Analgosedation in neonates

focus on palliative care

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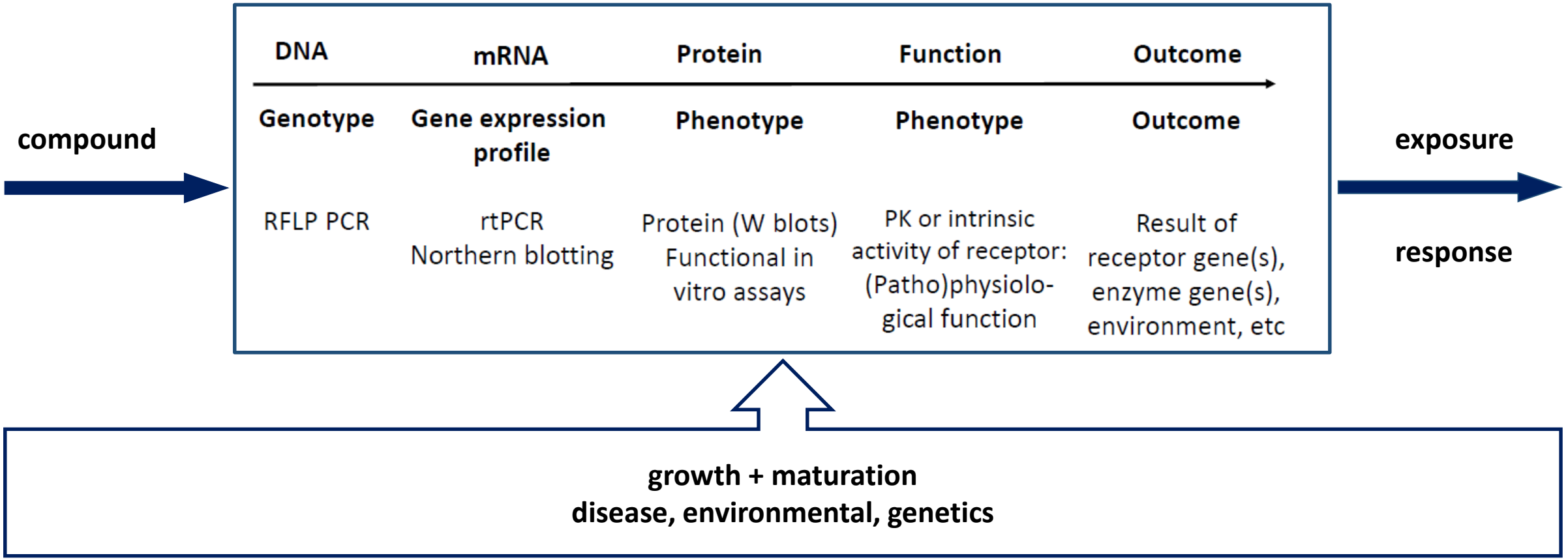
developmental pharmacokinetics and -dynamics



the toolbox, however

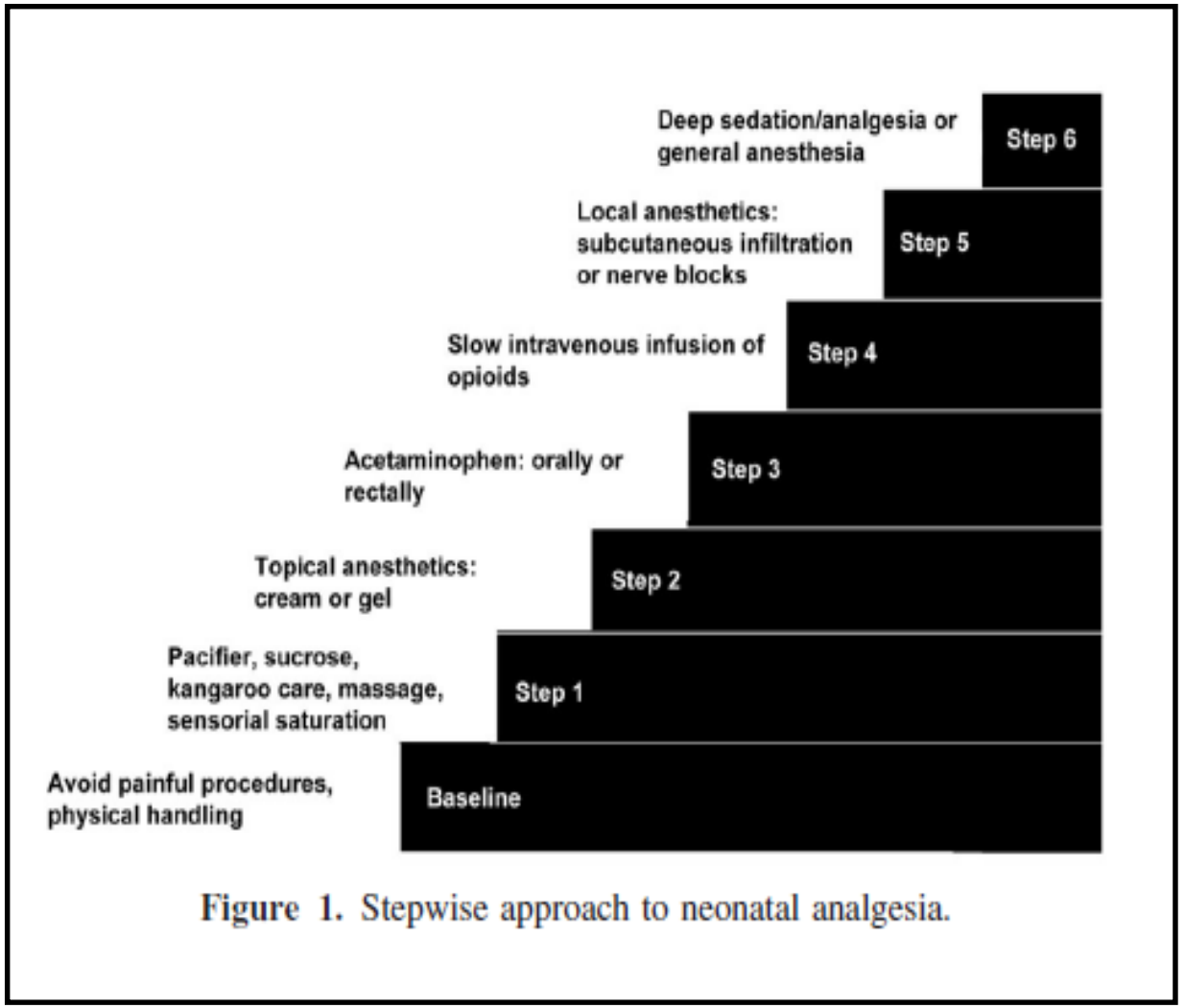


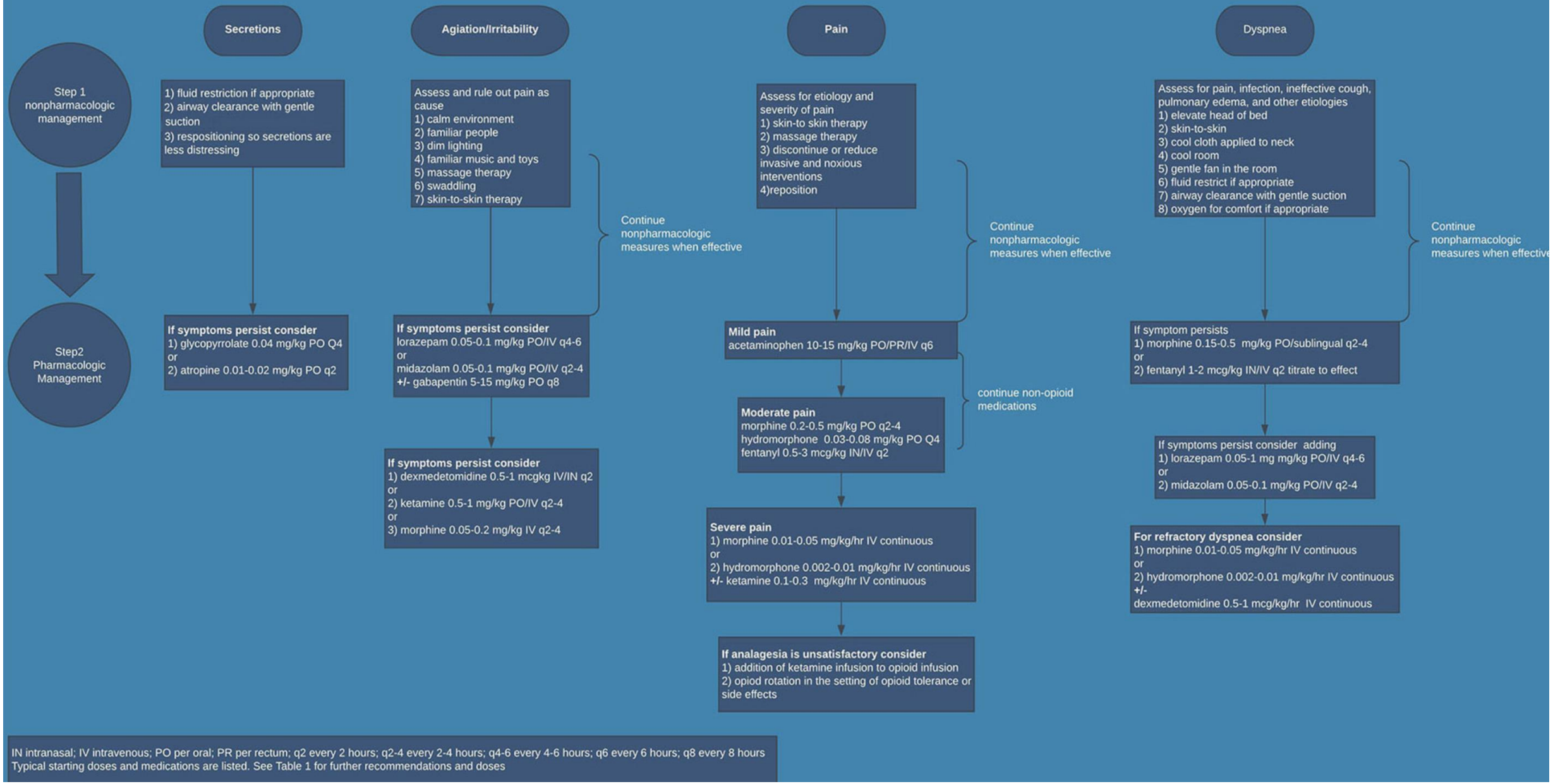
Figure 1. Stepwise approach to neonatal analgesia.

