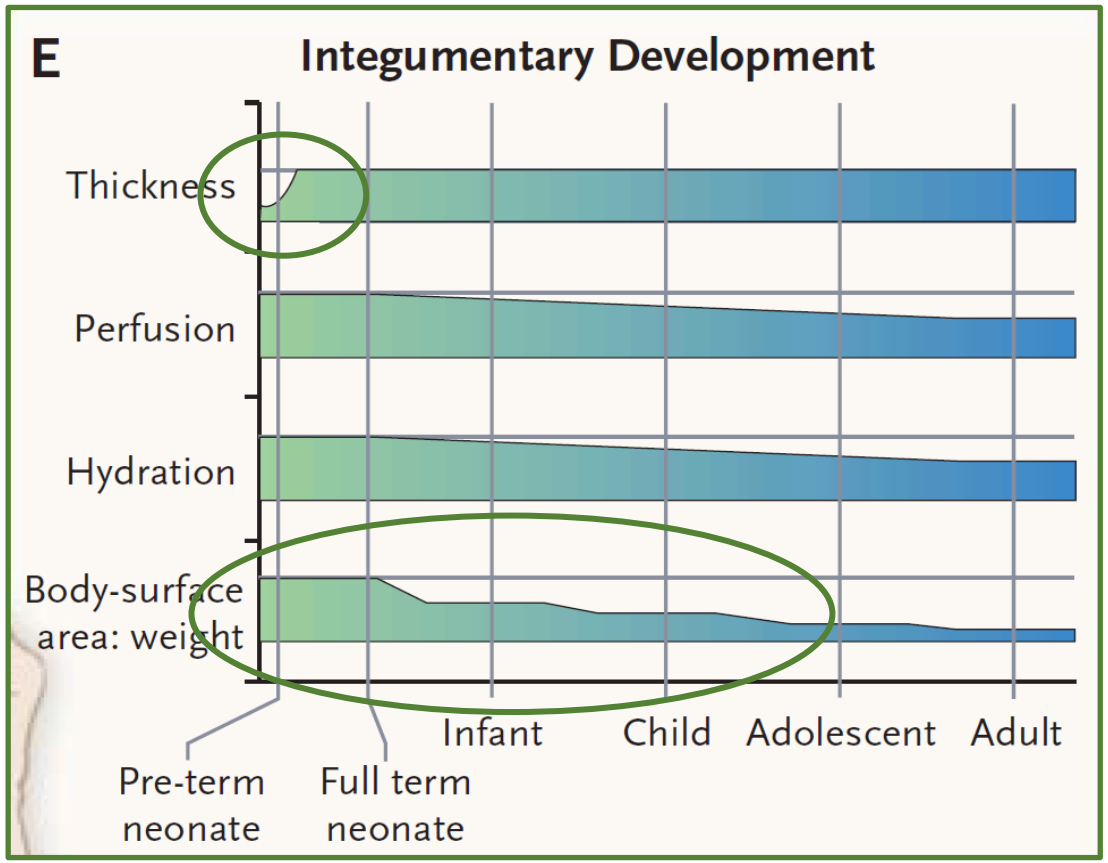


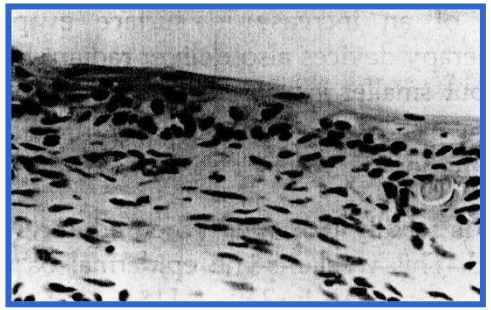


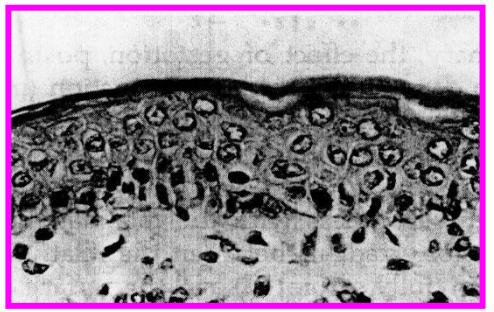


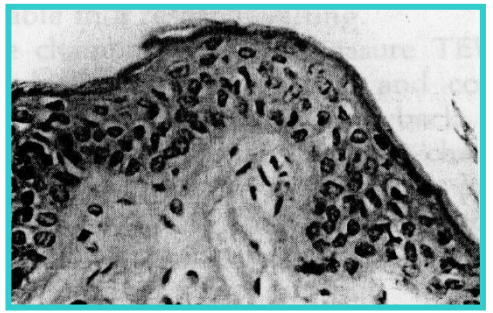
PROSA2022

absorption, skin: BSA > permeability









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

Kearns et al, NEJM 2003

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.

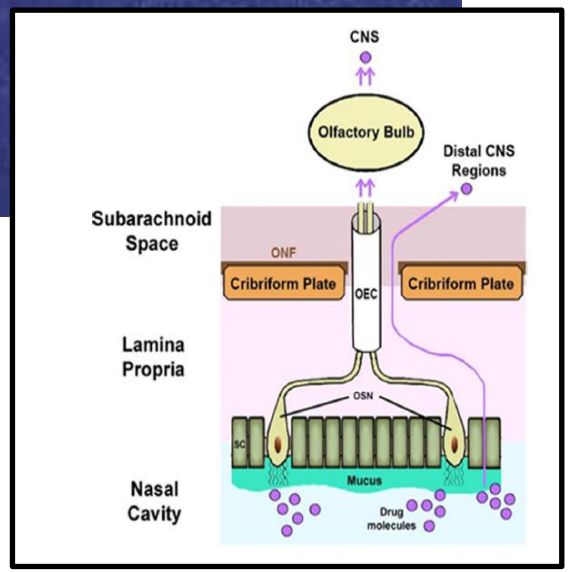
Preterm neonates are exposed to a range of painful procedures and topical anesthetics as EMLA are used routinely for pain management. Because premature neonates are low weight and consequently they are easily overdosed, routinely use of EMLA should be carefully evaluated.

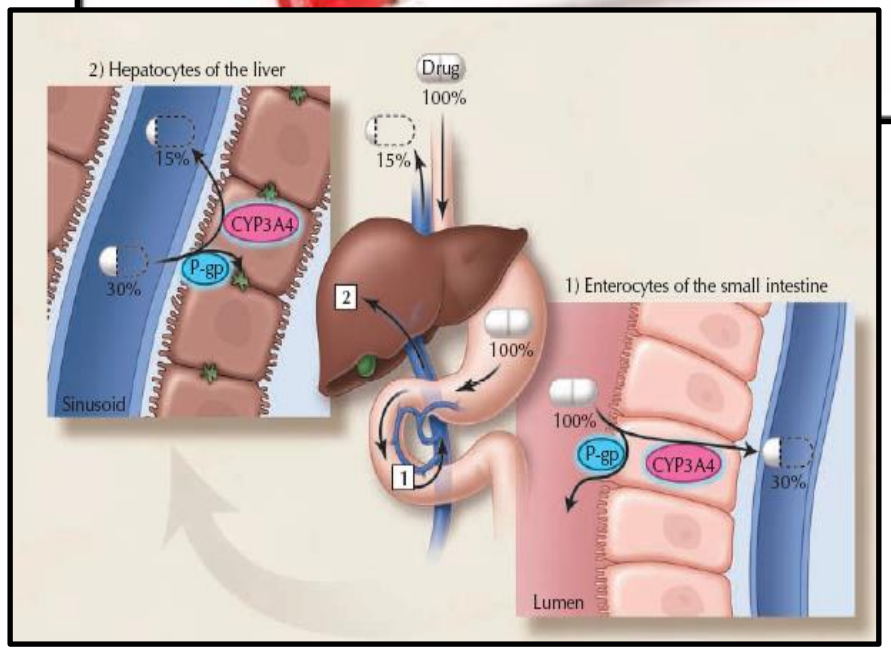
absorption, skin: BSA > permeability

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, *intramuscular injection* (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 *venipuncture*. 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 *venipuncture*. 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 *peripherally inserted central catheter (PICC) placement*. 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 *heel prick blood sampling*. 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





PROSA2022

DOI: 10.1111/pan.13454

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

Comparison of morphine concentration–time profiles following intravenous and intranasal diamorphine in children

S Kidd,[1] S Brennan,[1] R Stephen,[2] R Minns,[2] T Beattie[1]

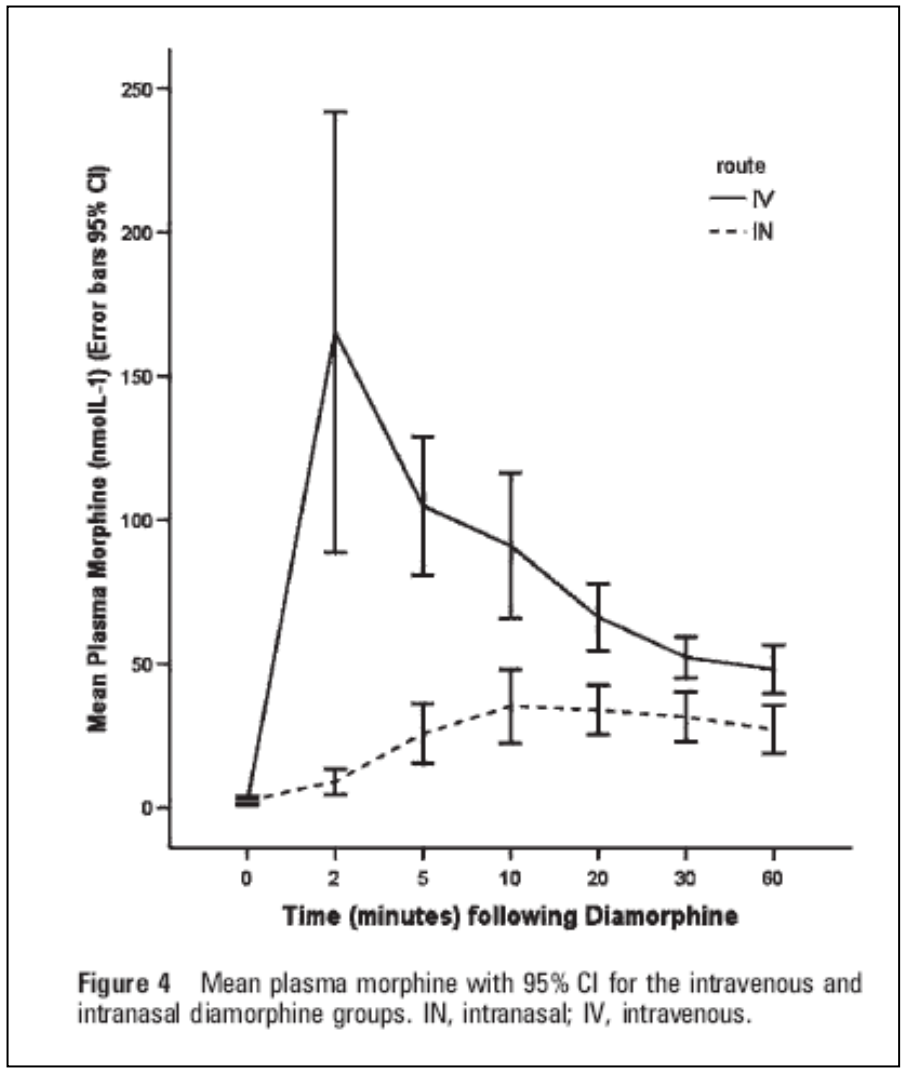
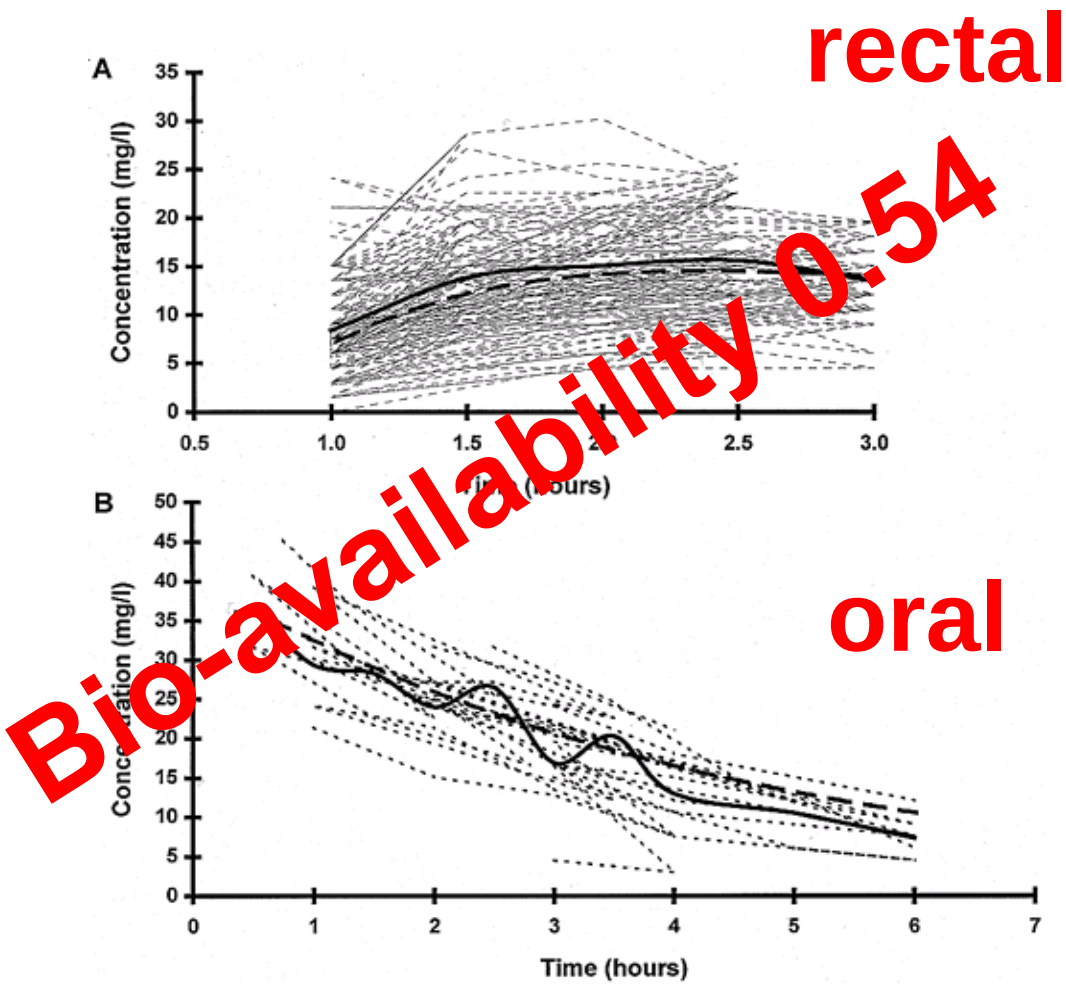


