pijnbestrijding bij de zuigeling: wat zijn de opties?

SAFE PEDRUG

Erasmus MC Rotterdam, the Netherlands
KU Leuven, Belgium
karel.allegaert@kuleuven.be

Erasmus MC
Universitair Medisch Centrum Rotterdam

KATHOLIEKE UNIVERSITEIT LEUVEN

karel allegaert


If a procedure is painful in adults, it should be considered painful in newborns, even if they are preterms.

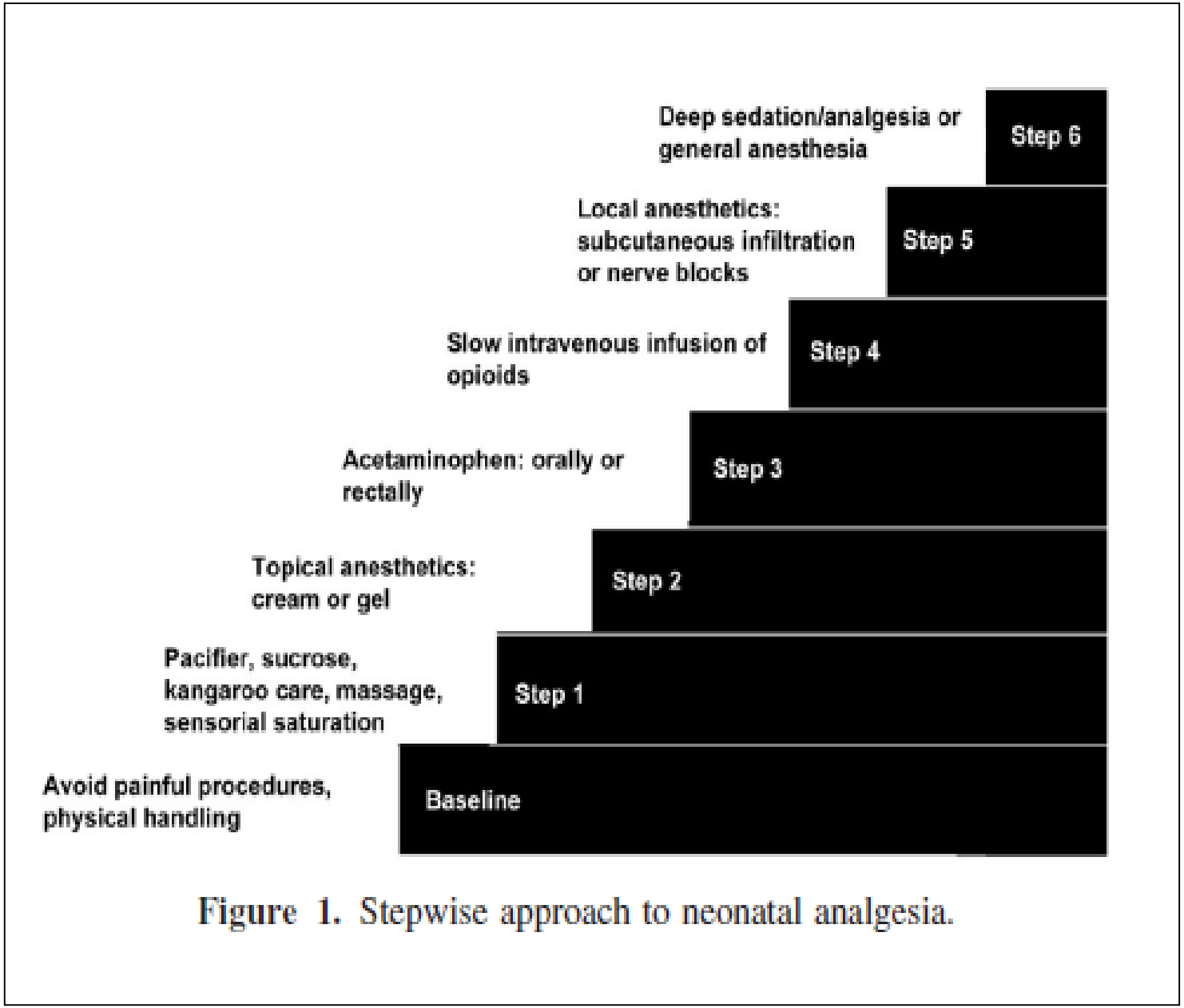
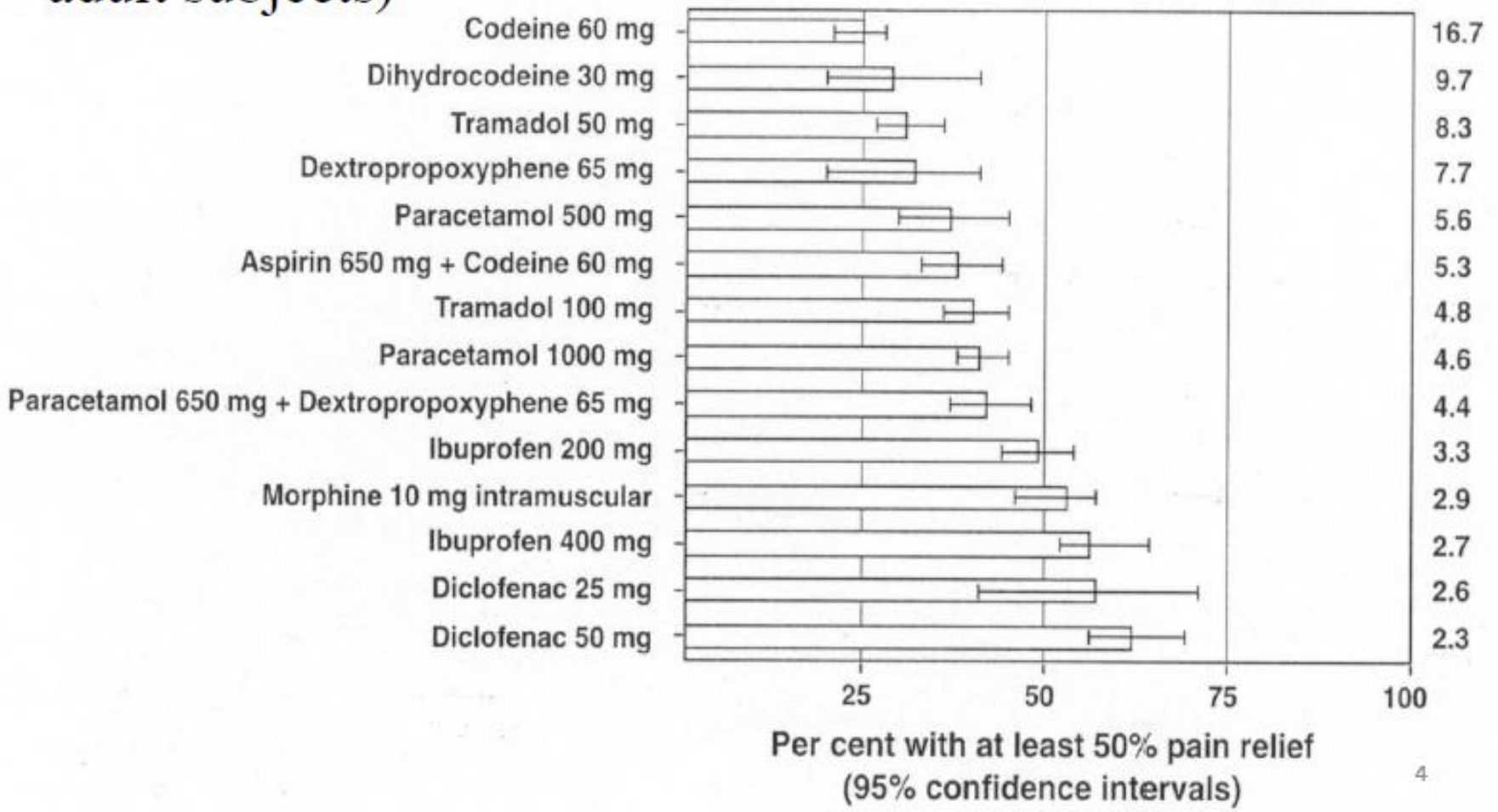