TABLE 1 | Neonatal end-of-life symptom management: suggested pharmacologic medications.

Medication	Class	Symptom	Starting dose (per kg) with route and frequency	Comments
Acetaminophen	COX2 inhibitor	Fever Mild pain	15 mg PO/PR q6 6–8 mg IV q8	As an adjuvant for pain
Atropine	Anticholinergic	Secretions	0.01–0.02 mg PO q2	No strong evidence
Dexmedetomidine	Selective alpha 2 agonist	Agitation Pain	0.5–1 mcg IV/IN q2 0.5–1 mcg/kg/hr IV continuous	
Fentanyl	Opioid	Pain Dyspnea	0.5–2 mcg IN/IV q2 1–4 mcg/kg/hr IV continuous	Quicker onset of action
Gabapentin	anticonvulsant	Agitation Neuroirritability	5–15 mg PO q8	
Glycopyrrolate	Anticholinergic	Secretions	0.01–0.02 mg IV q4 0.04–0.1 mg PO q4	No strong evidence
Ketamine	Dissociative anesthetic	Agitation Pain	0.5–1 mg PO/IV q2-4	
Lorazepam	Benzodiazepine	Agitation Dyspnea	0.05–0.1 mg PO/IV q4-6	
Methadone	Opioid	Pain	0.05–0.2 mg IV/PO q12-24 (initially q4 for 3 doses)	
Midazolam	Benzodiazepine	Agitation Dyspnea	0.05–0.1 mg IV q2-4 0.2–0.3 mg Sublingual q2-4 0.25 mg IN q2-3 0.05 mg/kg/hr IV continuous	Short acting
Morphine	Opioid	Pain Dyspnea Agitation	0.05–0.2 mg IV/IM q2-4 0.15–0.5 mg PO/Sublingual q2-4 0.01–0.05 mg/kg/hr IV continuous	

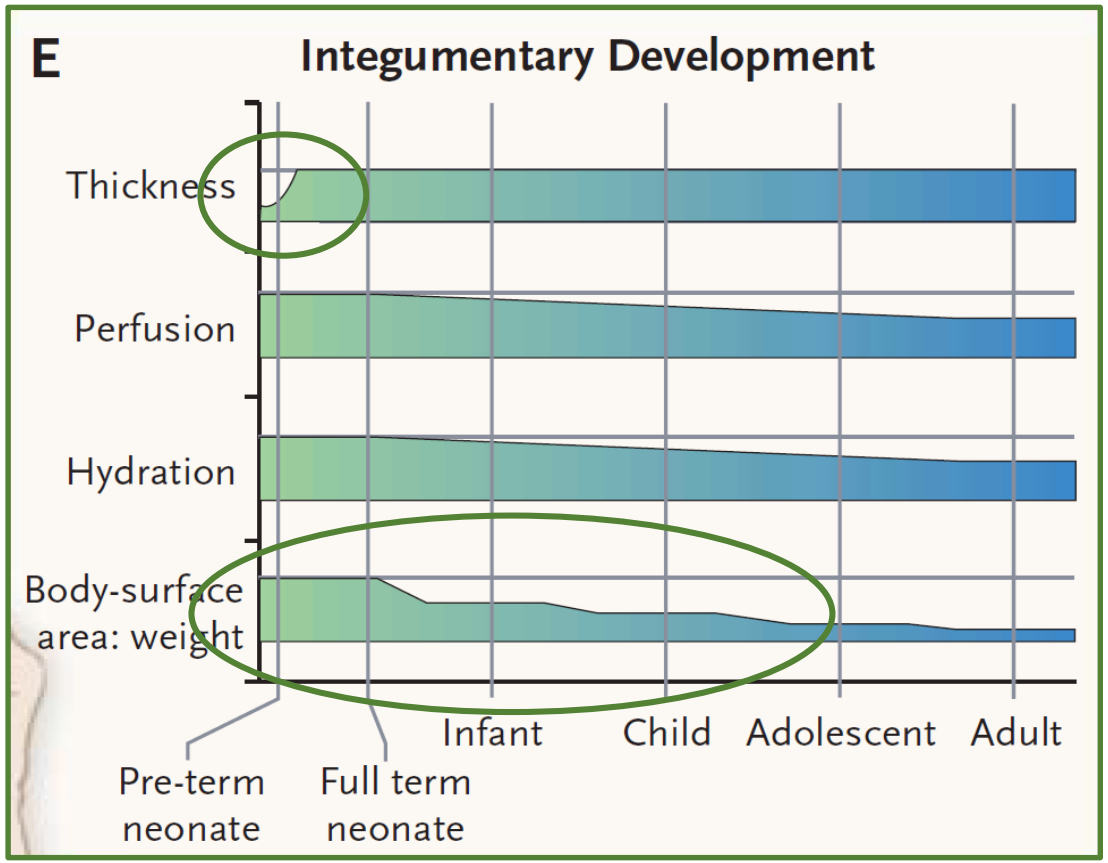
COX-2 inhibitor, Cyclooxygenase-2 enzyme inhibitor; IN, intranasal; IM, intramuscular; IV, intravenous; PO, per oral; PR, per rectum; q2, every 2 h; q2-4, every 2–4 h; q4-6, every 4–6 h; q6, every 6 h; q8, every q hours; q12-24, every 12–24 h.
It may not be appropriate to continue feedings. They can be difficult to digest and cause fluid overload.