Figure 4 Mean plasma morphine with 95% CI for the intravenous and intranasal diamorphine groups. IN, intranasal; IV, intravenous.

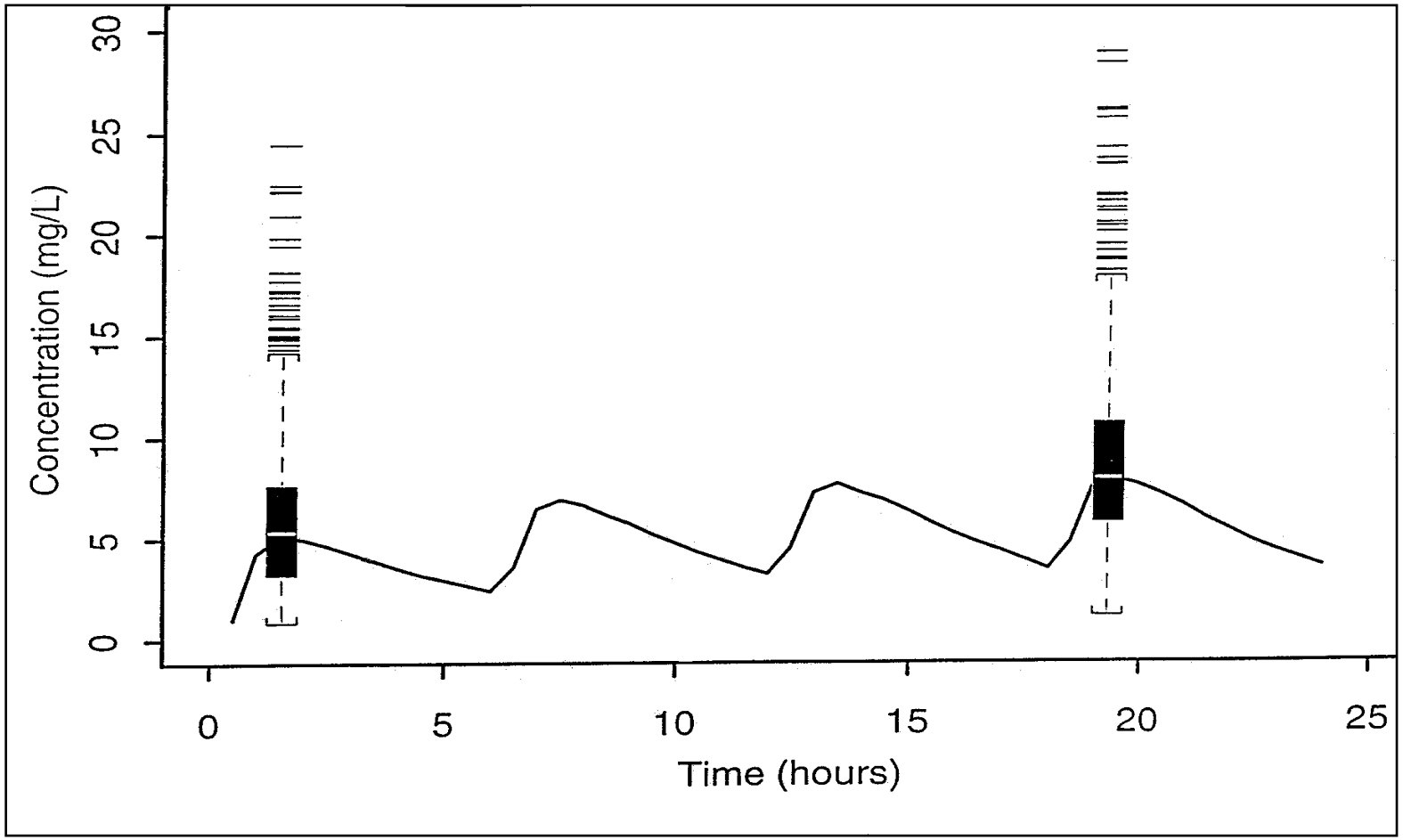
PROSA2022

absorption, rectal to oral paracetamol (ENT, children)



Anderson et al, Anesthesiology 1999

absorption, rectal to oral paracetamol (ENT, children)



Anderson et al, Anesthesiology 1999

distribution
body composition, (non)maturational covariates

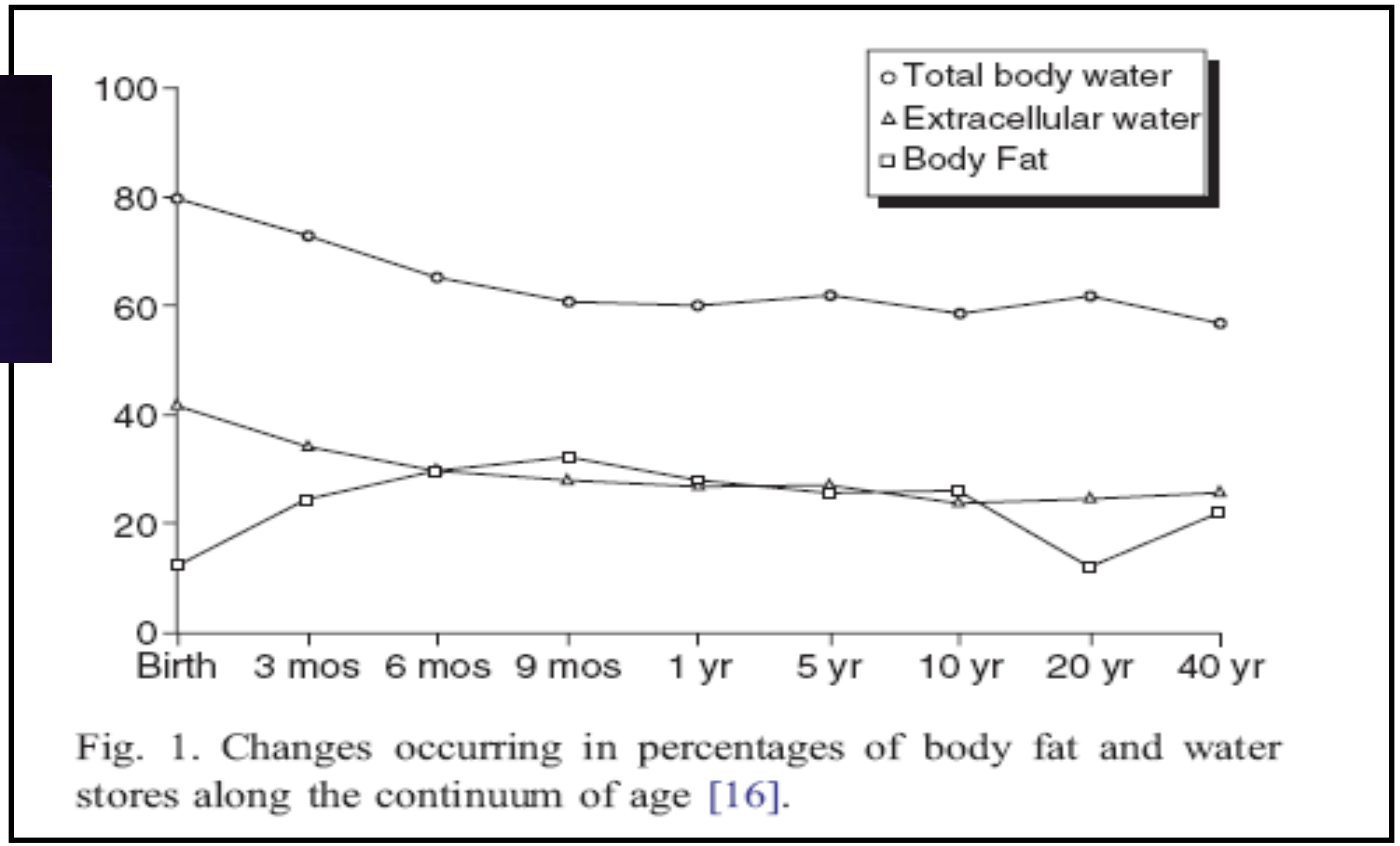


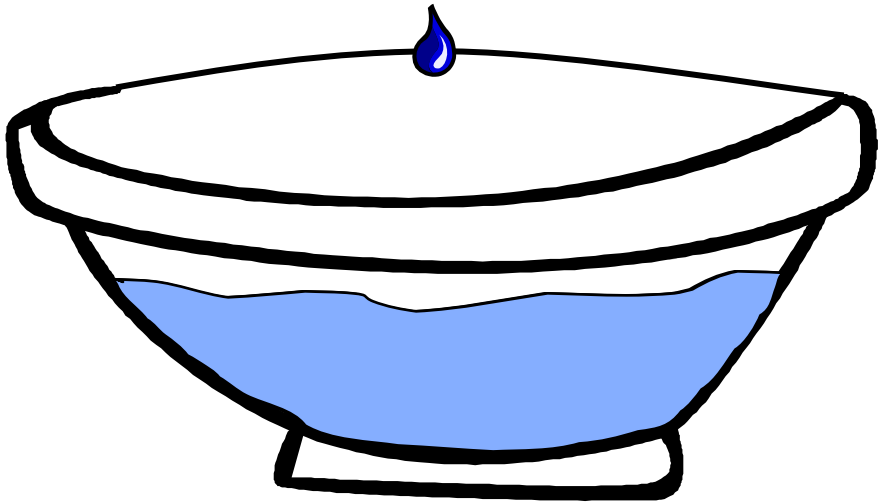
Fig. 1. Changes occurring in percentages of body fat and water stores along the continuum of age [16].