Figure 1. Stepwise approach to neonatal analgesia.

Analgesics Have Mediocre Efficacy - from H. McQuay, A. Moore "An Evidence-Based Resource for Pain Relief", Oxford Press – meta-analyses with >50,000 adult subjects)

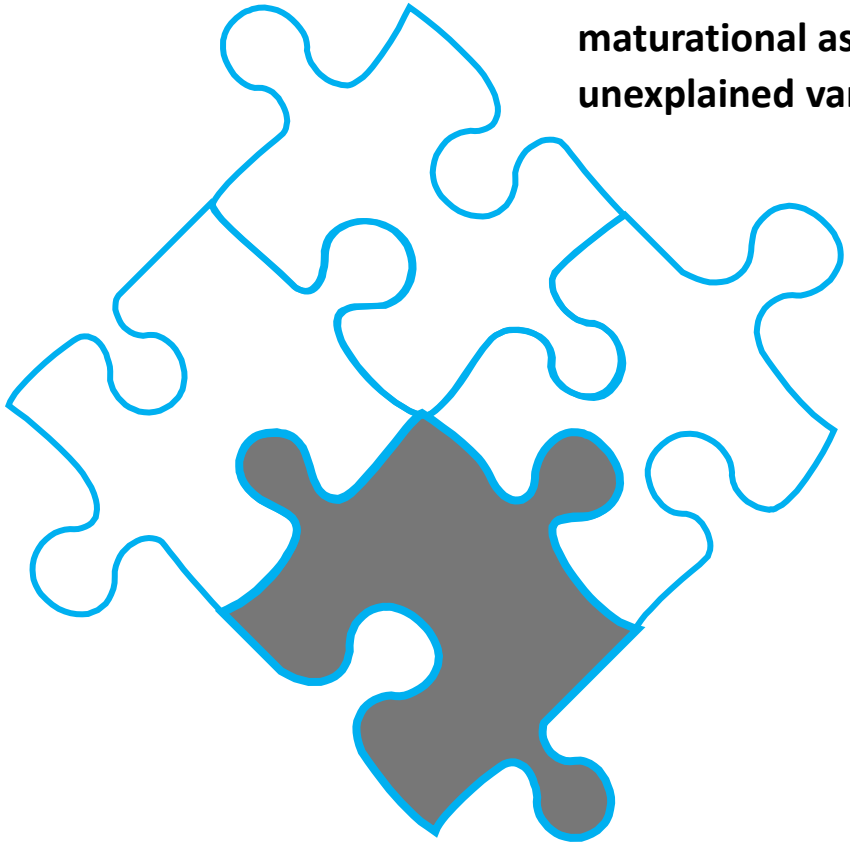


treatment

maturational aspects
unexplained variability

assessment

pain scales
intersubjectivity



prevention

relevant
limited

individualized approach

SUGGESTIE 1

Pain in babies may cause later harm

Photodisc file

Study in newborn rats suggests early trauma rewires nervous system

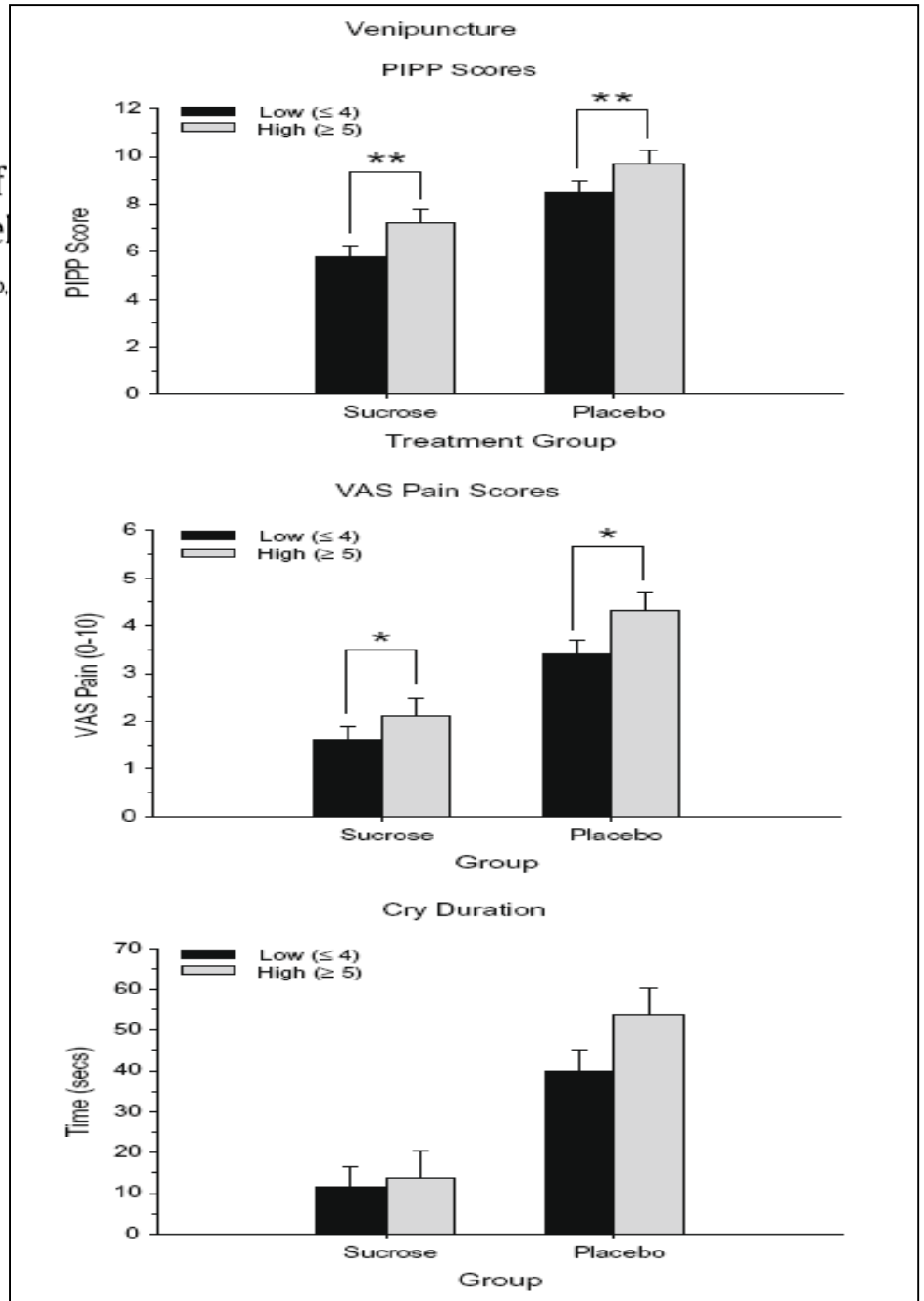
Debate has been raging in the medical community over how newborns experience pain and the impact later on.