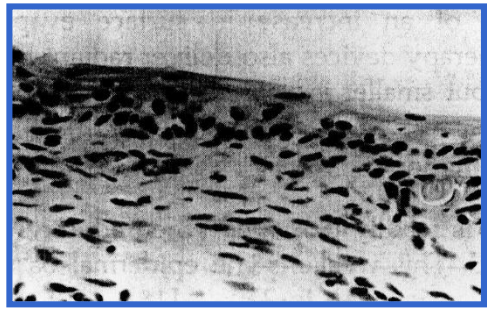
Cortezzo et al, Front Pediatr 2020

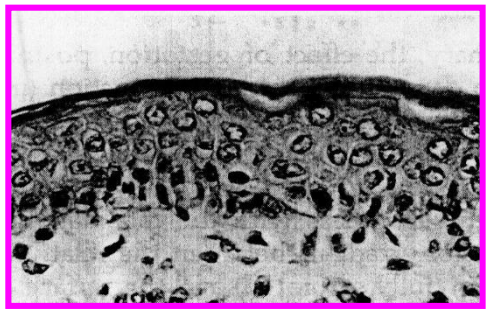


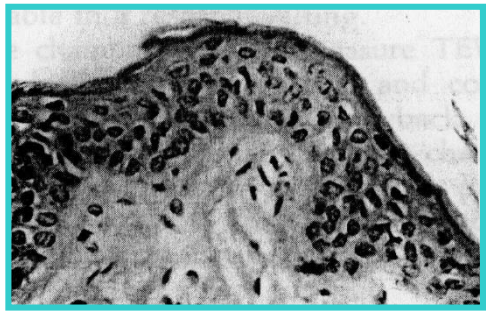
Cortezzo et al, Front Pediatr 2020

absorption, skin: BSA > permeability





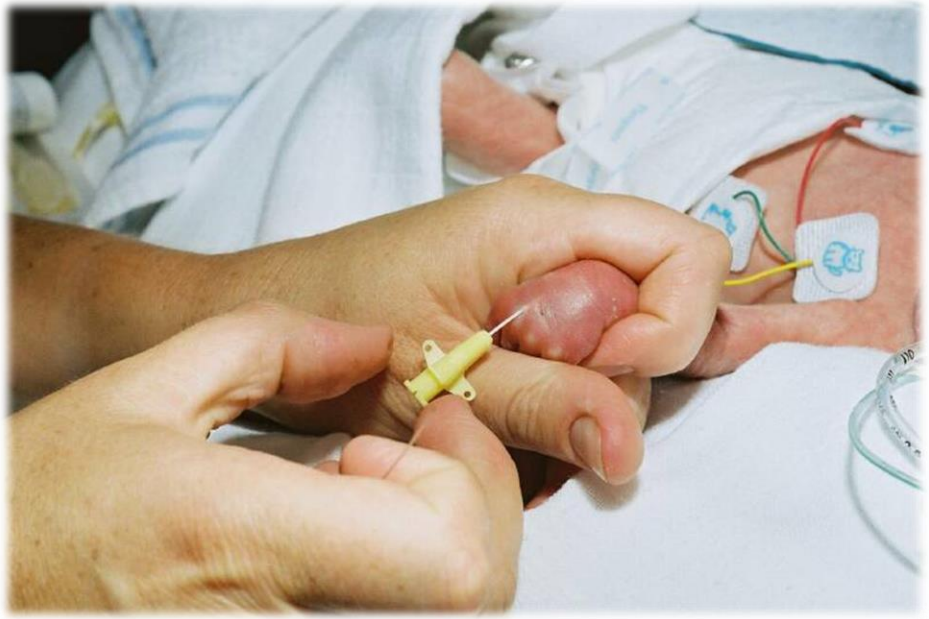


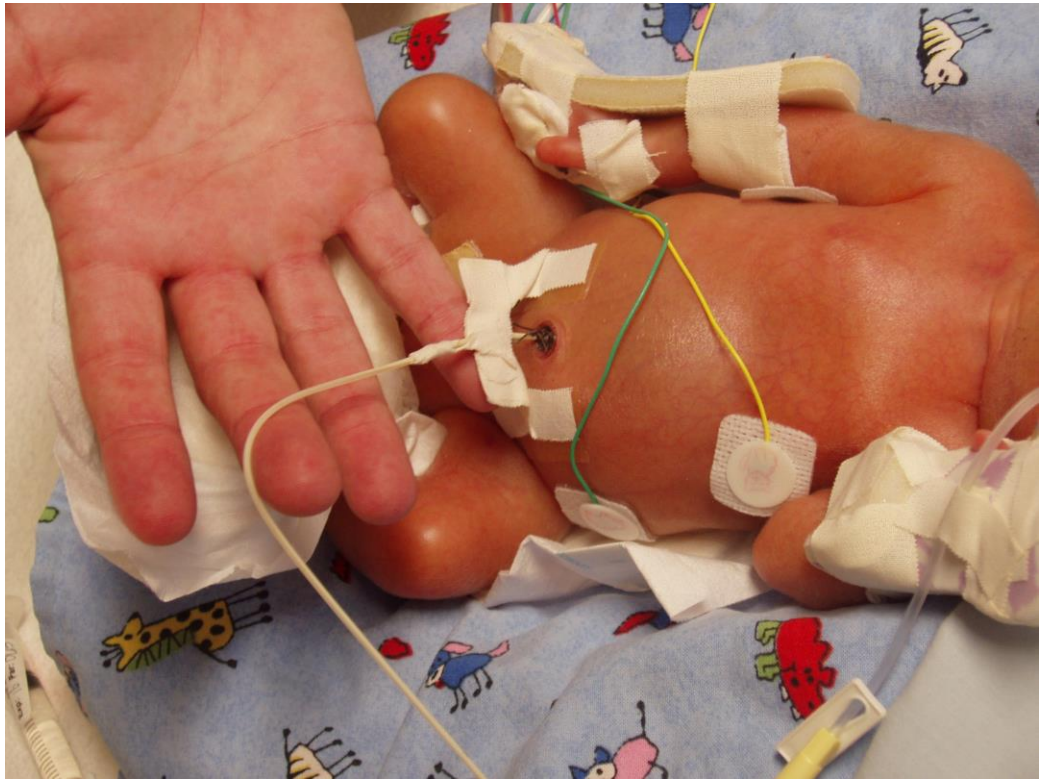


higher BSA/kg in young children: risk for inadverted absorption

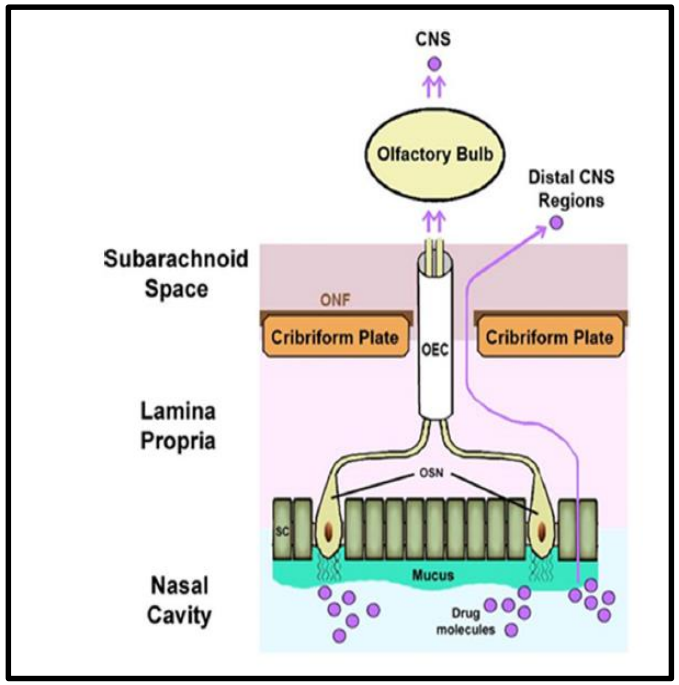
Kearns et al, NEJM 2003

absorption, skin: BSA > permeability