% total body water (extra cellular) decreases significantly over infancy

relevant for distribution of water soluble drugs (C_{max}, V_d, loading dose approach)

Rakhmanina et al, Adv Drug Deliver 2006

distribution volume

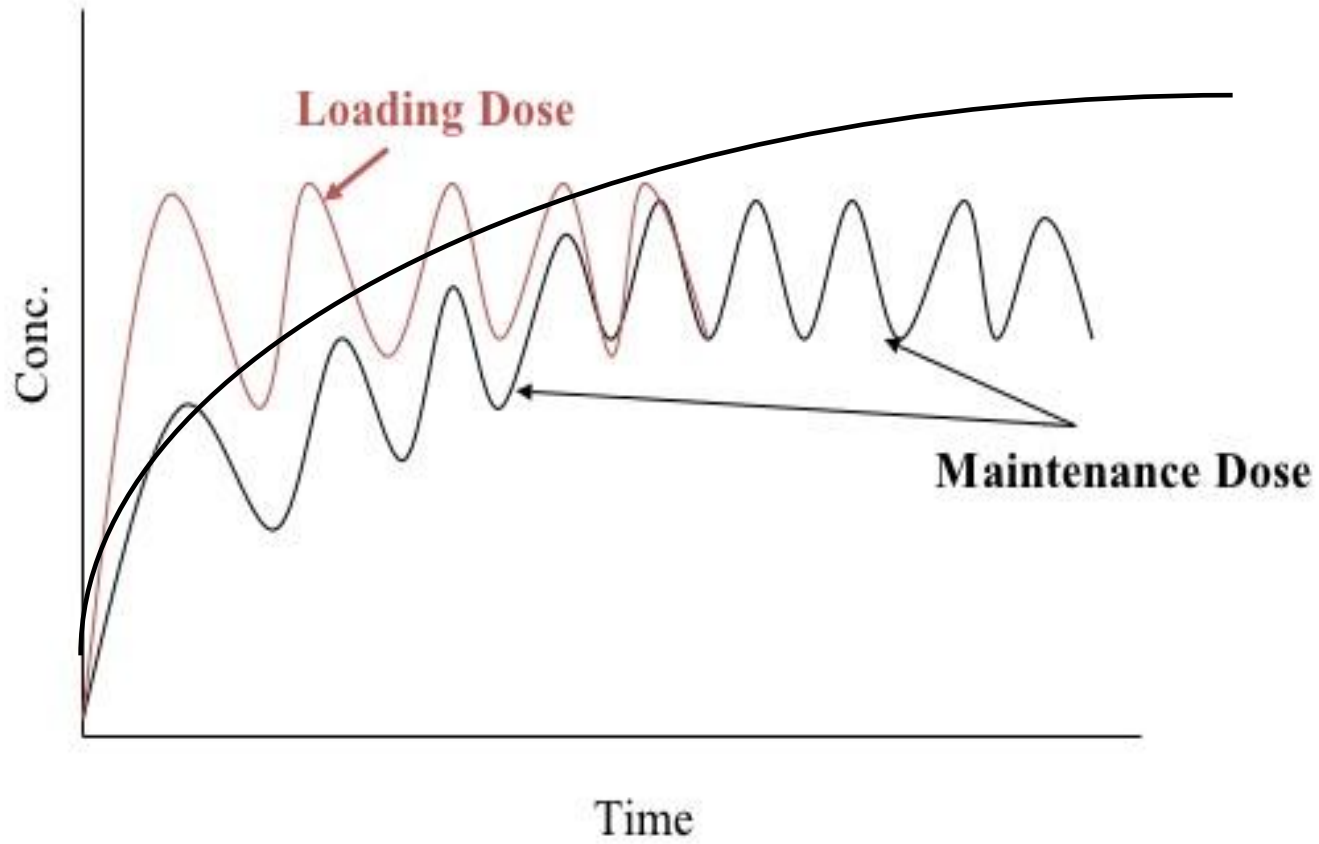


distribution volume: relevance

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



distribution volume: relevance

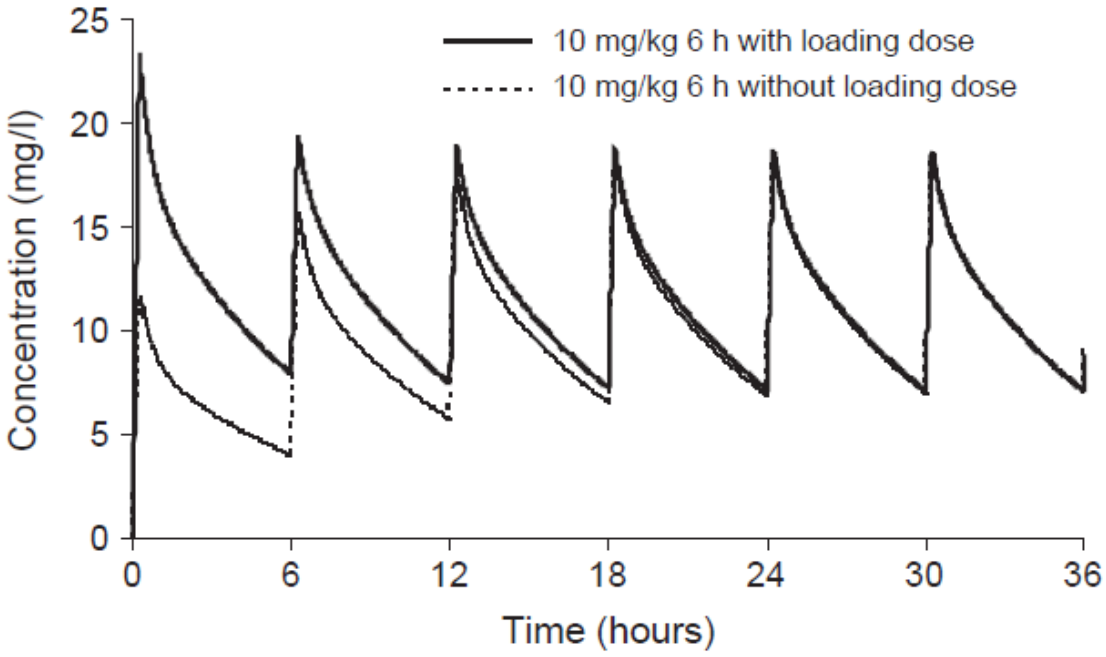
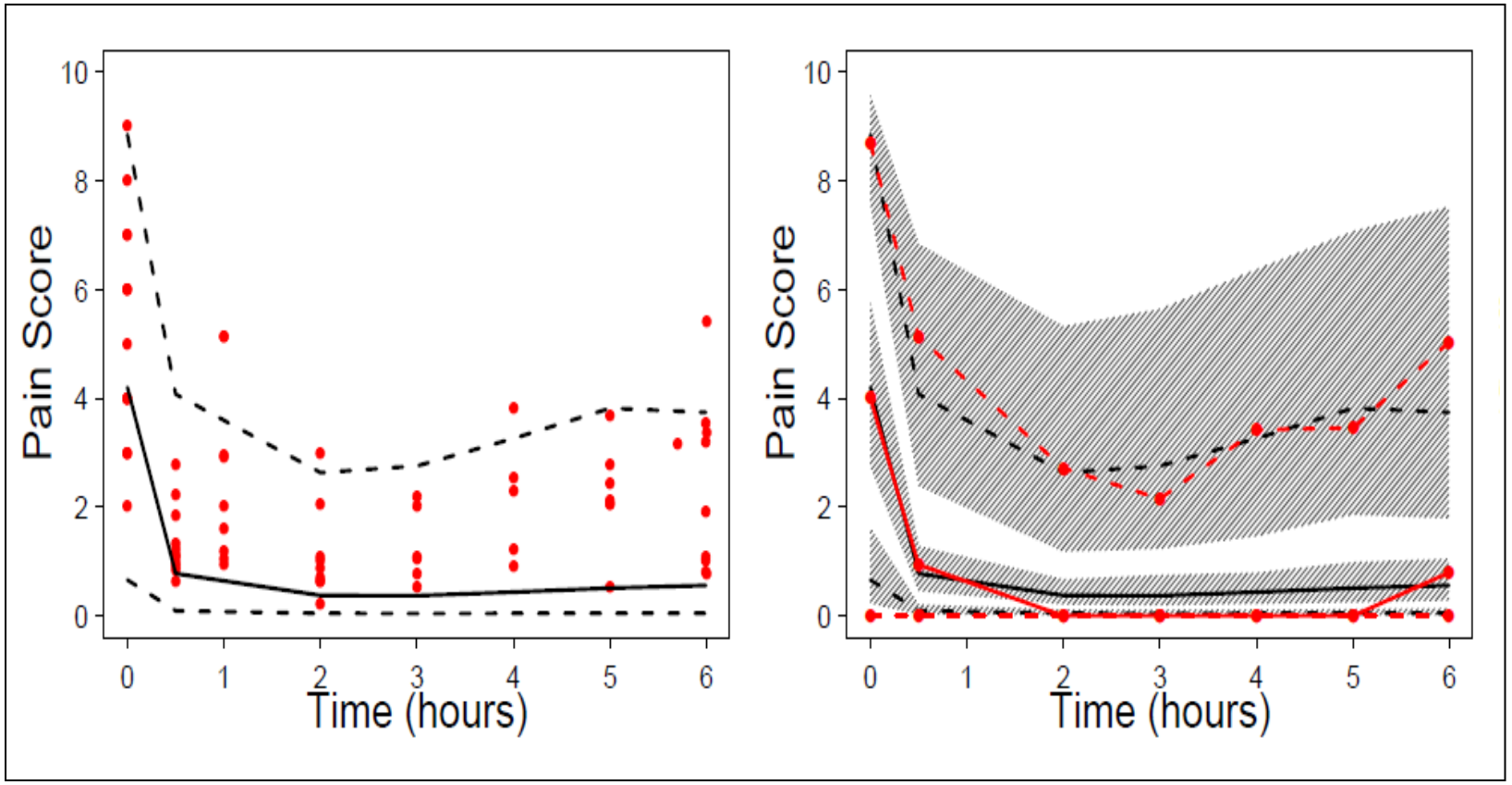


Figure 3 A typical concentration profile for neonates of 28–44 weeks' premenstrual age given a paracetamol loading dose of 20 mg/kg (black continuous line) or not given a loading dose (grey continuous line), followed by a maintenance dose of 10 mg/kg every 6 h. A mean concentration of 11 mg/l is achieved.

pooled iv paracetamol in neonates. Arch Dis Child 2011

distribution volume: relevance

'minor' pain syndromes



Pediatr Anesth, 2014

Effect of Intravenous Paracetamol on Postoperative Morphine Requirements in Neonates and Infants Undergoing Major Noncardiac Surgery

A Randomized Controlled Trial

Ilse Ceelie, MD, PhD
Saskia N. de Wildt, MD, PhD
Monique van Dijk, MSc, PhD
Margreeth M. J. van den Berg, MD
Gerbrich E. van den Bosch, MD
Hugo J. Duivenvoorden, PhD
Tom G. de Leeuw, MD
Ron Mathôt, PharmD, PhD
Catherijne A. J. Knibbe, PharmD, PhD
Dick Tibboel, MD, PhD

Importance Continuous morphine infusion as standard postoperative analgesic therapy in young infants is associated with unwanted adverse effects such as respiratory depression.