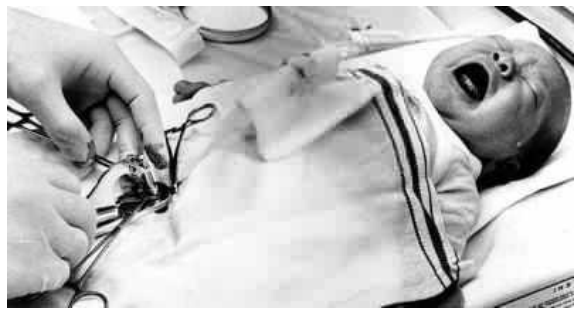
REUTERS

July 27 — Newborns who have painful, but often life-saving, medical procedures in the early weeks of life may have a lower pain threshold in later years, according to a new animal study released Thursday.

Influence of
on the devel

Anna Taddio [a,b,





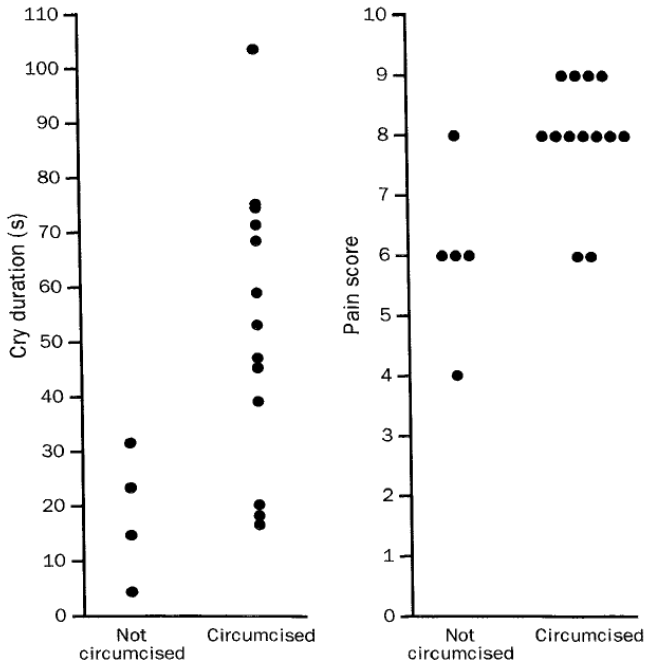
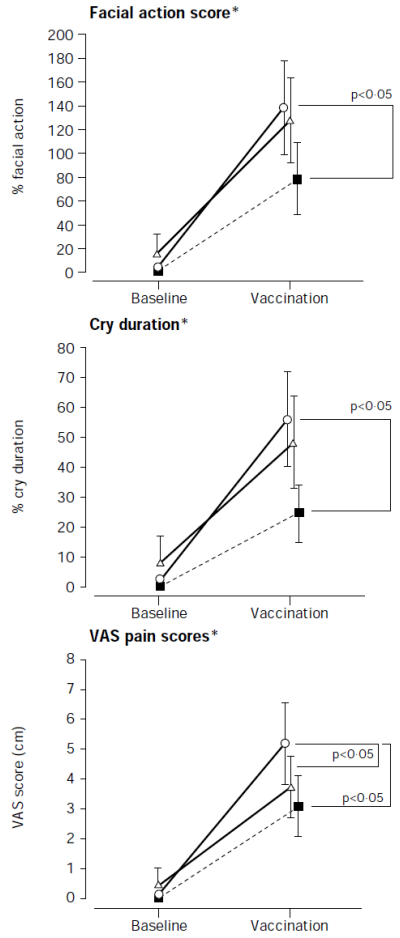


Figure: **Pain response during HIB injection in circumcised and uncircumcised boys**
Data not available for cry on 1 infant. p=0·02 for cry, p=0·01 for behavioural pain score.



Infant pain response to vaccination for infants in all groups
VAS=visual analogue scale.
*Values shown as mean (95% CI).