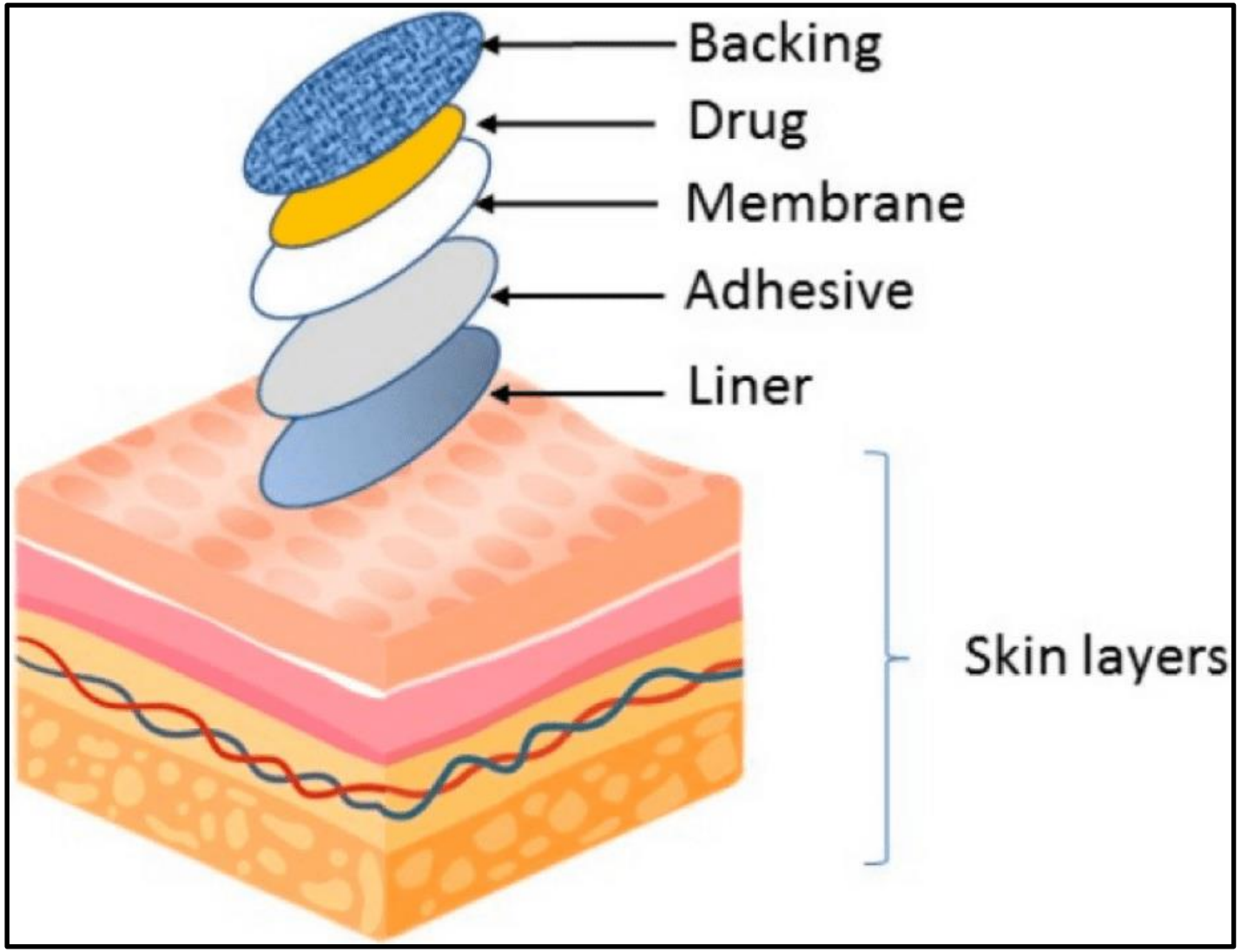




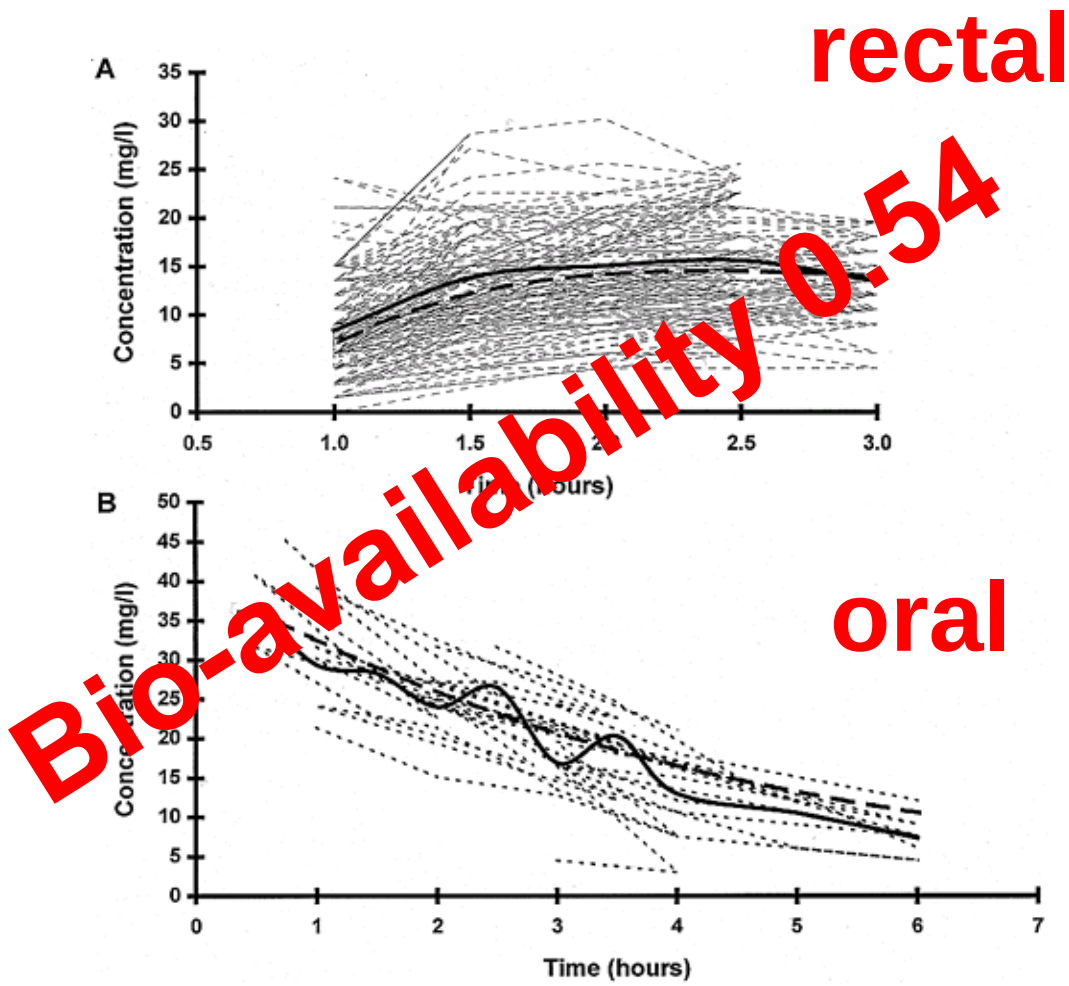
absorption, skin: BSA > permeability



absorption, skin: BSA > permeability

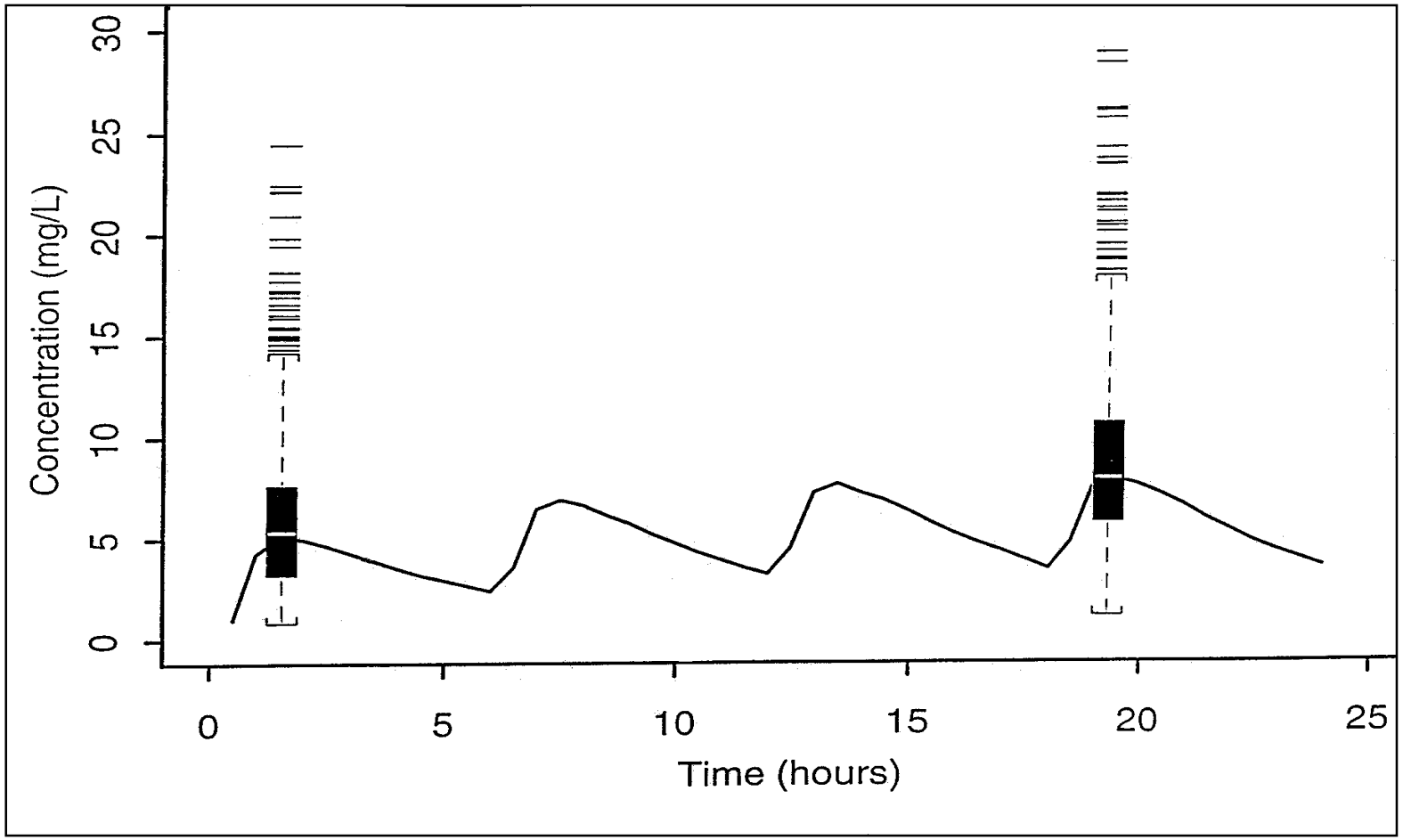


absorption, rectal to oral acetaminophen



Anderson et al, Anesthesiology 1999

absorption, rectal to oral acetaminophen



Anderson et al, Anesthesiology 1999

distribution
body composition, (non)maturational covariates

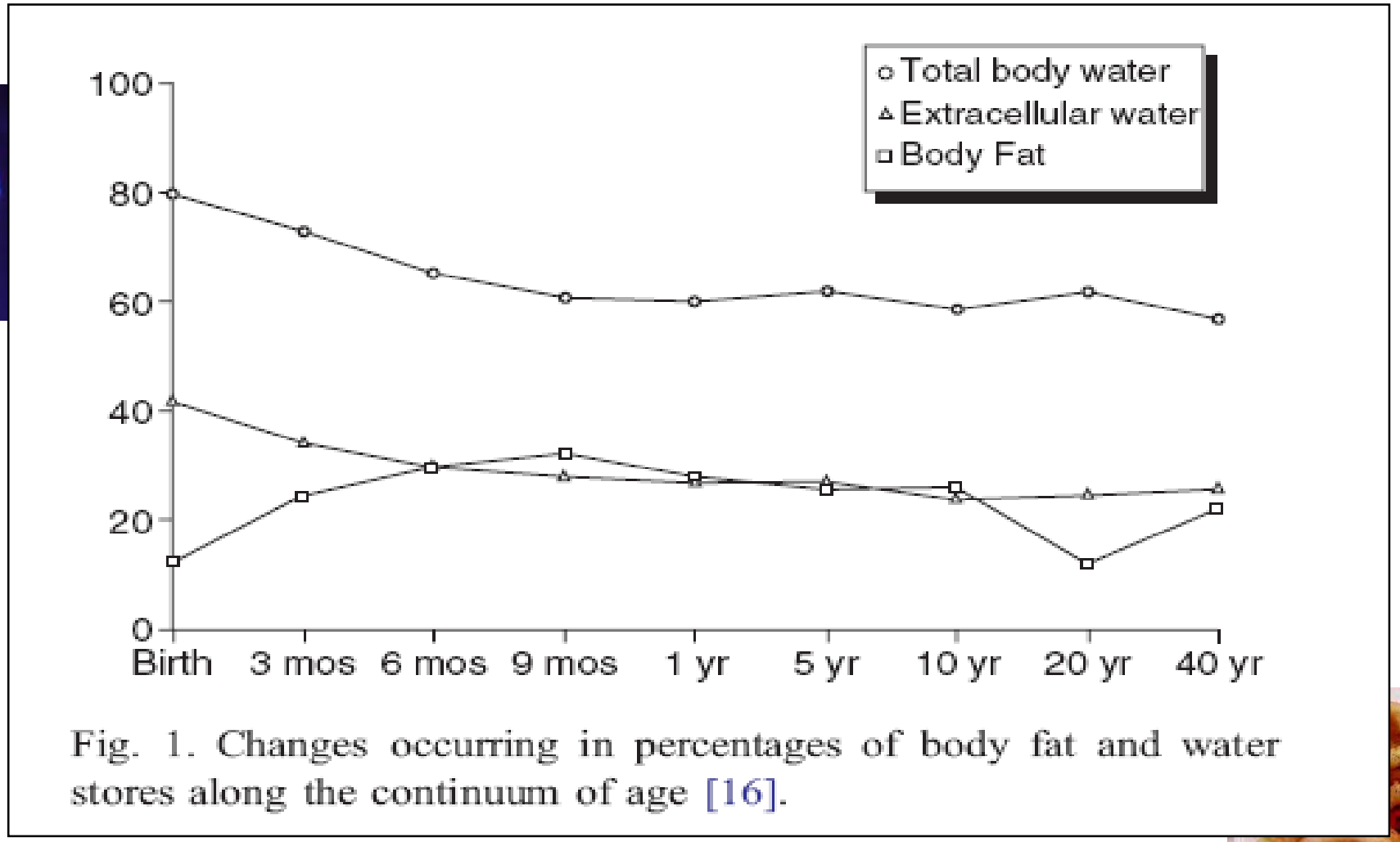
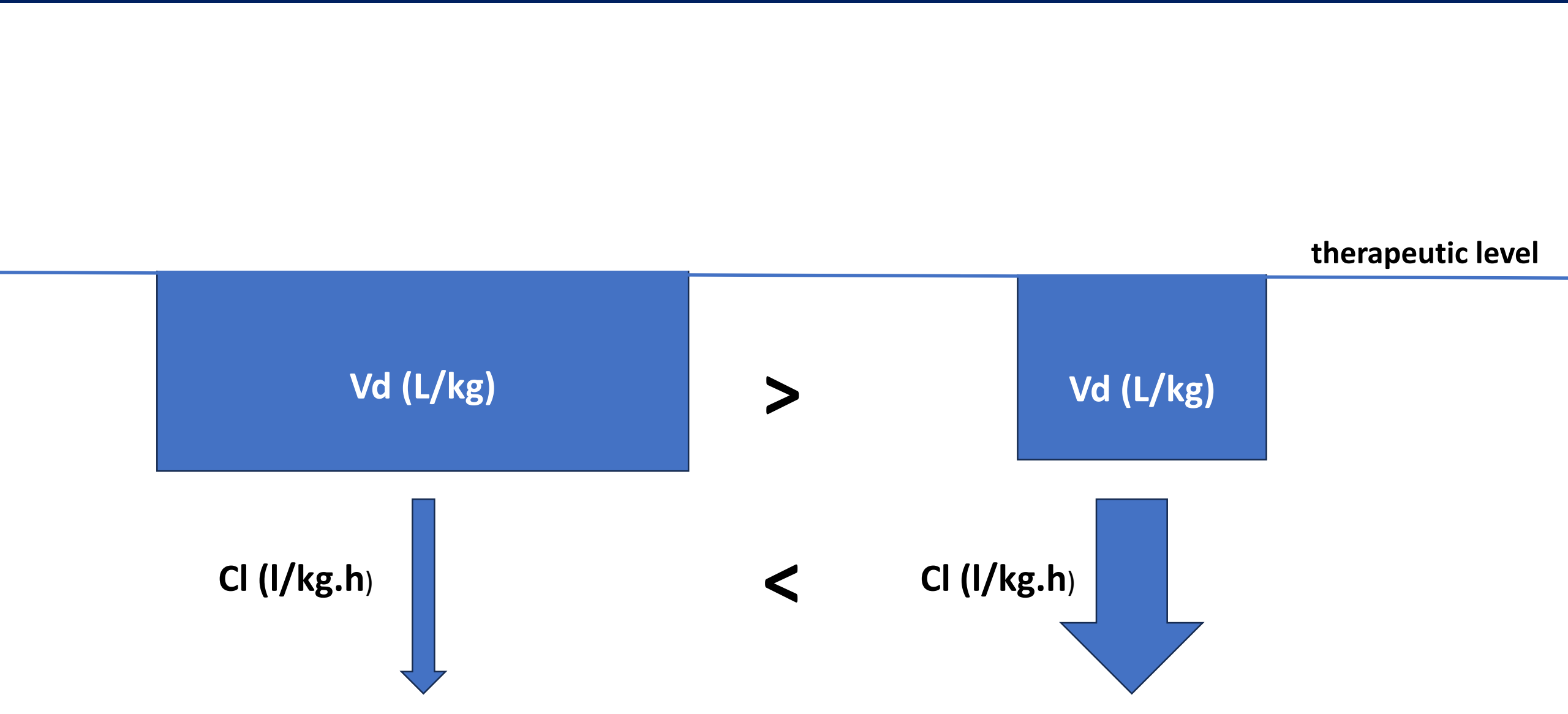