Objective To determine whether intravenous paracetamol (acetaminophen) would significantly (>30%) reduce morphine requirements in neonates and infants after major surgery.

Design, Setting, and Patients Single-center, randomized, double-blind study conducted in a level 3 pediatric intensive care unit in Rotterdam, the Netherlands. Patients were 71 neonates or infants younger than 1 year undergoing major thoracic (noncardiac) or abdominal surgery between March 2008 and July 2010, with follow-up of 48 hours.

Interventions All patients received a loading dose of morphine 30 minutes before the end of surgery, followed by continuous morphine or intermittent intravenous paracetamol up to 48 hours postsurgery. Infants in both study groups received morphine (boluses and/or continuous infusion) as rescue medication on the guidance of the validated pain assessment instruments.

Main Outcome Measures Primary outcome was cumulative morphine dose (study and rescue dose). Secondary outcomes were pain scores and morphine-related adverse effects.

Results The cumulative median morphine dose in the first 48 hours postoperatively was 121 (interquartile range, 99-264) μg/kg in the paracetamol group (n=33) and 357 (interquartile range, 220-605) μg/kg in the morphine group (n=38), $P<.001$, with a between-group difference that was 66% (95% CI, 34%-109%) lower in the paracetamol group. Pain scores and adverse effects were not significantly different between groups.

Conclusion and Relevance Among infants undergoing major surgery, postoperative use of intermittent intravenous paracetamol compared with continuous morphine resulted in a lower cumulative morphine dose over 48 hours.

Trial Registration trialregister.nl Identifier: NTR1438

JAMA. 2013;309(2):149-154 www.jama.com

THE TREATMENT OF PAIN IN young children has improved after the publications by Anand et al[1,2] in 1987 that made clear that neonates have well-developed nociceptive pathways and therefore are capable of experiencing pain. Because untreated pain is both an unwanted experience and ultimately may lead to adverse consequences,[3-6] opioids were introduced and have been used ever since.[7] Opioid therapy, however, is associated with adverse effects, in particular respiratory depression.[8] Re-

PROSA2022

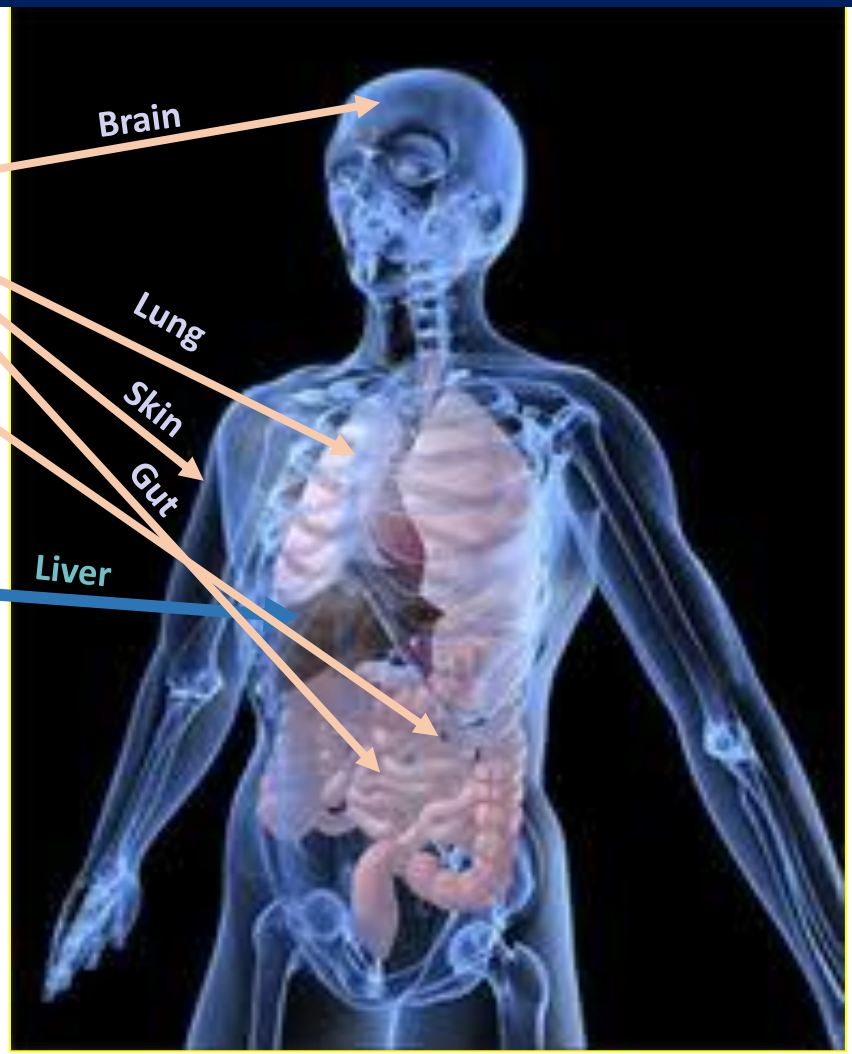
after procedural pain (heel prick), uniform negative