Anand *et al.* New Engl J Med 1987
Taddio *et al.* JAMA 2002
Taddio *et al.* Lancet 1995 and 1997

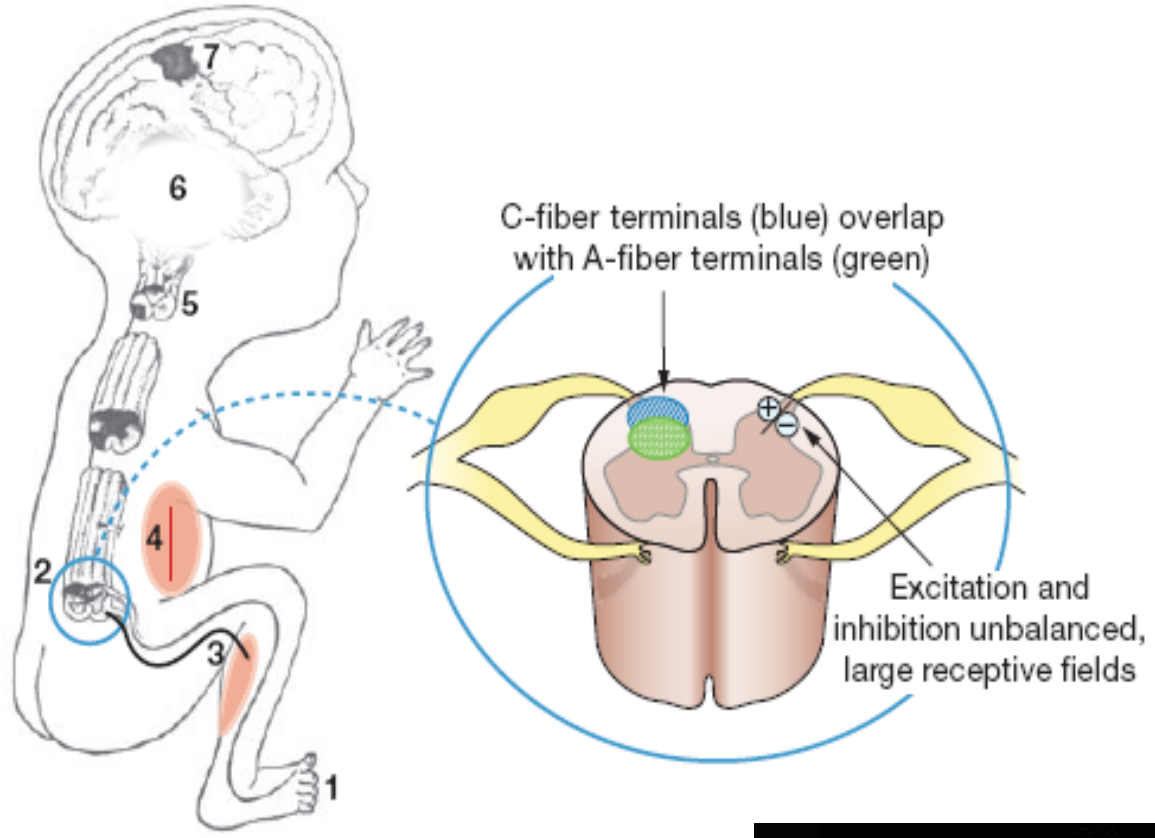
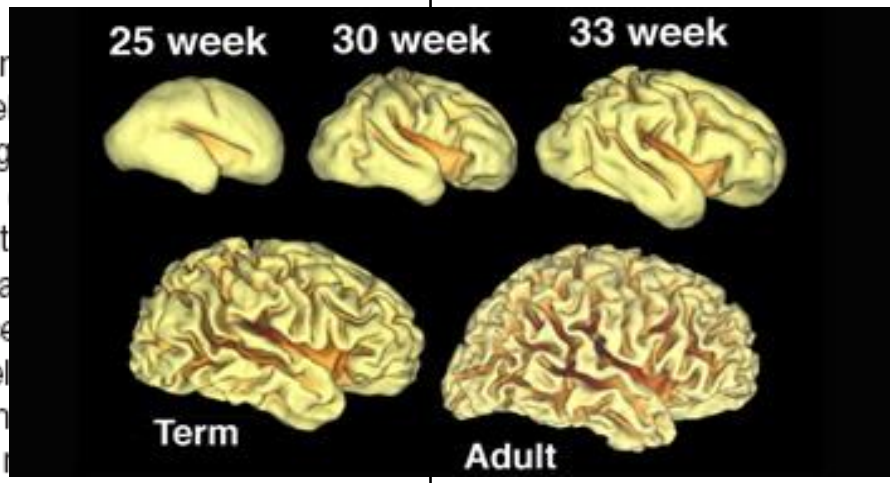
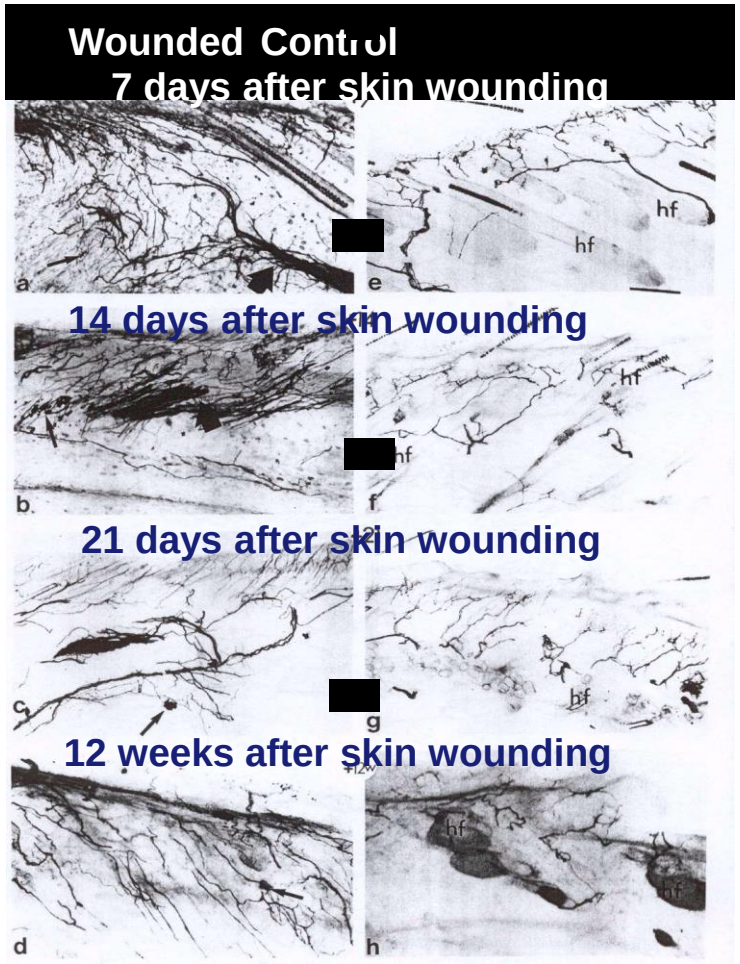