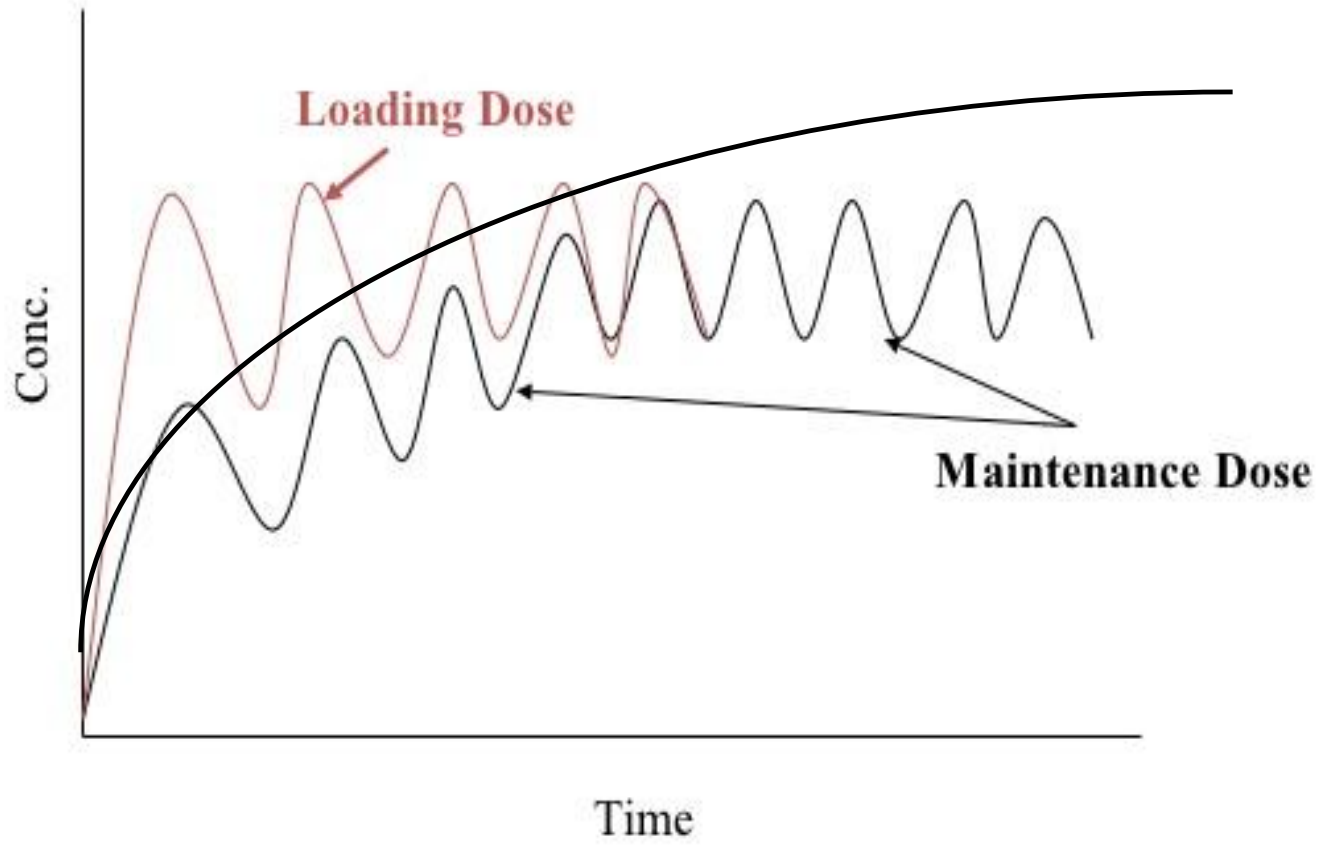
Fig. 1. Changes occurring in percentages of body fat and water stores along the continuum of age [16].

Rakhmanina et al, Adv Drug Deliver 2006

distribution volume and clearance
newborn versus adult



distribution volume: relevance (continuous)



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 (intermittent)

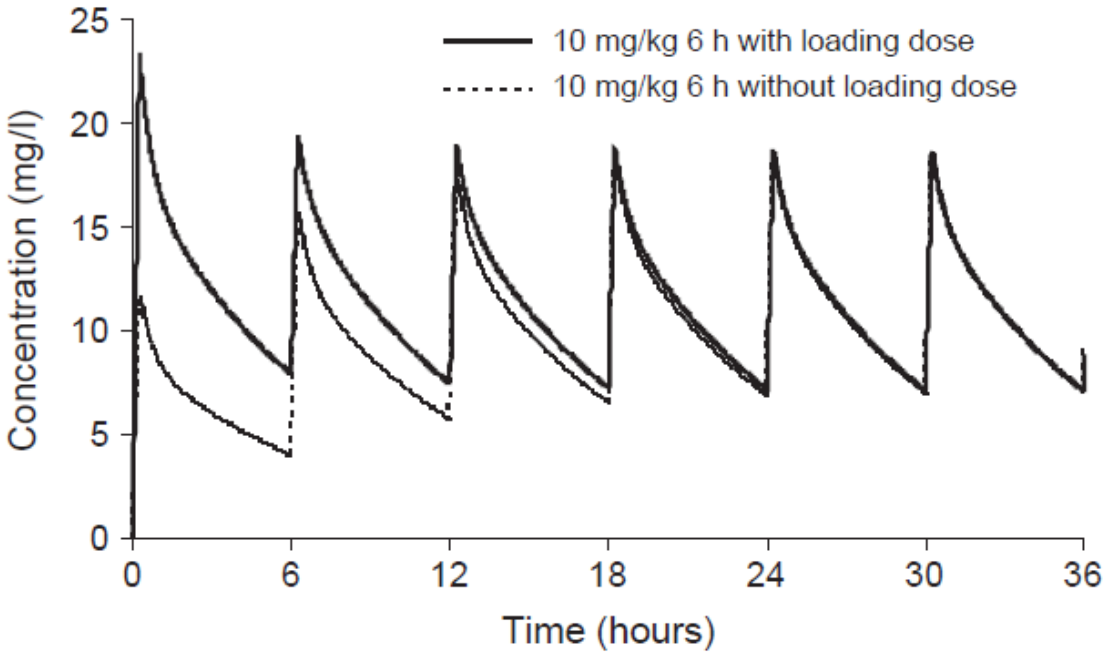
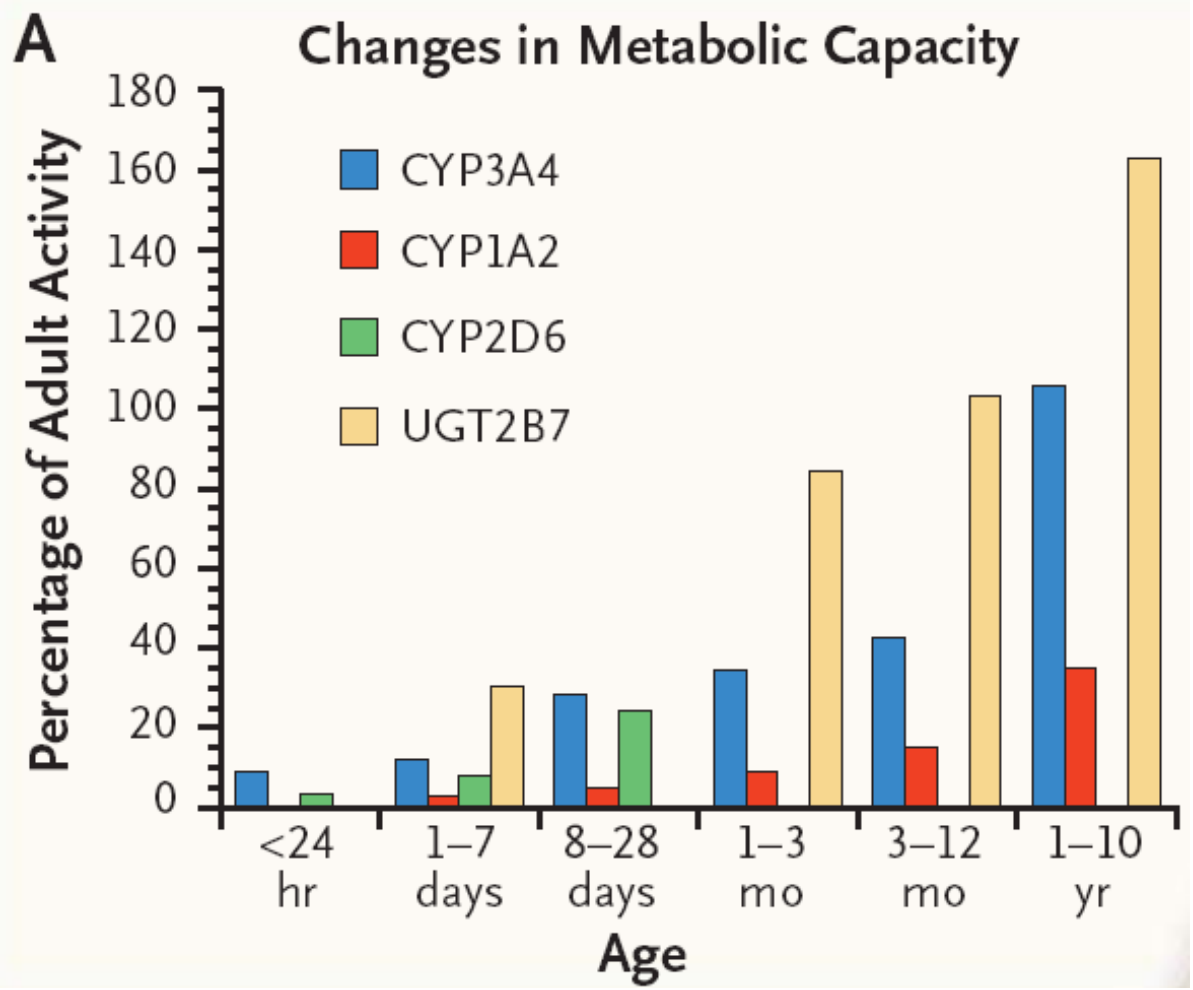