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

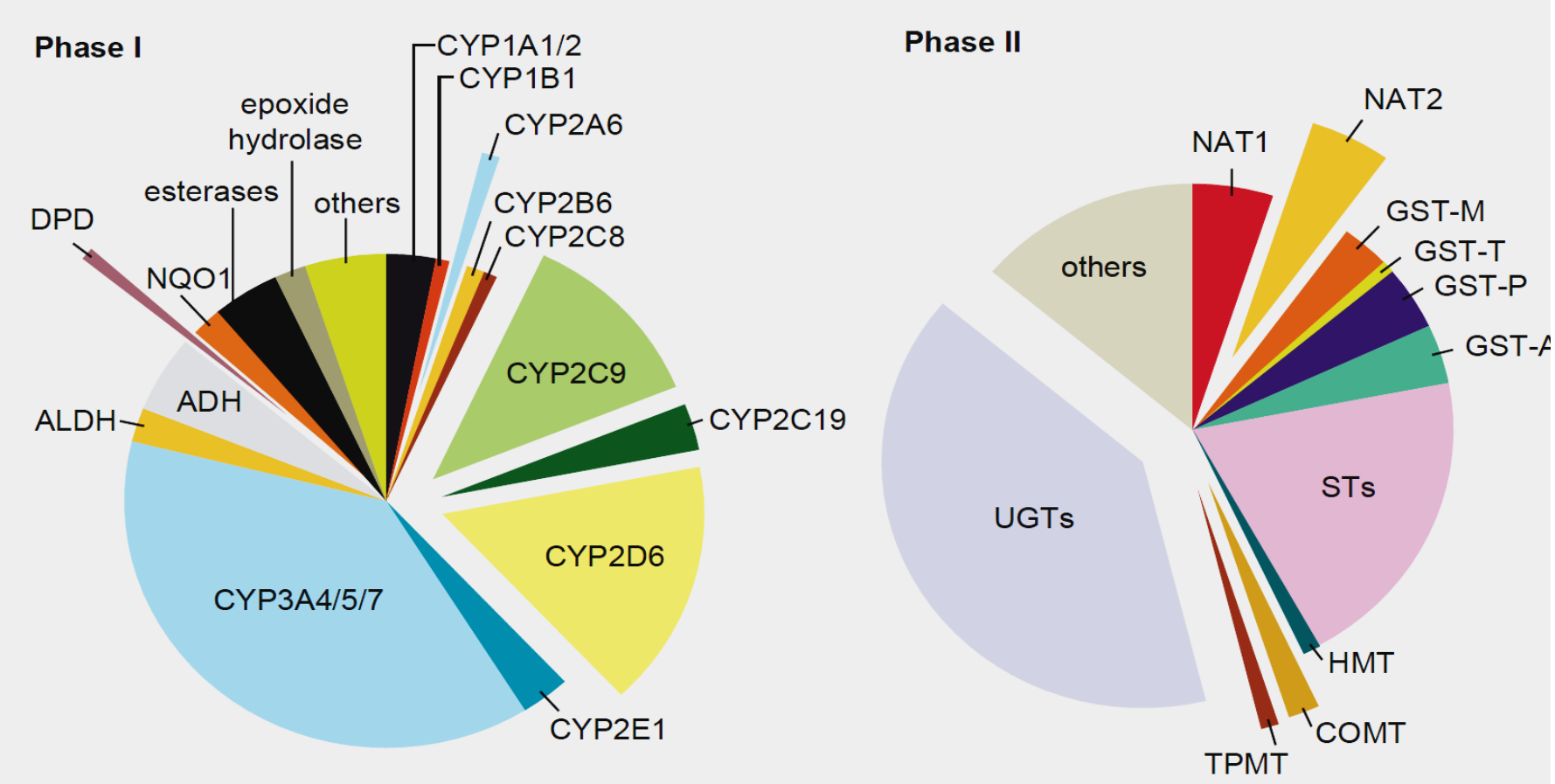
Extrahepatic enzymes

Hepatic enzymes



Slide provided by J van den Anker

Phase I and phase II metabolism, enzymes



Evans et al, Science 1999

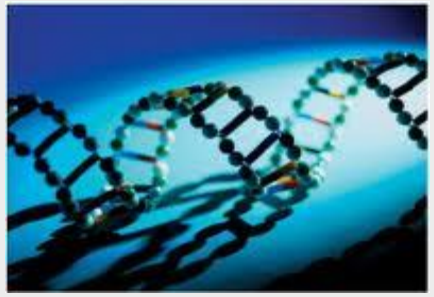
PROSA2022

Phase I and phase II metabolism, enzymes

herbal medicine

disease

drugs



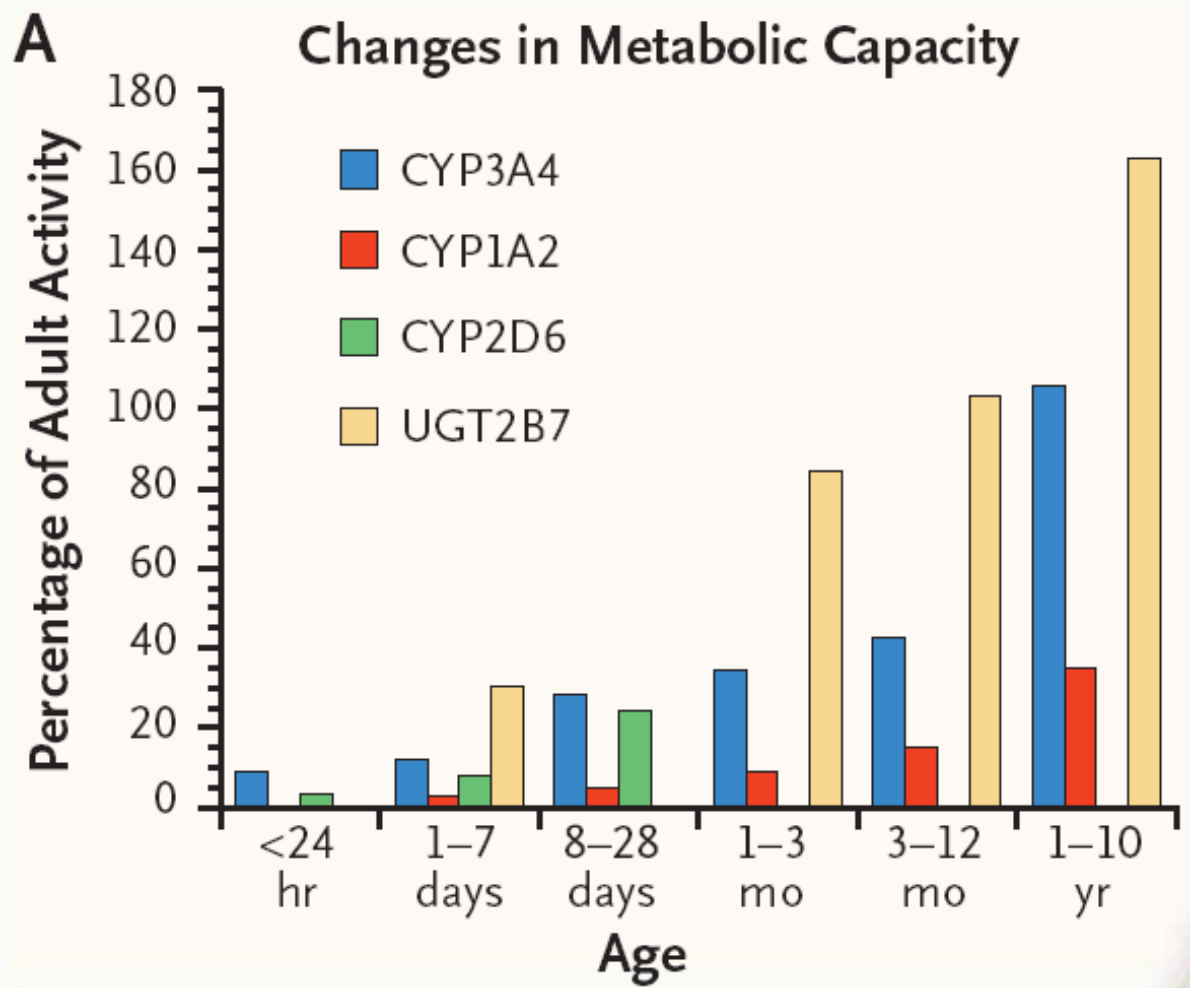
genetics

age

nutrition

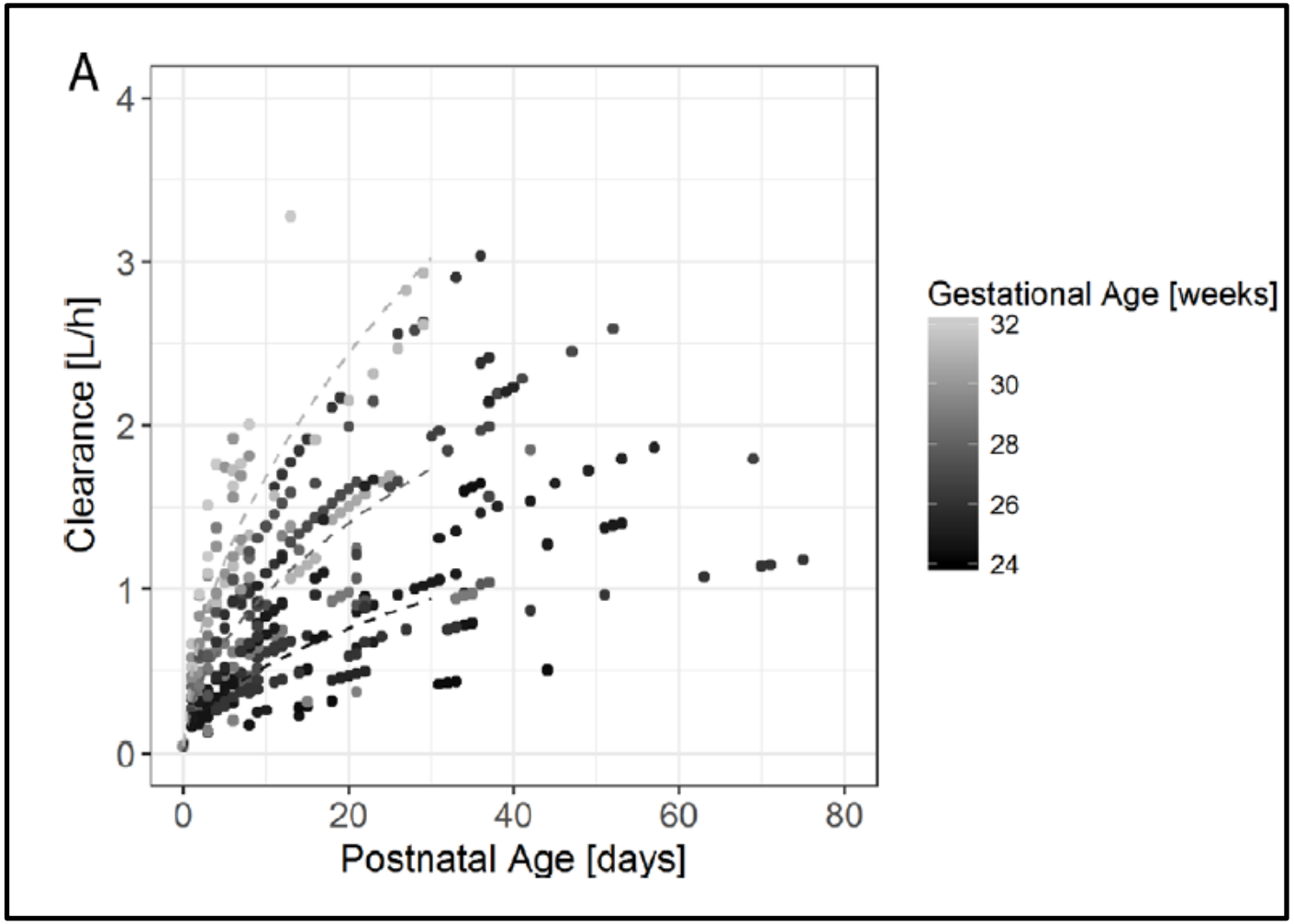
Slide provided by J van den Anker

Age related maturation is the common main driver, but…



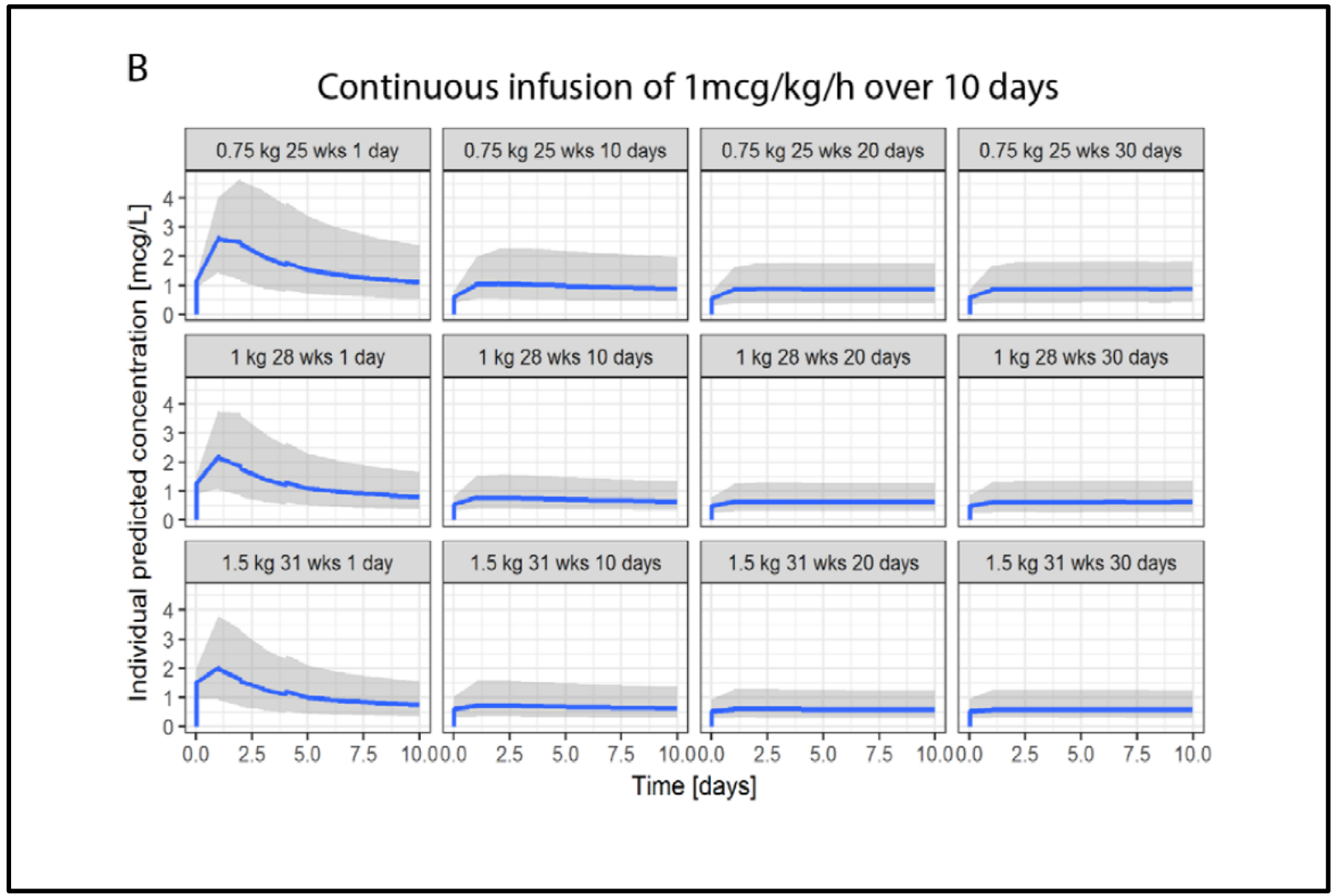