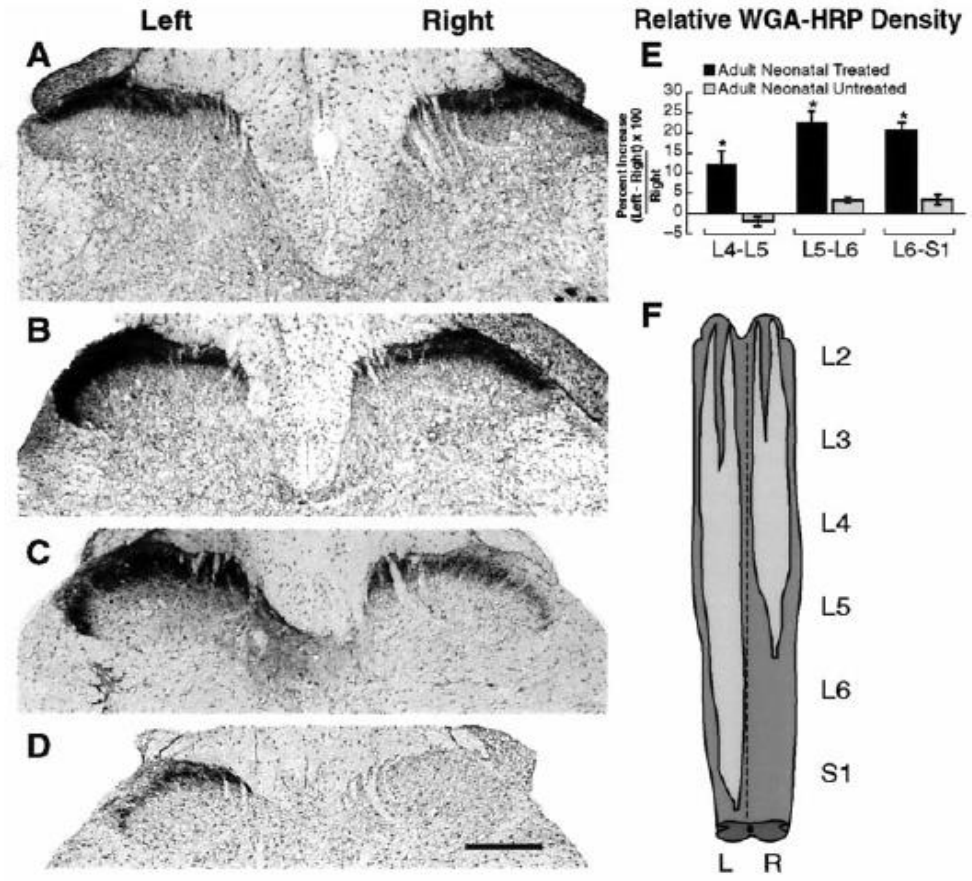
Figure 1 Key sites of developmental transition in infan
areas of the nervous system are indicated where deve
plasticity impact pain detection and treatment in this g
innervation is vulnerable and sensitive to tissue injury.
pathways undergo considerable postnatal reorganizat
reflex pathways are diffuse and poorly tuned. (**4**) Prima
before secondary hyperalgesia. (**5**) Endogenous desce
brainstem are unbalanced. (**6**) Extensive cortical devel
but little is known of the development of intracortical n
infancy. (**7**) The somatosensory cortex is activated by
early age, but little is known of activation in other cortical regions.





Reynolds & Fitzgerald. J Comp Neurol 1995; 358: 628-31

hyper(re-)innervation following neonatal skin laesions



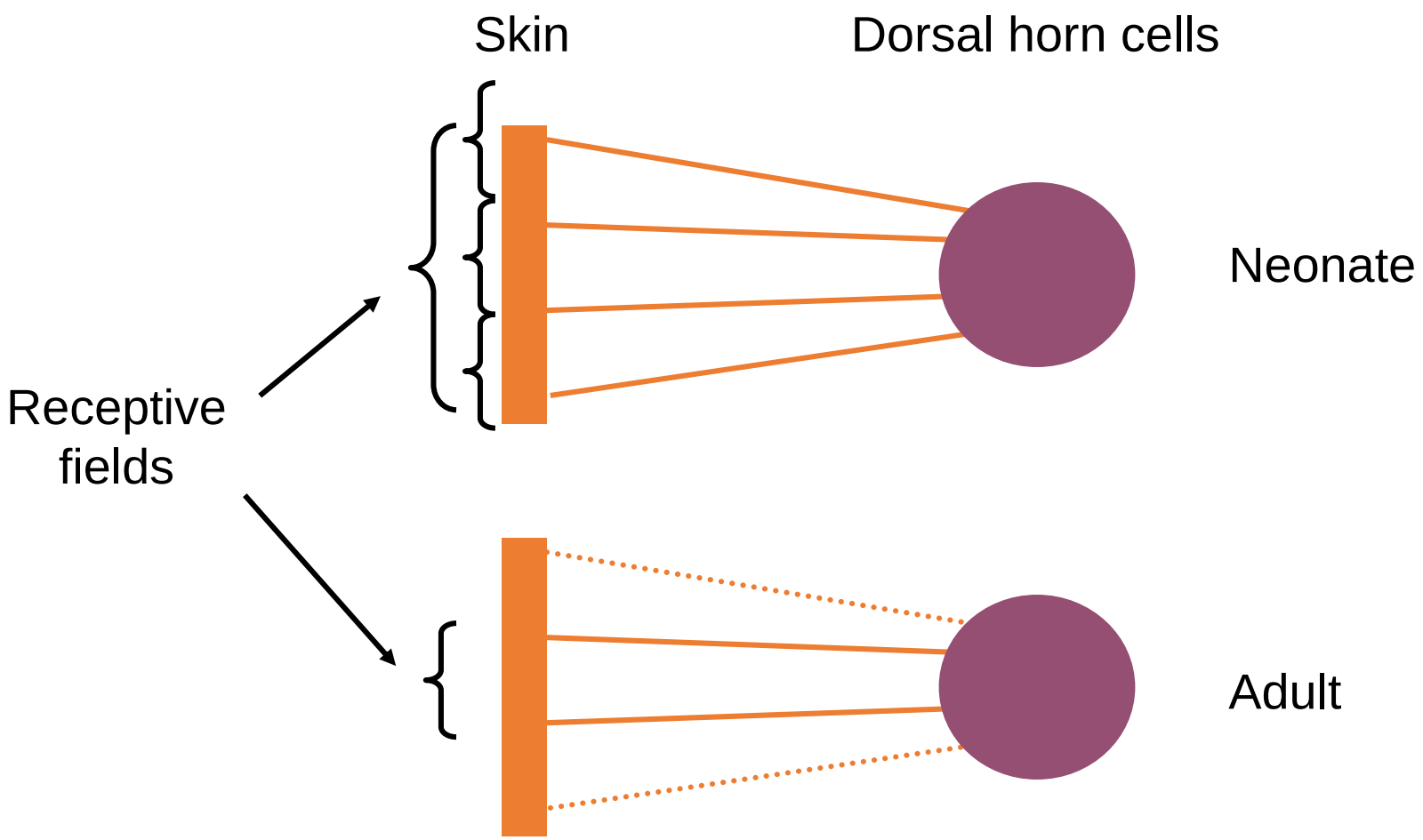
Maximal effect in rats: 6-9 days *(Anand & Scalzo 2000)*