Figure 3 A typical concentration profile for neonates of 28–44 weeks' premenstrual age given a paracetamol loading dose of 20 mg/kg (black continuous line) or not given a loading dose (grey continuous line), followed by a maintenance dose of 10 mg/kg every 6 h. A mean concentration of 11 mg/l is achieved.

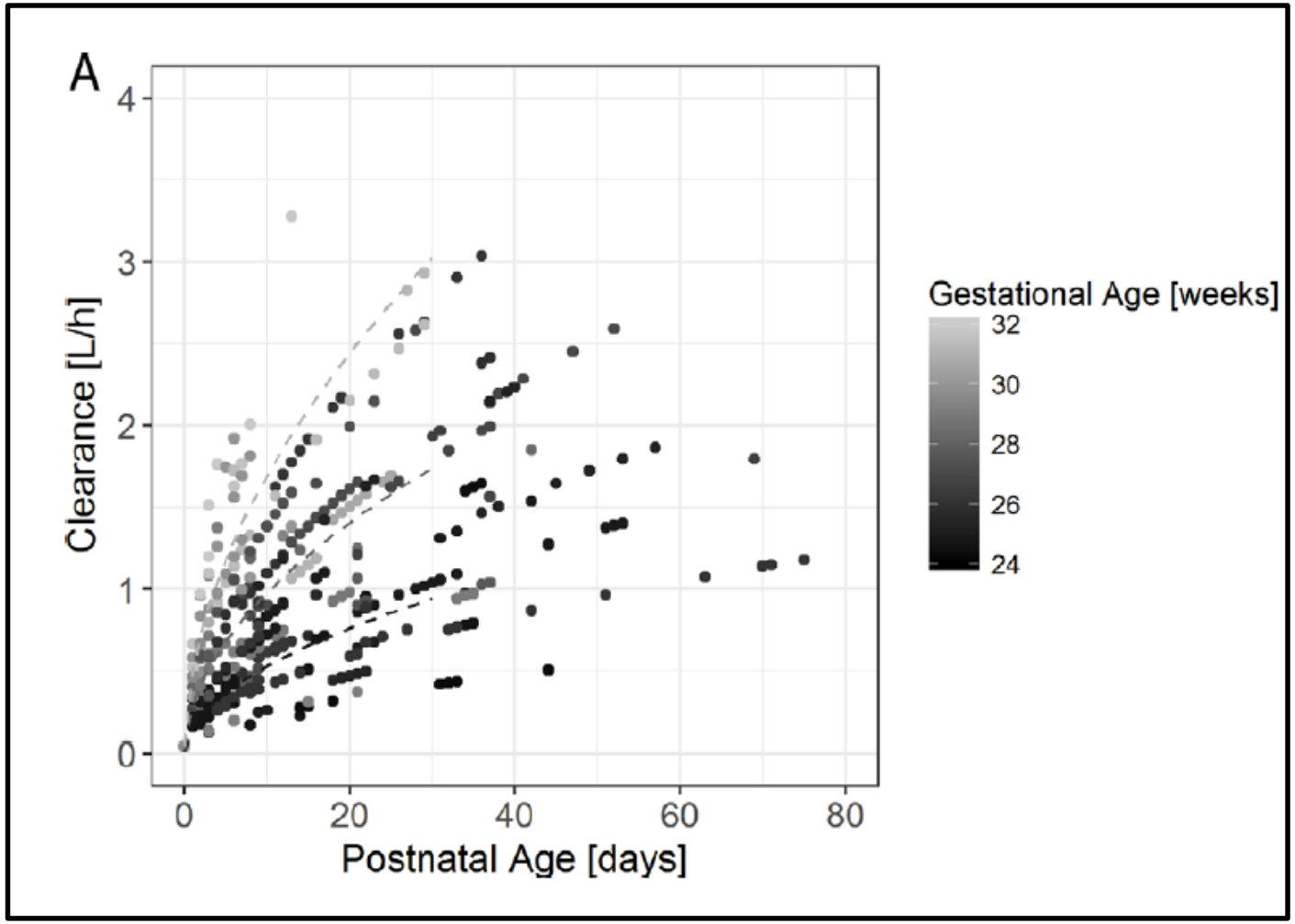
pooled iv paracetamol in neonates. Arch Dis Child 2011

Age related maturation is the common main driver, but…



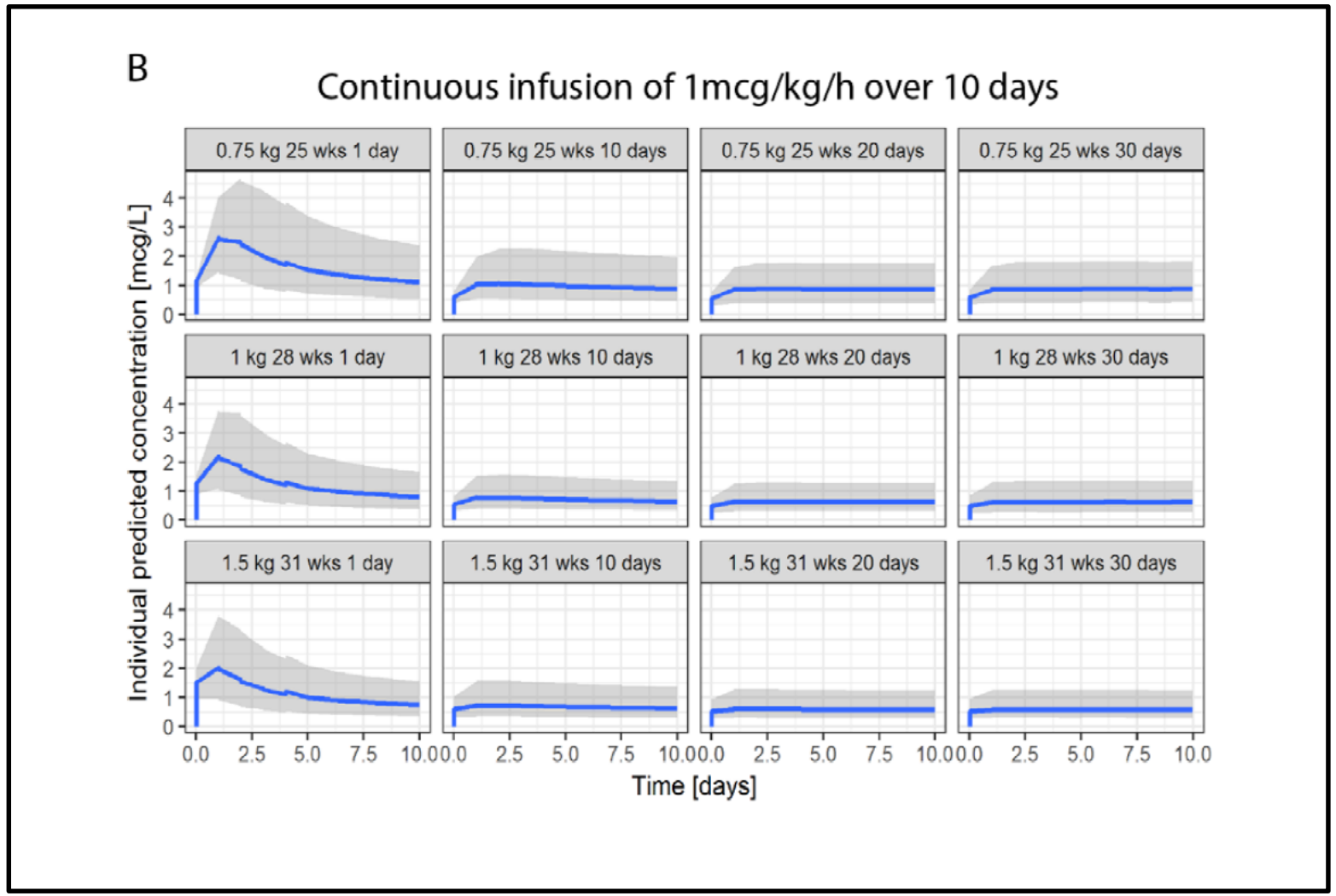
Kearns et al, NEJM 2003

fentanyl clearance as a first illustration



Völler S et al, Arch Dis Child 2019

fentanyl clearance as an illustration
tolerance or increased clearance/decreased exposure



Völler S et al, Arch Dis Child 2019

the framework (clin pharm) to work within

NSAIDS, fentanyl, morphine or dexmed ?