Kearns et al, NEJM 2003

fentanyl clearance as a first illustration



Völler S et al, Arch Dis Child 2019

fentanyl clearance as a first illustration

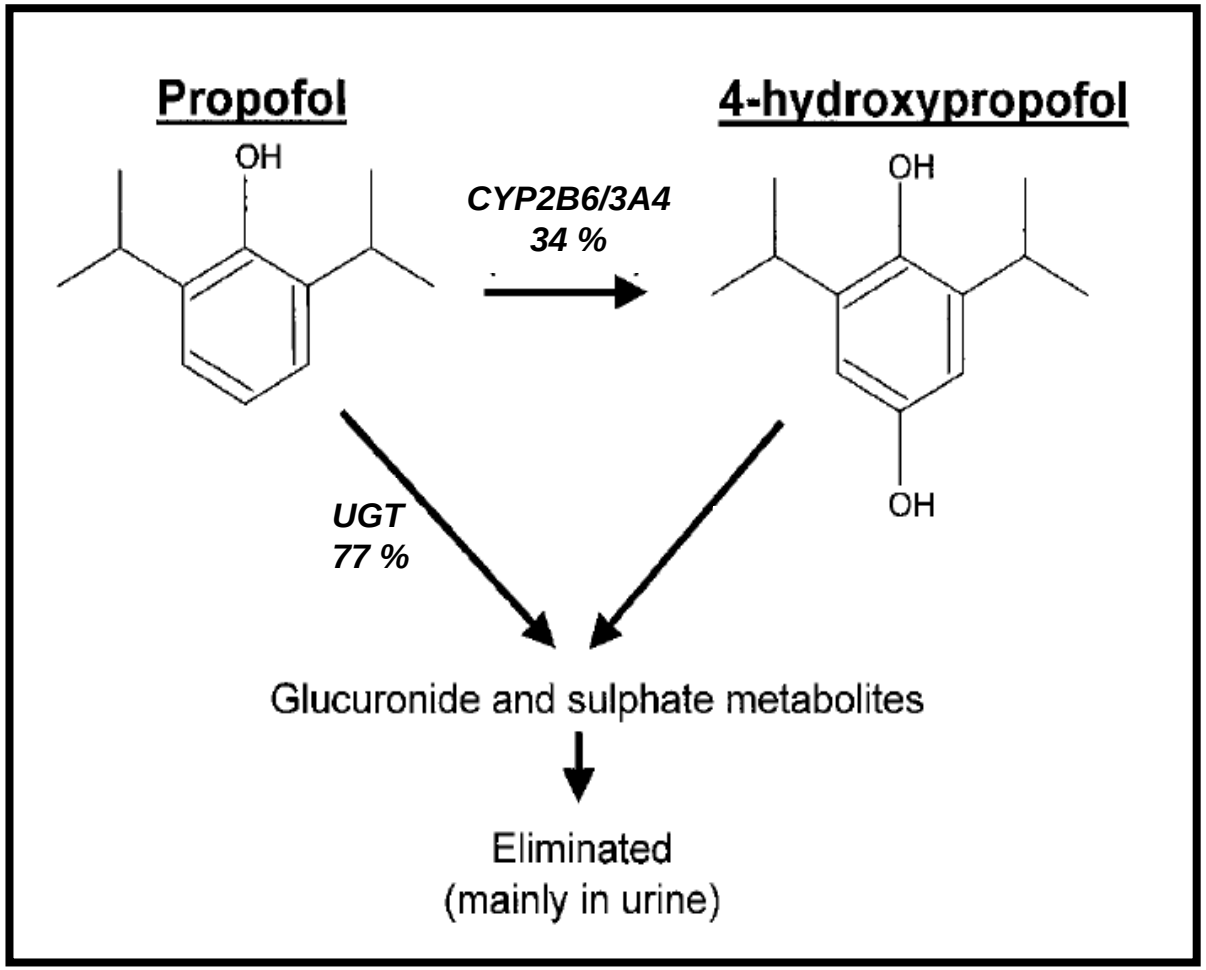


Völler S et al, Arch Dis Child 2019

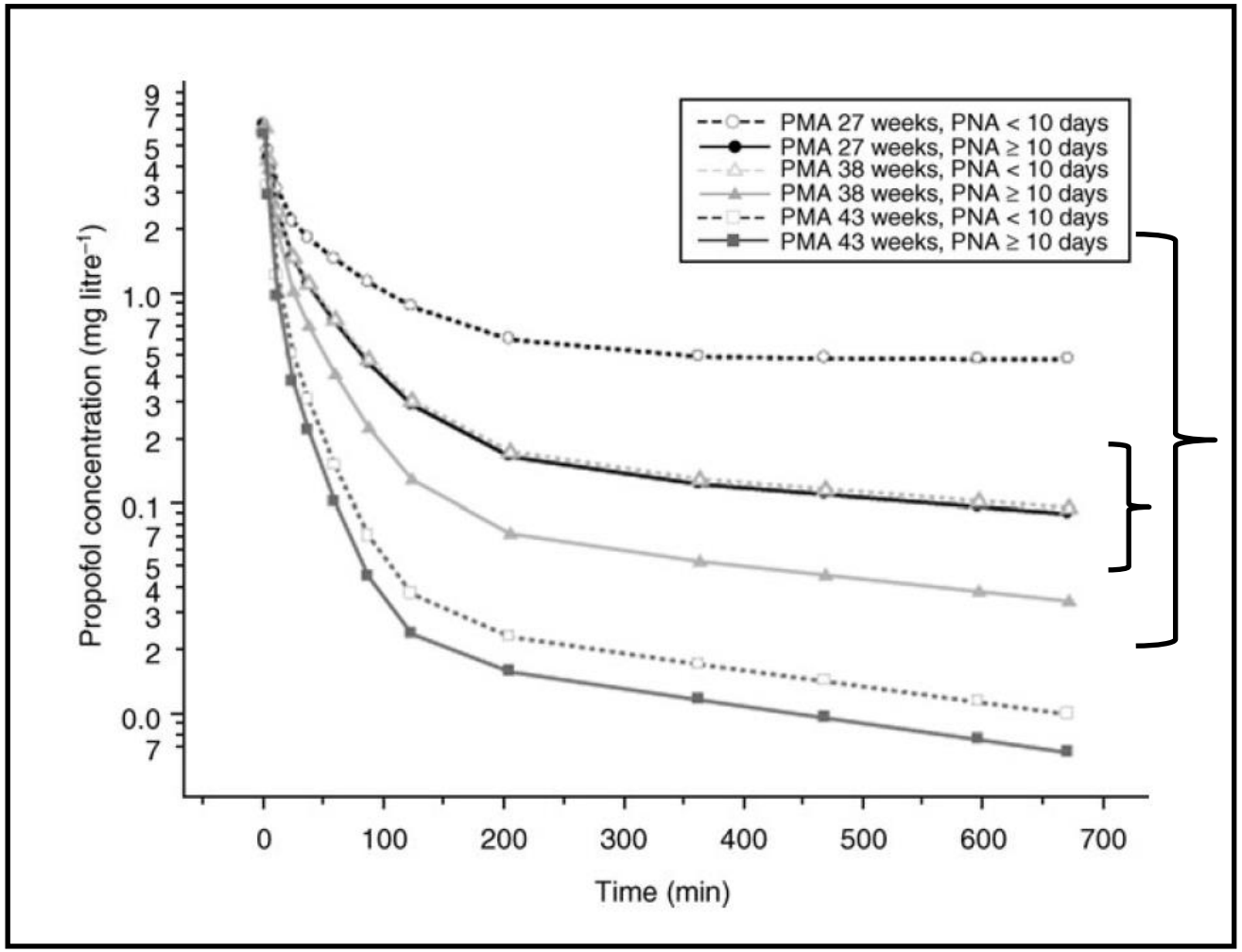
PROSA2022

propofol clearance as second illustration

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

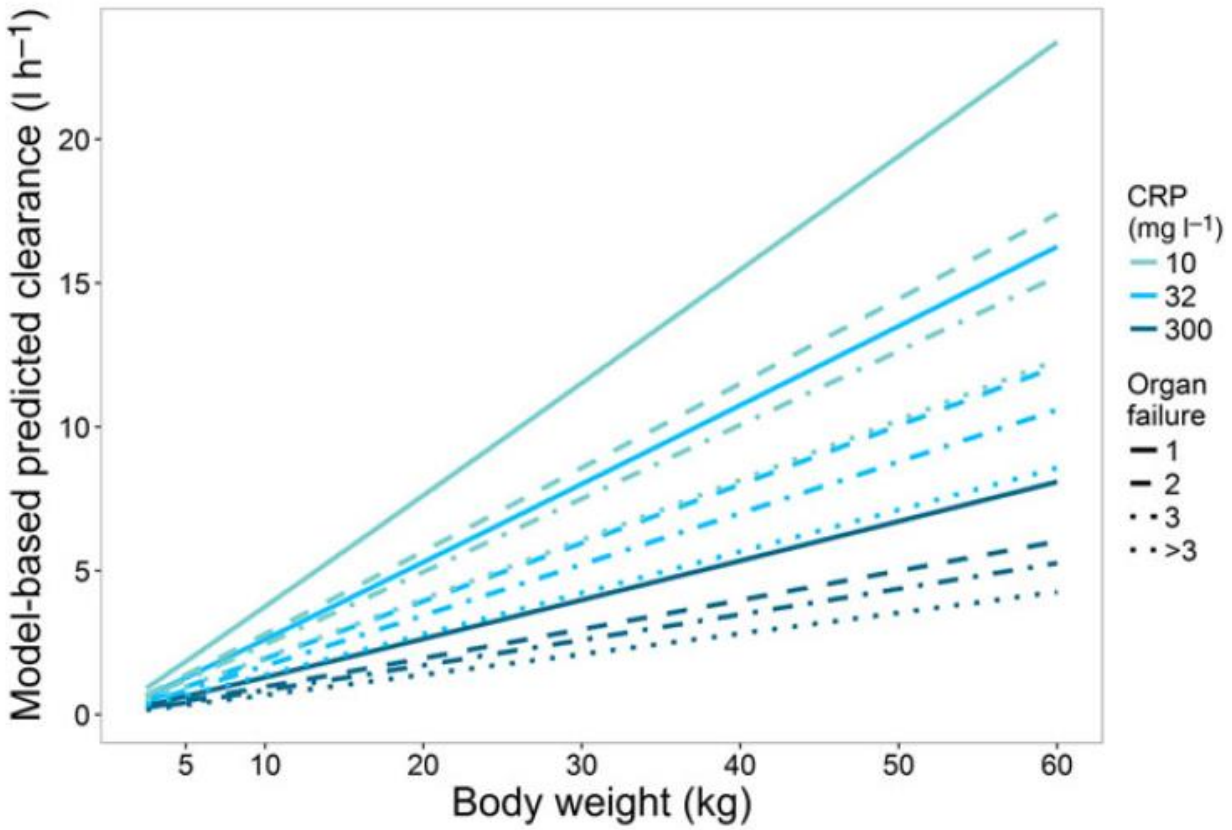


propofol clearance as second illustration



Allegaert et al, Br J Anaesth 2007

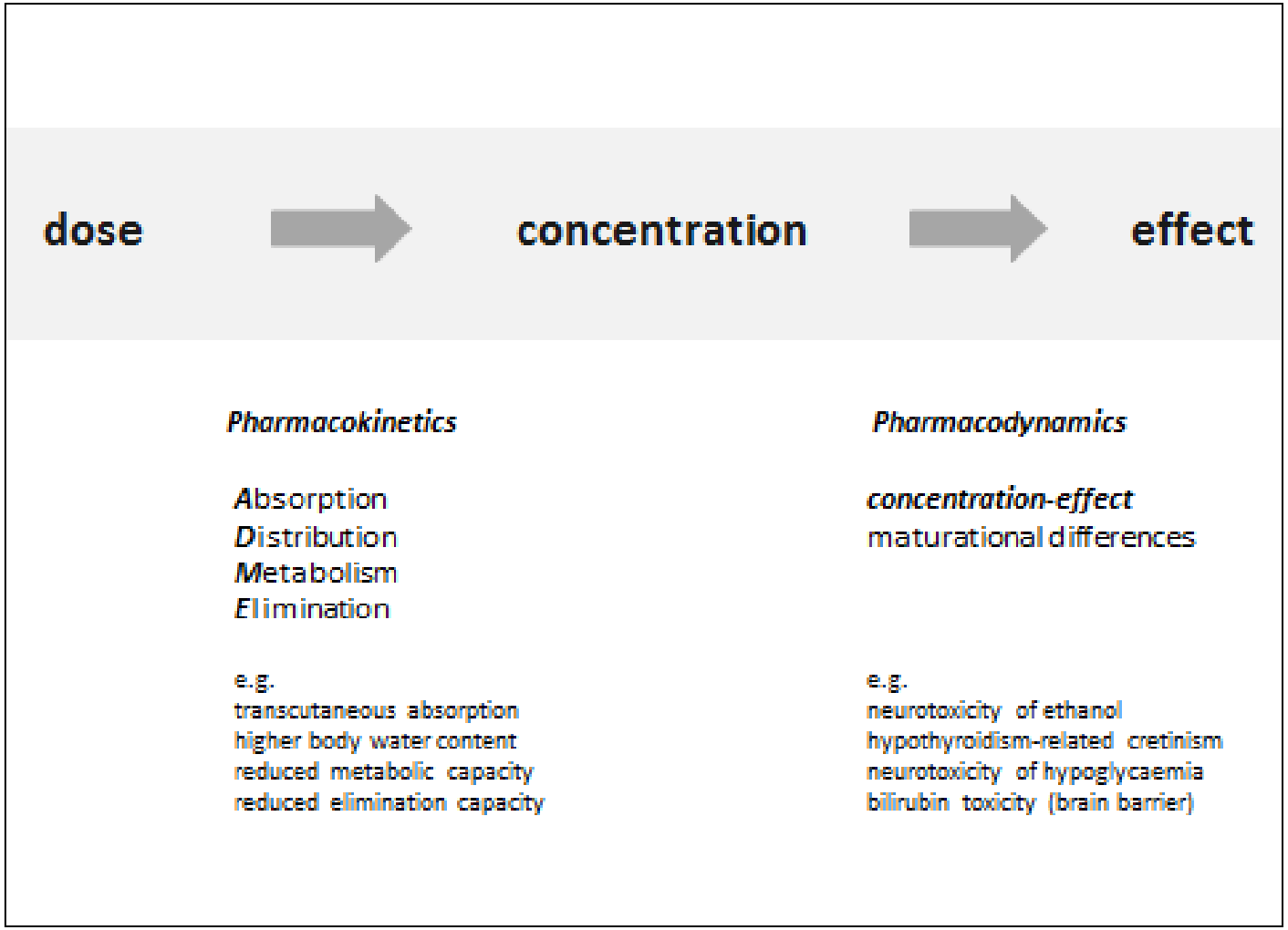
midazolam clearance as final illustration: age and disease !