No effect in rats: 14 days *(Ruda et al. 2000)*

Rat		Human
0 day	-	24 wks GA
7 days	-	full-term
14 days	-	1-year-old

Ruda et al. Science 2000; 189: 628-31/ Walker et al. Pain 2003; 105: 185-95

early insult rewires pain circuits


Skin
Dorsal horn cells
Receptive fields
Neonate
Adult

SUGGESTIE 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*

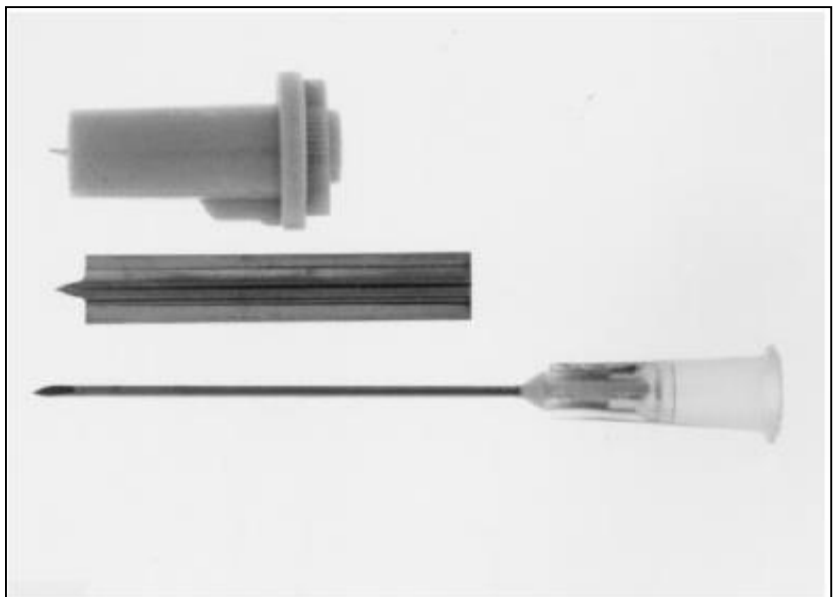


Fig 1. Three devices used for the PKU test. From the top: the CCS Minilancet used in the SL group, the Microlance used in the LL group, and the Microlance needle (0.9 × 40 mm) used in the VP group.

The 3 P's of Helping your Baby during Vaccinations
A Parent's Guide: Babies up to 1 year old

Vaccine injections can be painful and stressful for babies and parents, but you can really make a difference.

Plan Ahead

For your baby's next vaccine injection, plan with your health care provider to:

1) Apply topical anaesthetics to numb the skin – these are medicines you can buy at a pharmacy without a prescription.
2) Give your baby sugar water for comfort – make sugar water at home or at the clinic by mixing 1 teaspoon of sugar with 2 teaspoons of water.
3) Distract your baby – choose an age-appropriate item to bring.

Read the 3 P's of vaccination pain management below and combine these strategies to improve pain relief.
For more information and a video, visit the **SickKids** (The Hospital for Sick Children, Toronto, Canada) website:
www.aboutkidshealth.ca/pain-free-injections

Before Injection

STEP 1: PHARMACOLOGICAL (PAIN MEDICINE)

TOPICAL ANAESTHETICS

- Available products: lidocaine (Maxilene™), tetracaine (Ametop™), lidocaine-prilocaine (EMLA™).
- Apply to either the upper outer part of the leg (infants less than 1 year), or upper arm (infants 1 year old), 30 to 60 minutes before injection – check product instructions.
- If 2 or more injections are planned, apply to both legs or arms.
- May cause temporary reddening or whitening of skin – this is normal. If there is a rash, talk to your doctor – it could be an allergic reaction.
- Avoid acetaminophen (Tylenol™), ibuprofen (Advil™), ice and cold sprays before injection – they have not been proven to reduce injection pain. After injection, acetaminophen or ibuprofen may be used to relieve fever or discomfort.

SUGAR WATER

- Give your baby sugar water to drink right before the injection.

During Vaccine Injection

STEP 2: PHYSICAL (BODY POSITION AND ACTIVITY)

HOLD

- Hold your baby close during injection – in a hug or on your lap. This feels good and helps your baby stay still.
- Avoid holding your baby too tightly – this can increase pain and distress.

BREASTFEED

- Start breastfeeding your baby before injection and continue during and after injection.
- If 1 injection is planned, position your baby to expose 1 leg; expose both legs for 2 or more injections.
- If the baby cannot be breastfed, offer a bottle or pacifier starting before injection and continue during and after injection.