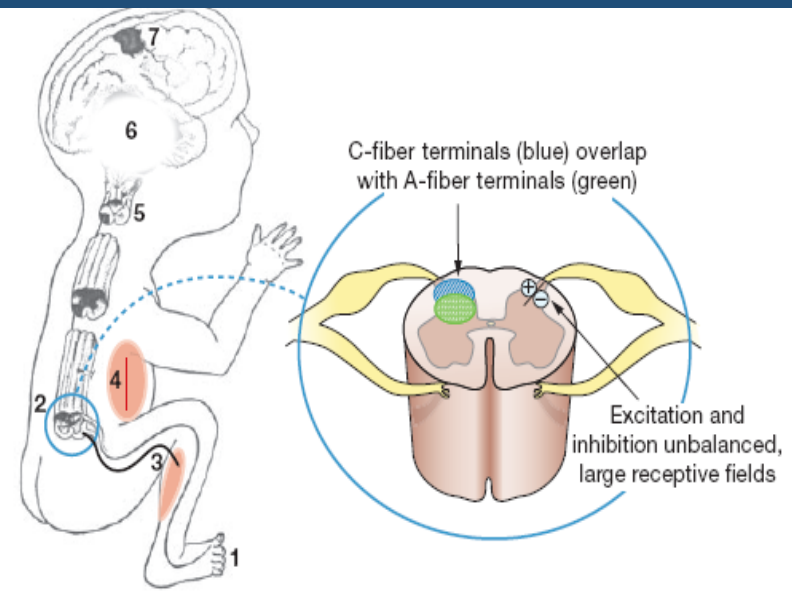
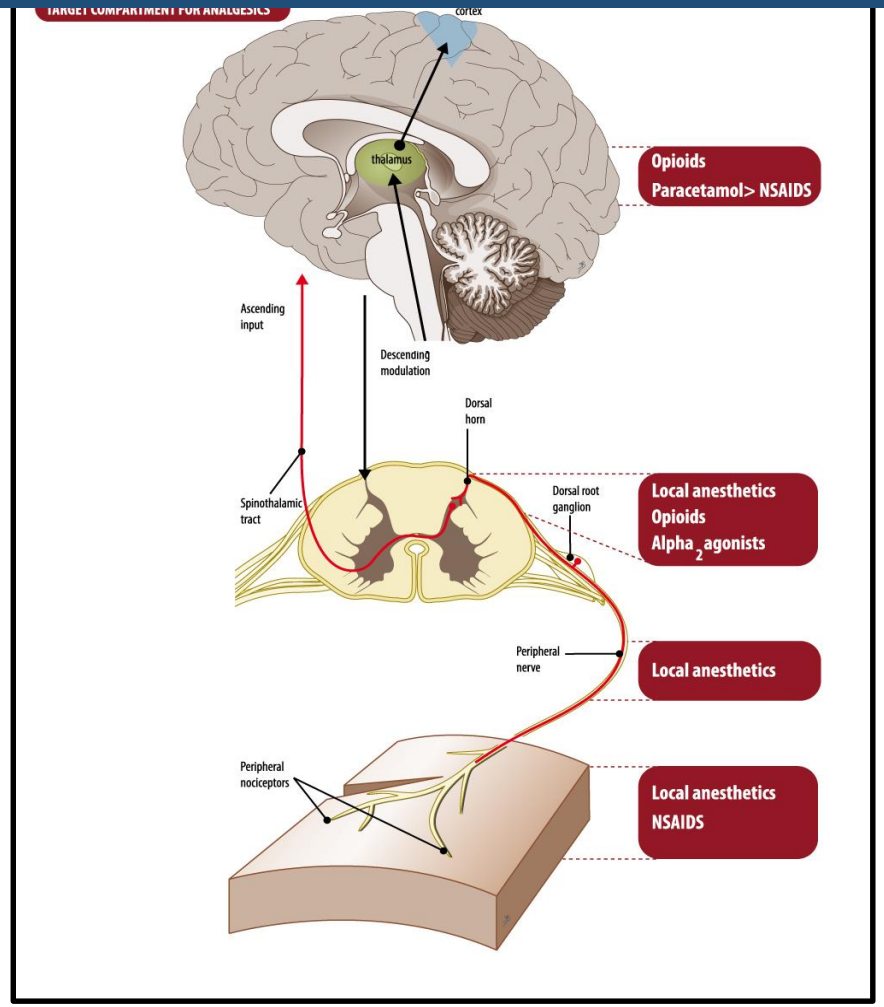
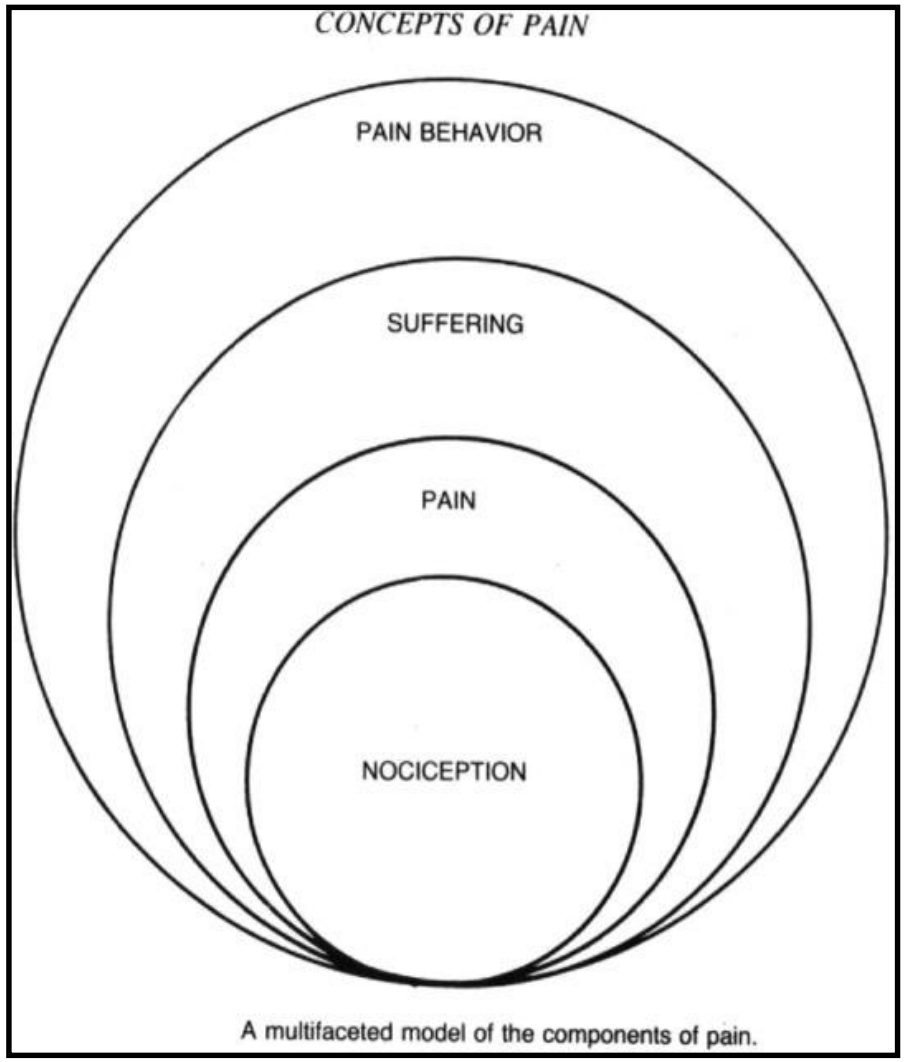


Figure 1 Key sites of developmental transition in infant pain pathways. The areas of the nervous system are indicated where developmental changes and plasticity impact pain detection and treatment in this group. (**1**) Peripheral innervation is vulnerable and sensitive to tissue injury. (**2**) Dorsal horn sensory pathways undergo considerable postnatal reorganization. (**3**) Nociceptive reflex pathways are diffuse and poorly tuned. (**4**) Primary hyperalgesia develops before secondary hyperalgesia. (**5**) Endogenous descending controls via the brainstem are unbalanced. (**6**) Extensive cortical development begins postnatally, but little is known of the development of intracortical network connections in infancy. (**7**) The somatosensory cortex is activated by noxious stimulation from an early age, but little is known of activation in other cortical regions.