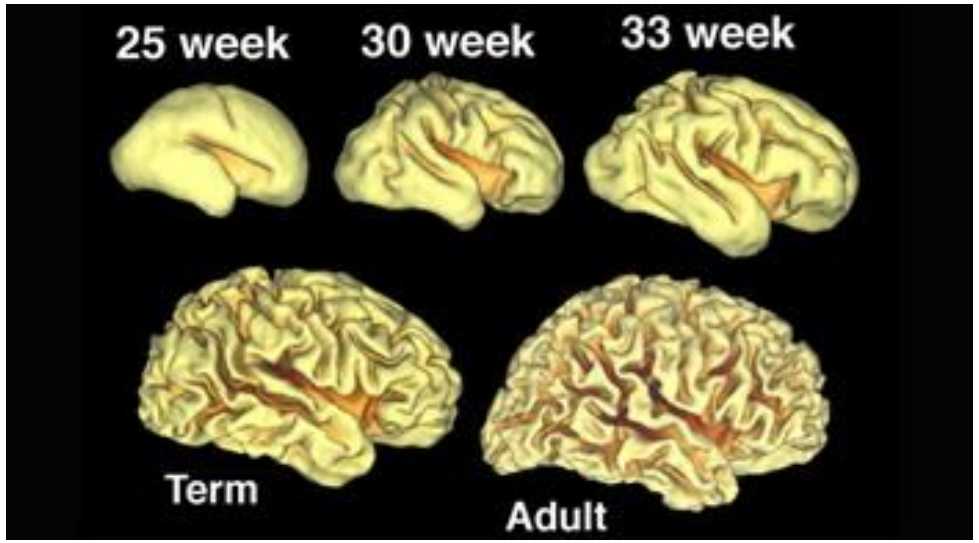
Brussee et al, Br J Clin Pharmacol 2018

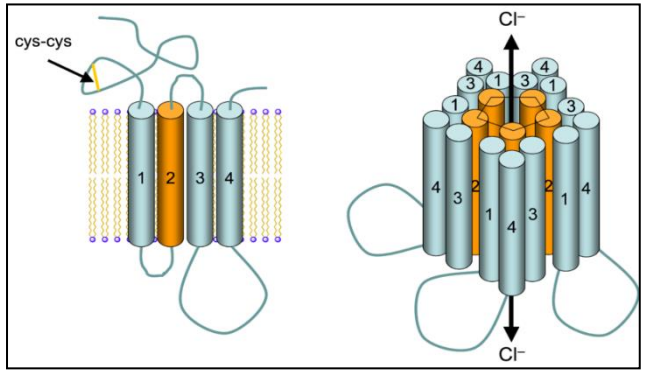
PROSA2022

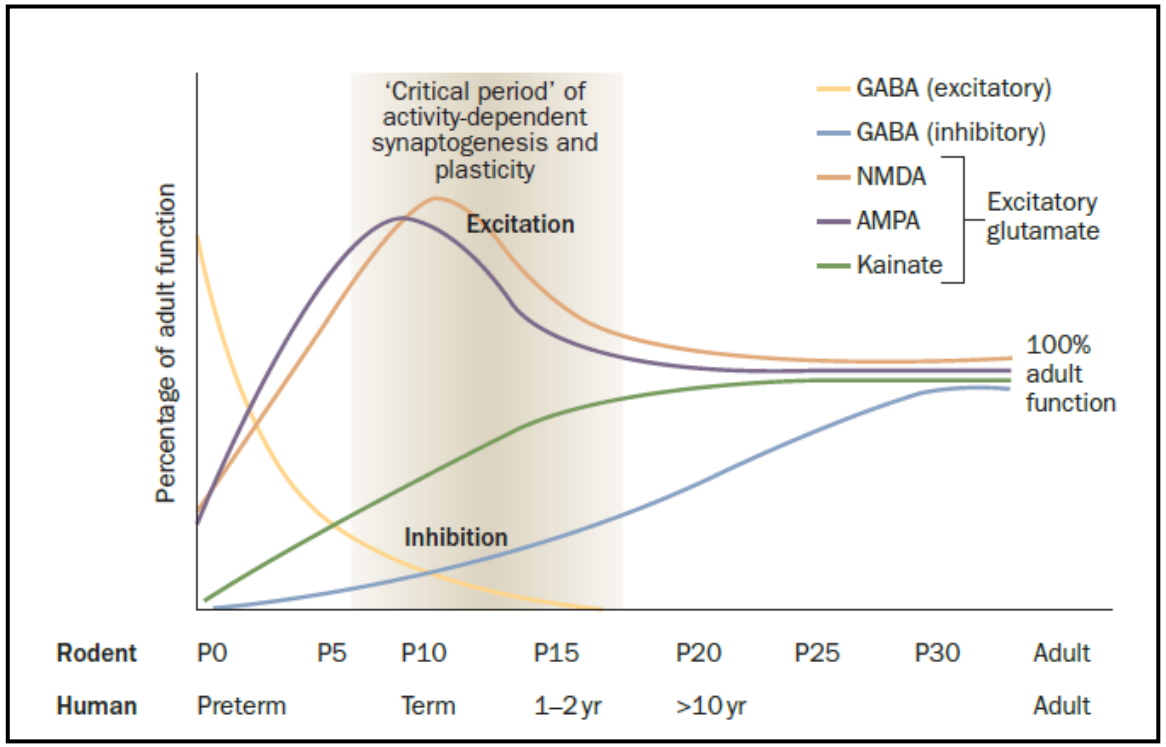
the framework (clin pharm) to work with: PD



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



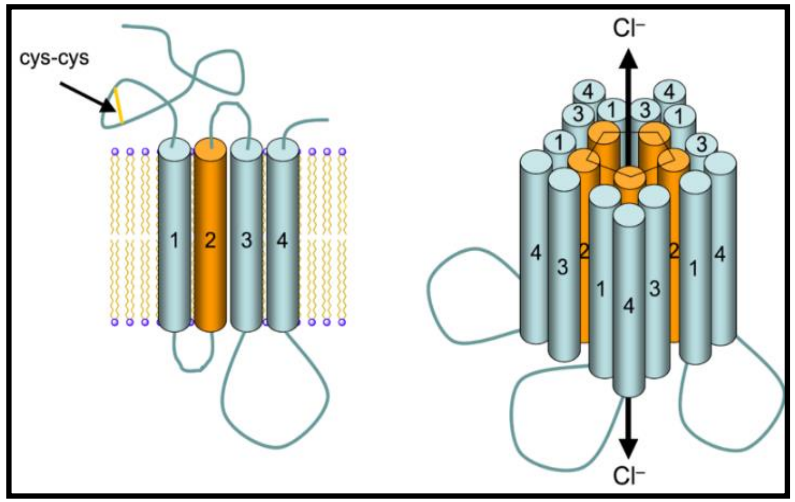


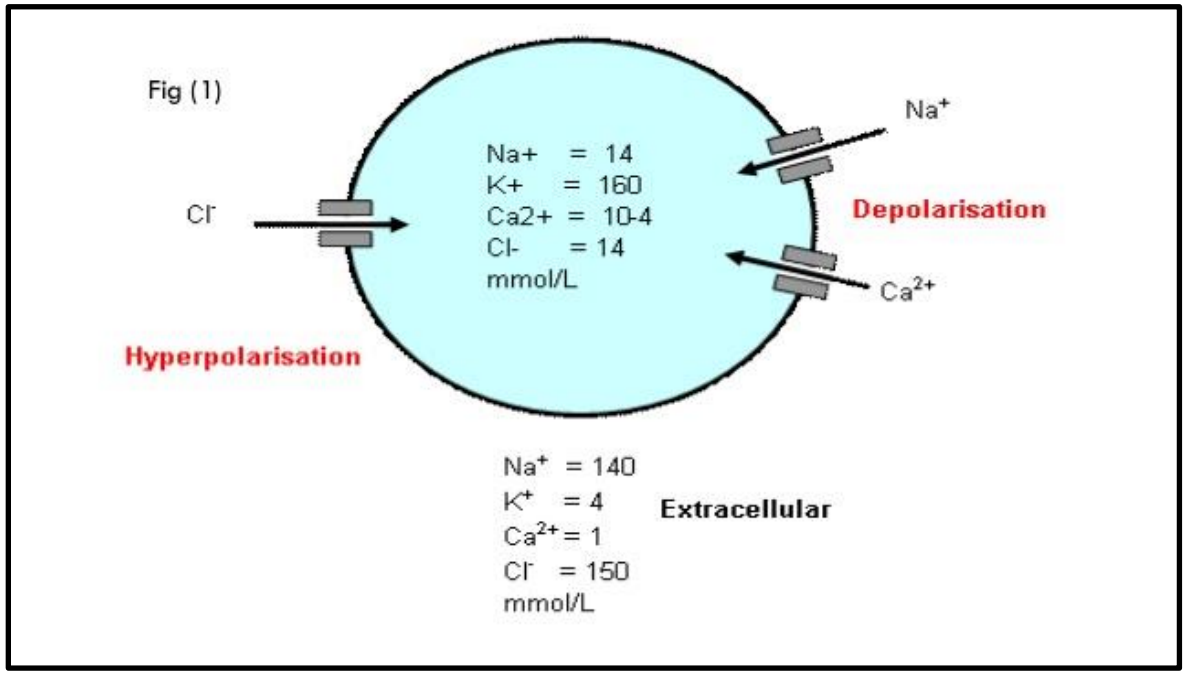


Rakhade et al, Nat Rev Neurol 2009

PROSA2022

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





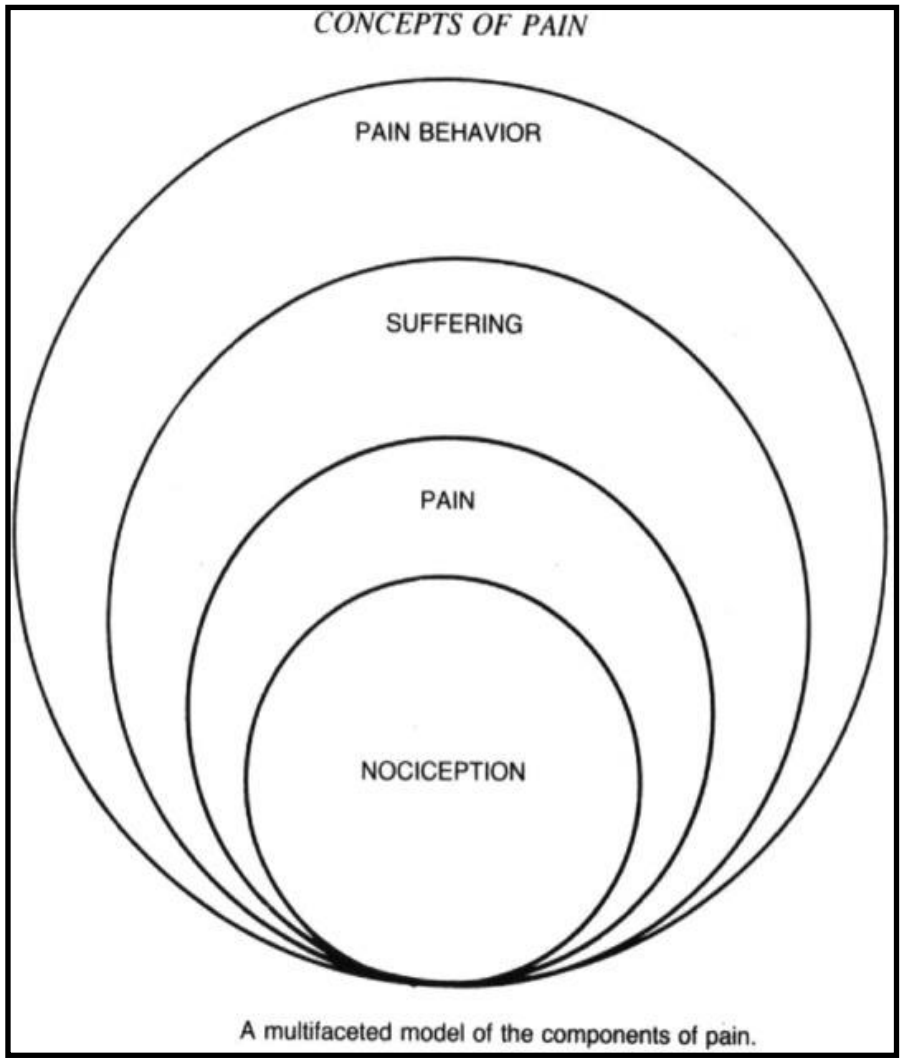
Open chloride receptor-channels induce hyperpolarisation by increasing intracellular chloride two types of receptors, GABA-a and GABA-b (G-protein coupled mechanism).