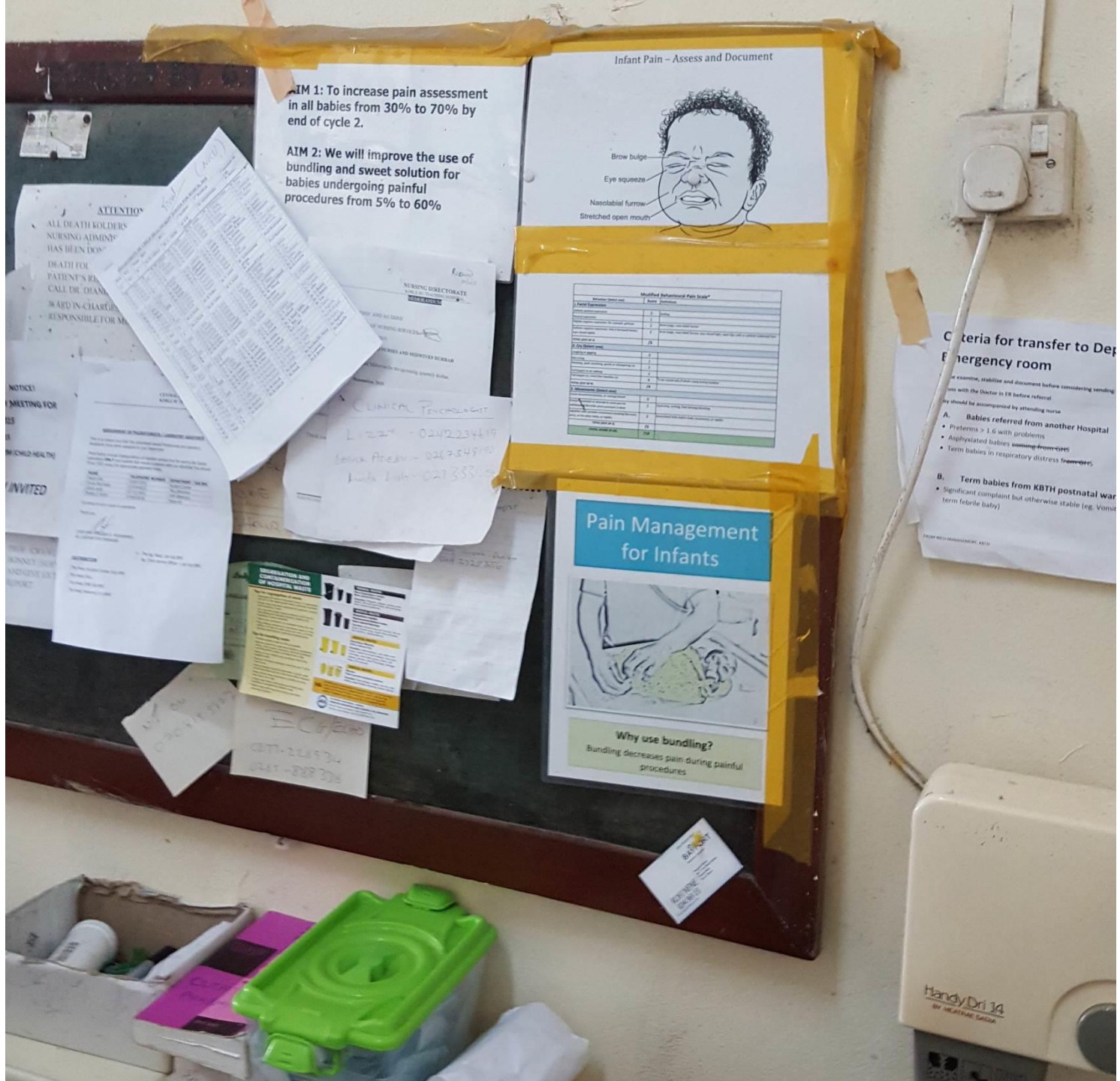
STEP 3: PSYCHOLOGICAL (THOUGHTS AND BEHAVIOURS)

BREATHE DEEPLY

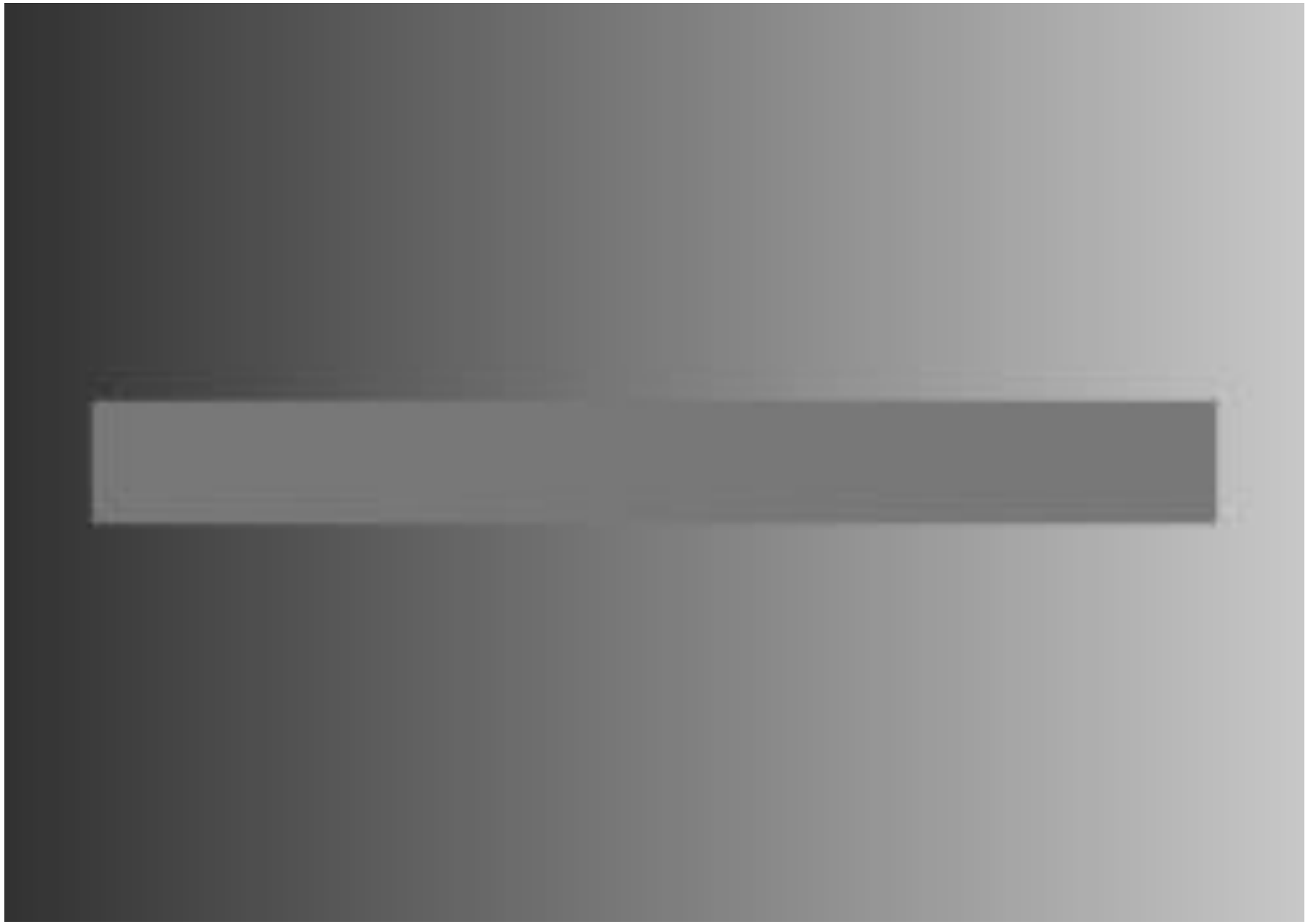
- Stay calm and use your normal speaking voice. This helps your baby stay calm – babies look to their parents for how to act and feel.
- If you are nervous, take a few slow, deep breaths to calm yourself before and during injection – breathe so your stomach expands, not your chest. You can do this while holding your baby.