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



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

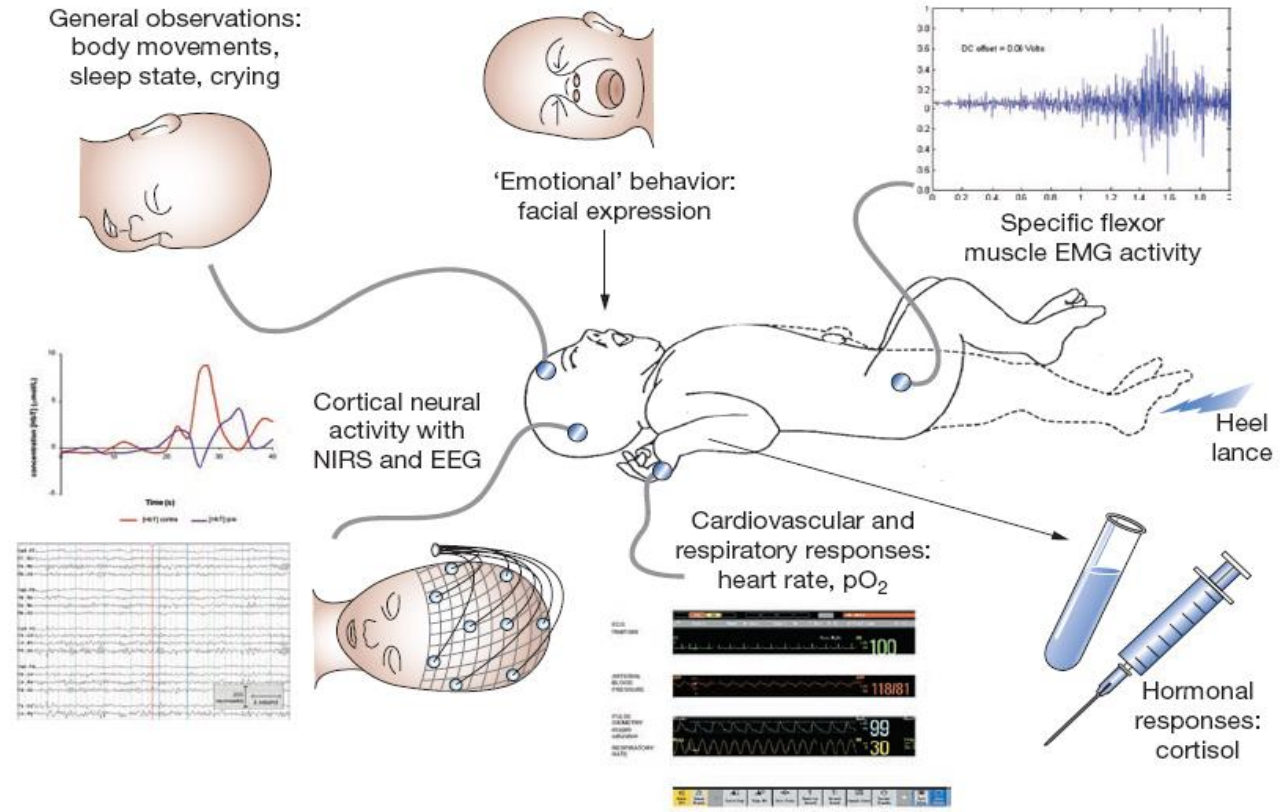


Figure 2 Methods of assessing infant pain. In the absence of language, infant pain is assessed by a number of different physiological methods. Some of these methods are integrated into current clinical pain assessment tools. The neurophysiological techniques EMG, EEG and NIRS are not used for routine pain assessment but are increasingly being used in research studies of infant pain. Abbreviations: EMG, electromyogram; NIRS, near-infrared spectroscopy; pO_2, 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

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

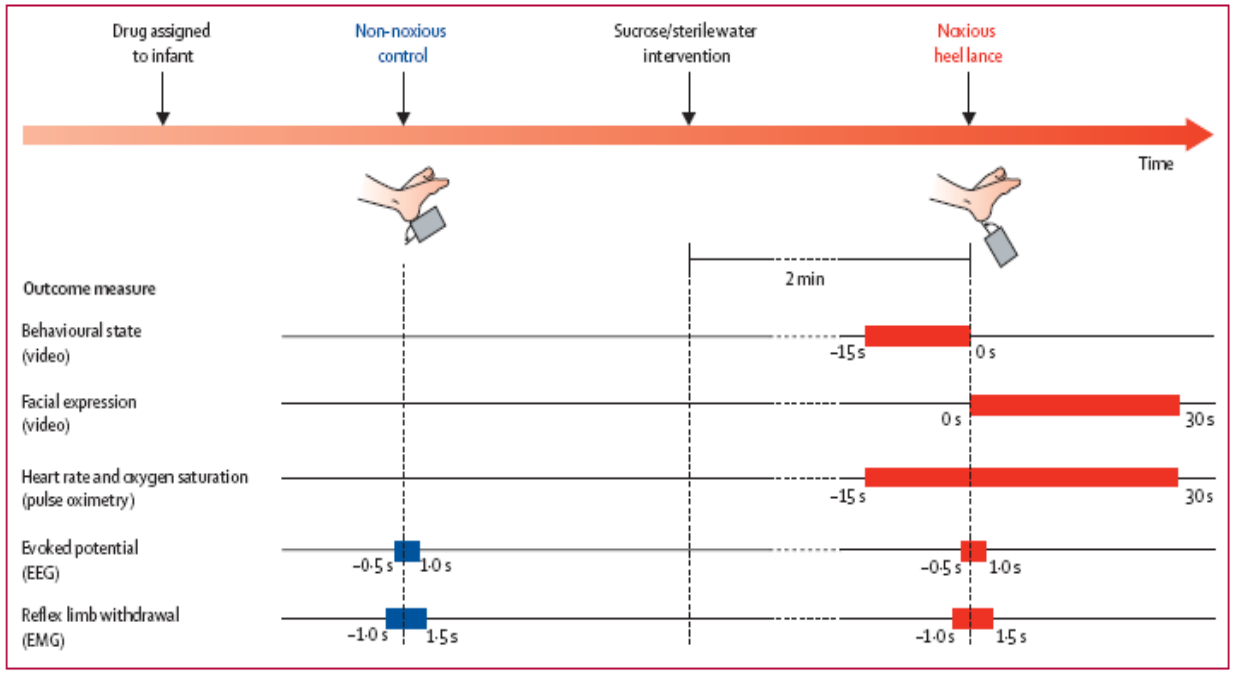


Figure 1: Experimental time line
EEG=electroencephalography. EMG=electromyography.

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

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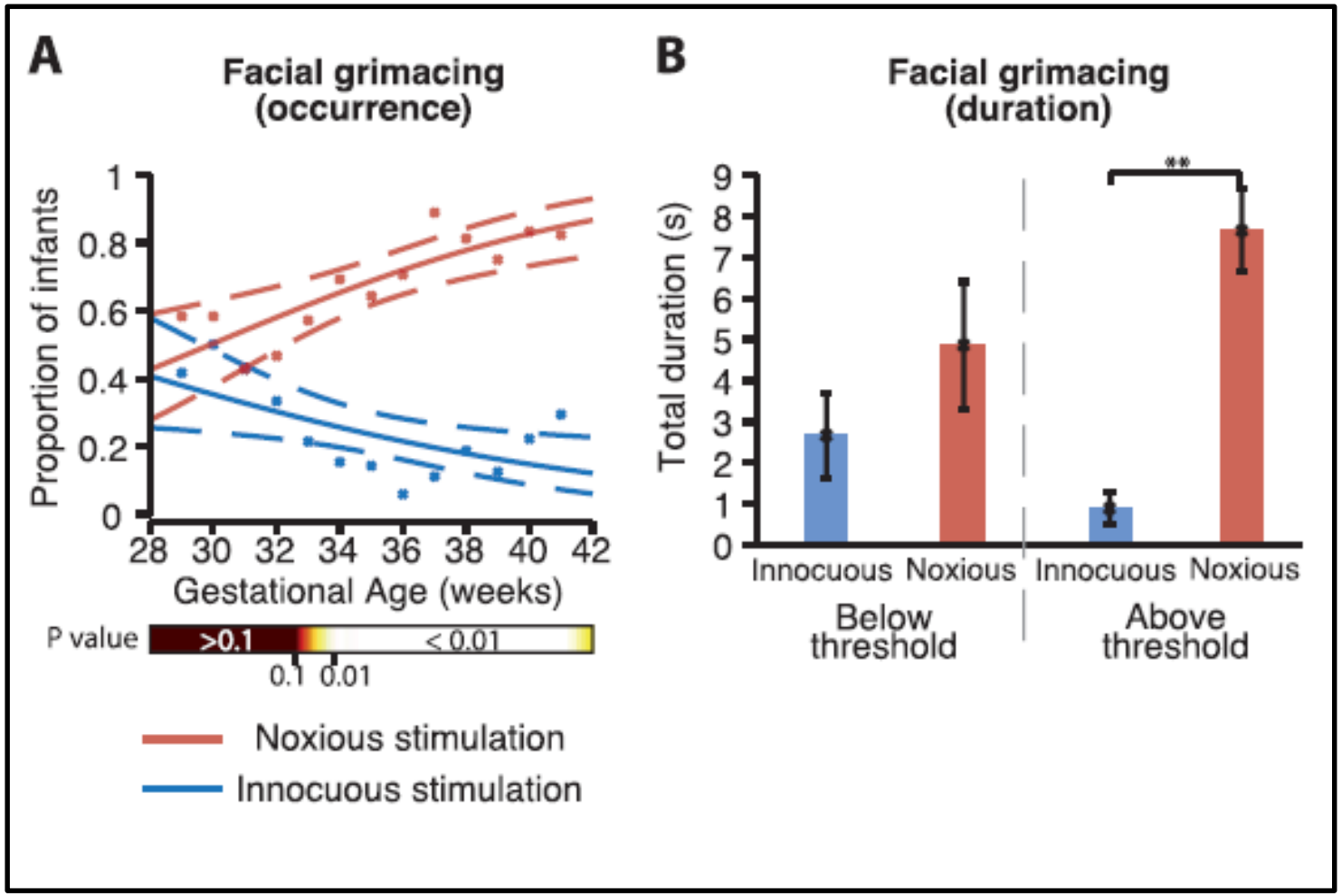
	Sucrose (N=20)	Sterile water (N=24)	p value
Primary outcome			
Nociceptive-specific brain activity (mean weight)	0·10 (0·04–0·16)	0·08 (0·04–0·12)	0·46
Secondary outcomes			
Mean baseline heart rate (bpm)	132·6 (124·3–140·9)	131·8 (122·2–141·5)	0·90
Mean baseline oxygen saturation (%)	99·4% (98·8–100·1)	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


PIEDRAS
Cervicales
Gastritis
y gases
Tos y
TENSIÓN
ARTERIAL
Celulitis
Diabetes
ELIMINAR
GRASAS
GASTRITIS
GASES
NO
TOCAR
Colesterol

Development of a Perinatal Palliative Care Model at a Level II Perinatal Center Supported by a Pediatric Palliative Care Network

Marco Bolognani[1,2], Paola Daniela Morelli[2], Isabella Scolari[2], Cristina Dolci[2], Valentina Fiorito[2], Francesca Uez[2], Silvia Graziani[1], Barbara Stefani[1,2], Francesca Zeni[1,2], Gino Gobber[2], Elena Bravi[2], Saverio Tateo[2] and Massimo Soffiati[1]*

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