GABA release reduction and K efflux

Compounds of interest: benzodiazepines, propofol

Rakhade et al, Nat Rev Neurol 2009

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



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

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

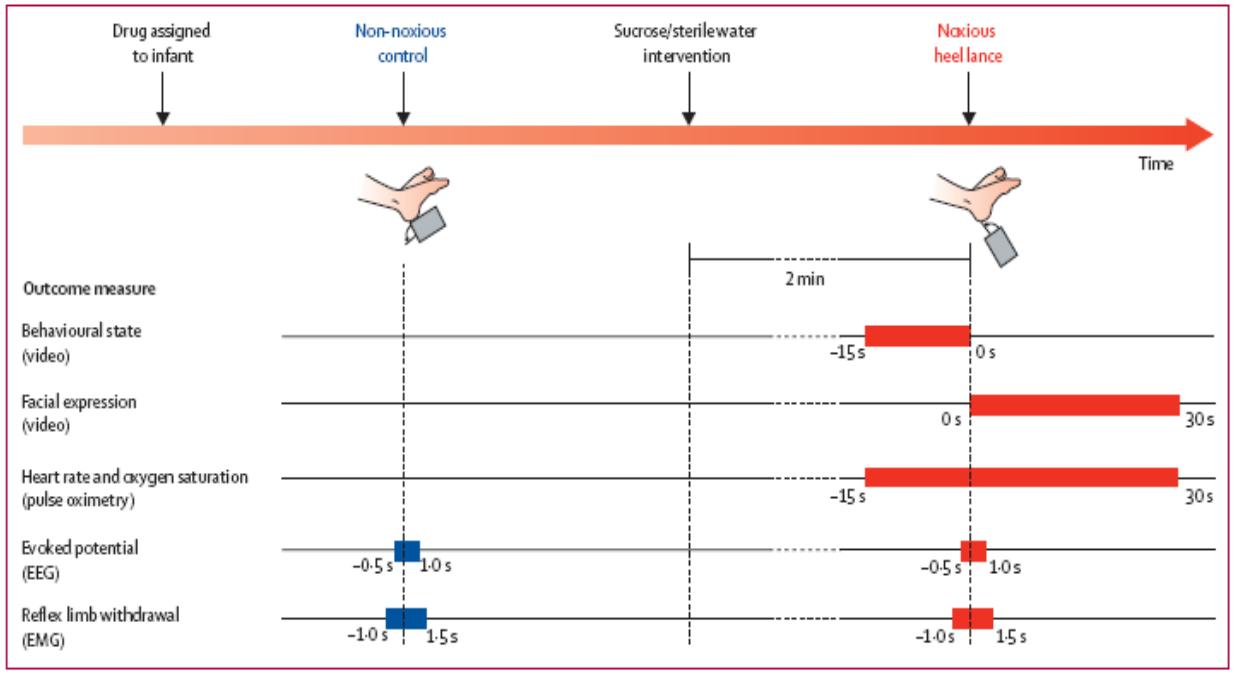


Figure 1: Experimental time line
EEG=electroencephalography. EMG=electromyography.

PROSA2022

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

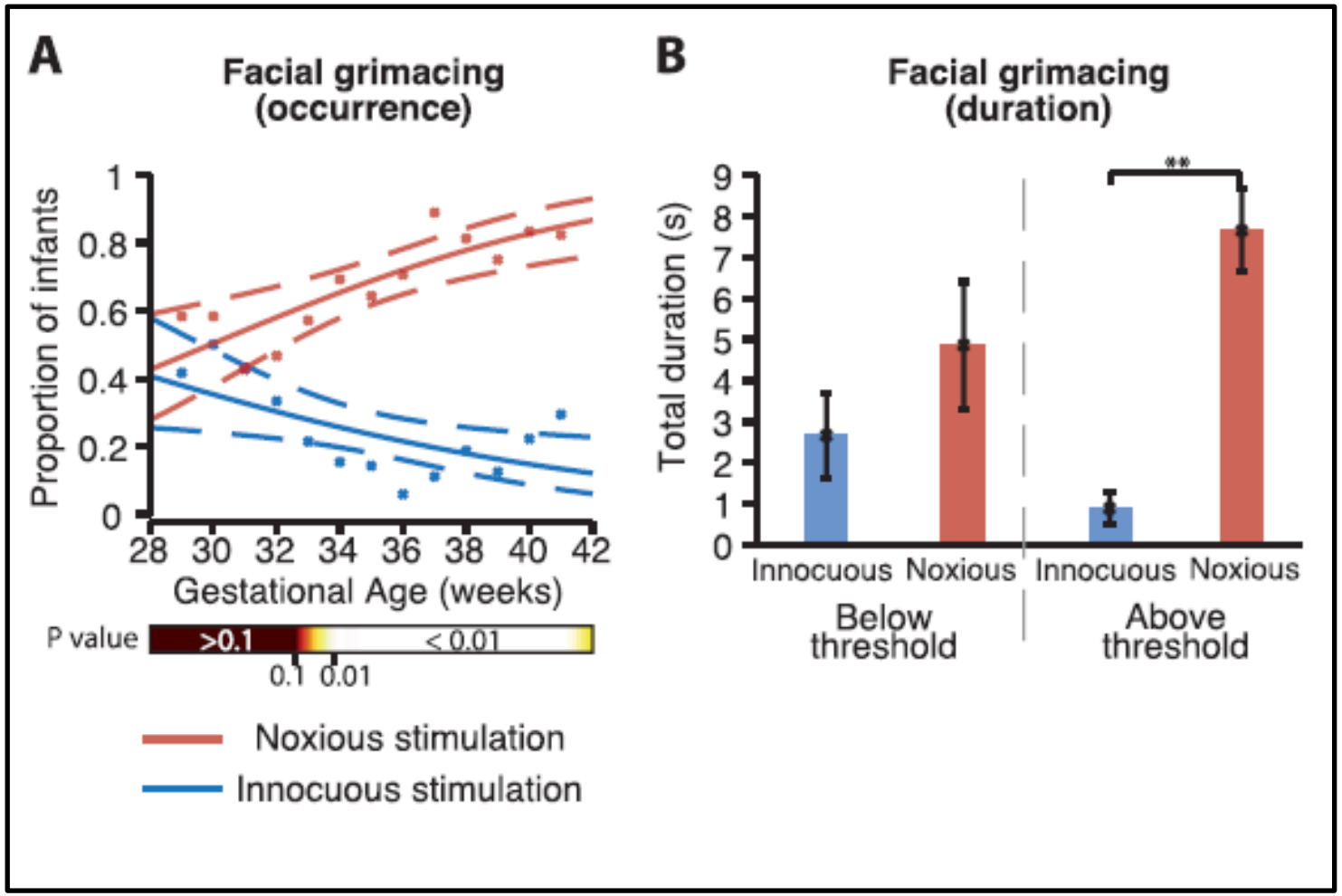
Oral sucrose as an analgesic drug for procedural pain in newborn infants: a randomised controlled trial

Rebeccah 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 (μV)	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

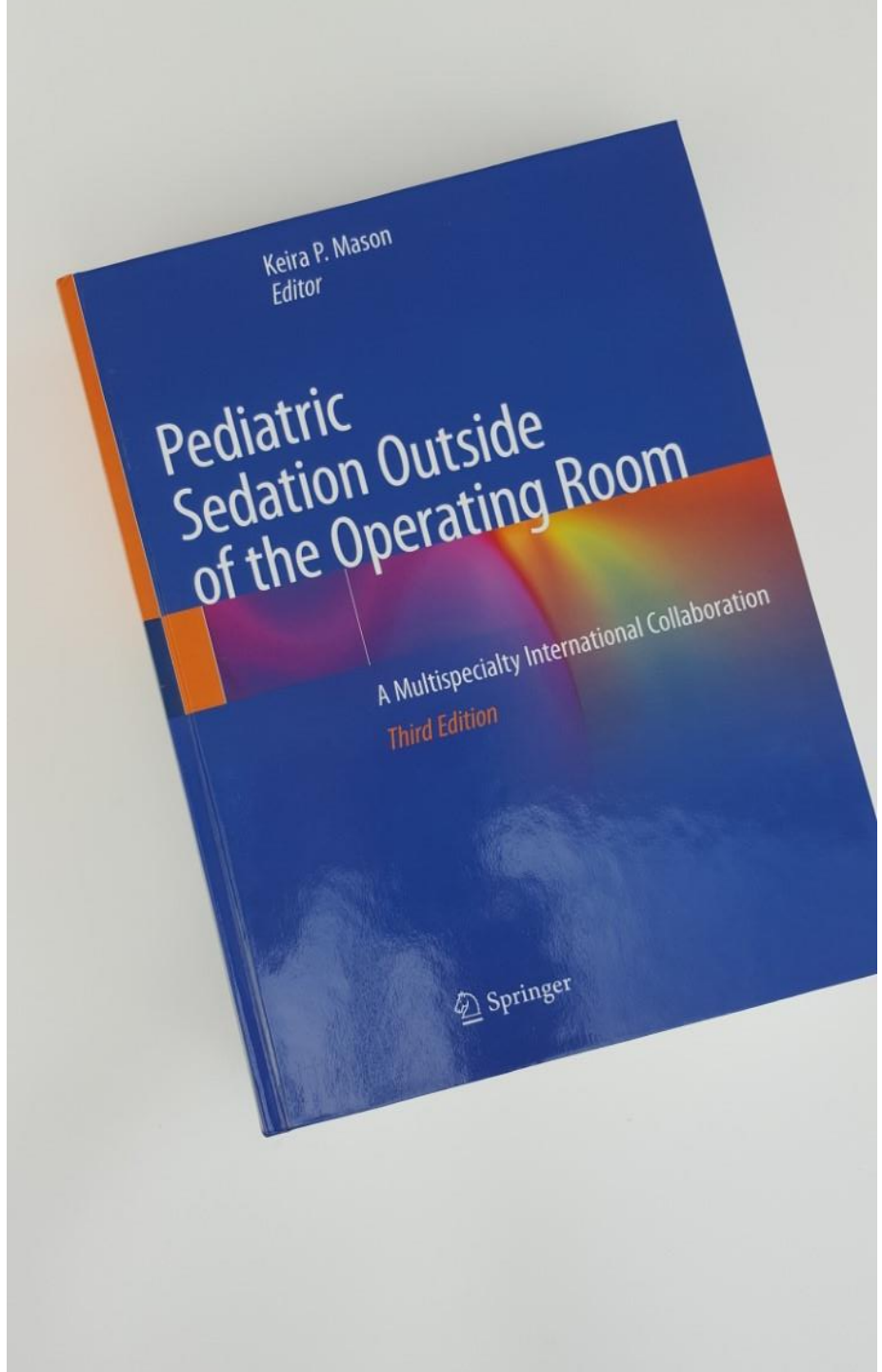
Data are mean (95% CI) or n/N (%). bpm=beats per min. PIPP=premature infant pain profile.

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



Green et al, Pain 2019

PROSA2022


Keira P. Mason
Editor
Pediatric
Sedation Outside
of the Operating Room
A Multispecialty International Collaboration
Third Edition
Springer