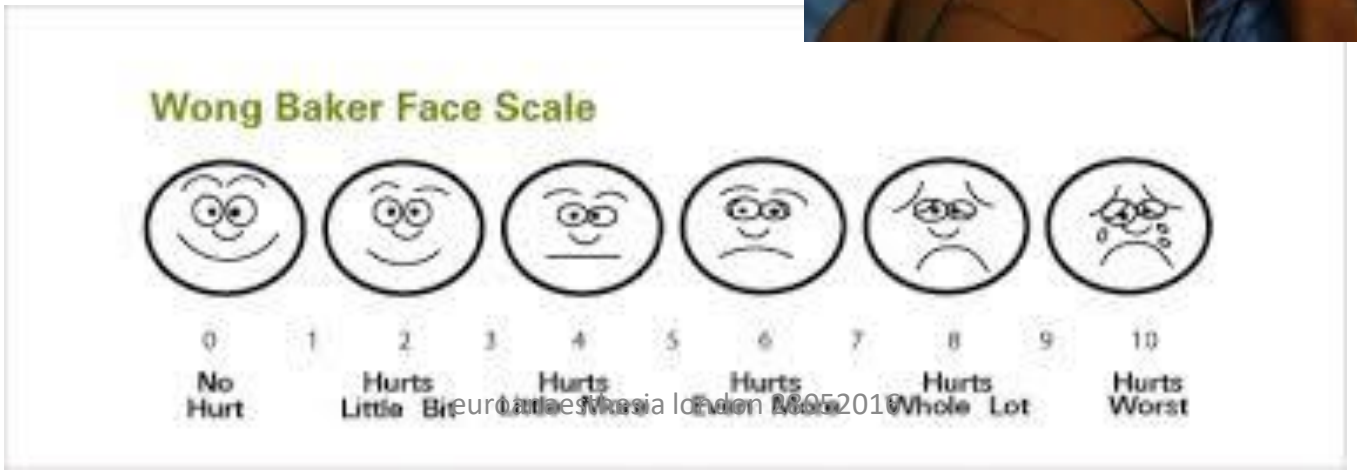
DISTRACT

- Help keep your baby's attention away from the injection.
- Distractions you can use: rocking, cuddling, singing, talking, sucking (breast-feeding or pacifier). Distract with objects or toys (bubbles, pop-up books, rattles) when your baby is calm enough to do so; otherwise, distress can be increased.


AIM 1: To increase pain assessment in all babies from 30% to 70% by end of cycle 2.
AIM 2: We will improve the use of bundling and sweet solution for babies undergoing painful procedures from 5% to 60%
Infant Pain – Assess and Document
Brow bulge
Eye squeeze
Nasolabial furrow
Stretched open mouth
Pain Management for Infants
Why use bundling?
Bundling decreases pain during painful procedures
Handy Dri 14

SUGGESTIE 3




Wong Baker Face Scale
0
No Hurt
2
Hurts Little Bit
4
Hurts Little More
6
Hurts Even More
8
Hurts Whole Lot
10
Hurts Worst

PAIN assessment

Tools include:

- Behavioural parameters:

  movement, crying, facial movements (nasolabial furrow, eye squeeze, brow bulge), etc… all relatively sensitive for pain

- Physiological parameters:

  heart rate, blood pressure, etc

If you want to use it for clinical care the pain assessment tool needs cut-off points/scores:

Cut off point for pain (above that score analgesia is needed)

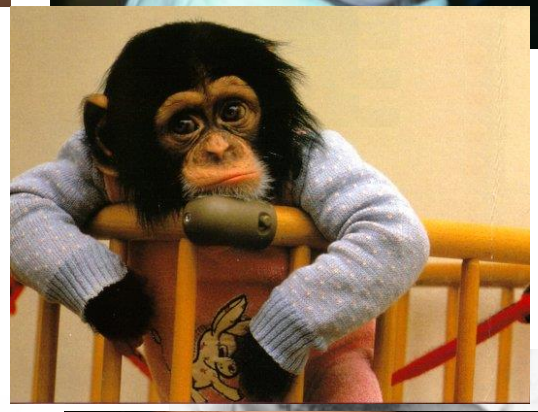
(Cut off point for over-sedation: above that score analgesia needs to be lowered)

Different facial expressions: which faces show pain?










Facial expression of pain

Most sensitive:

- **Brow bulging**
- **Eyes sqeezed**
- **Nosalabial furrow**
- **Horizontal strechted mouth**
- **Cupped tongue**

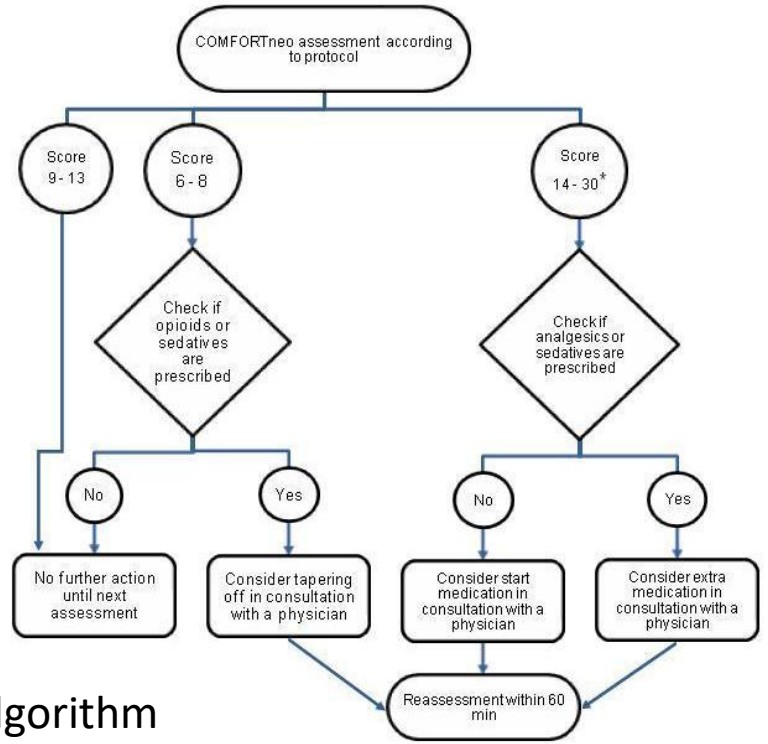
JWB Peters, 2001.

PAIN assessment

To have appropriate pain assessment and evaluation of therapy an algorithm is needed:

Including validated scores

and cut-off points



Example: Pain and Analgesia algorithm

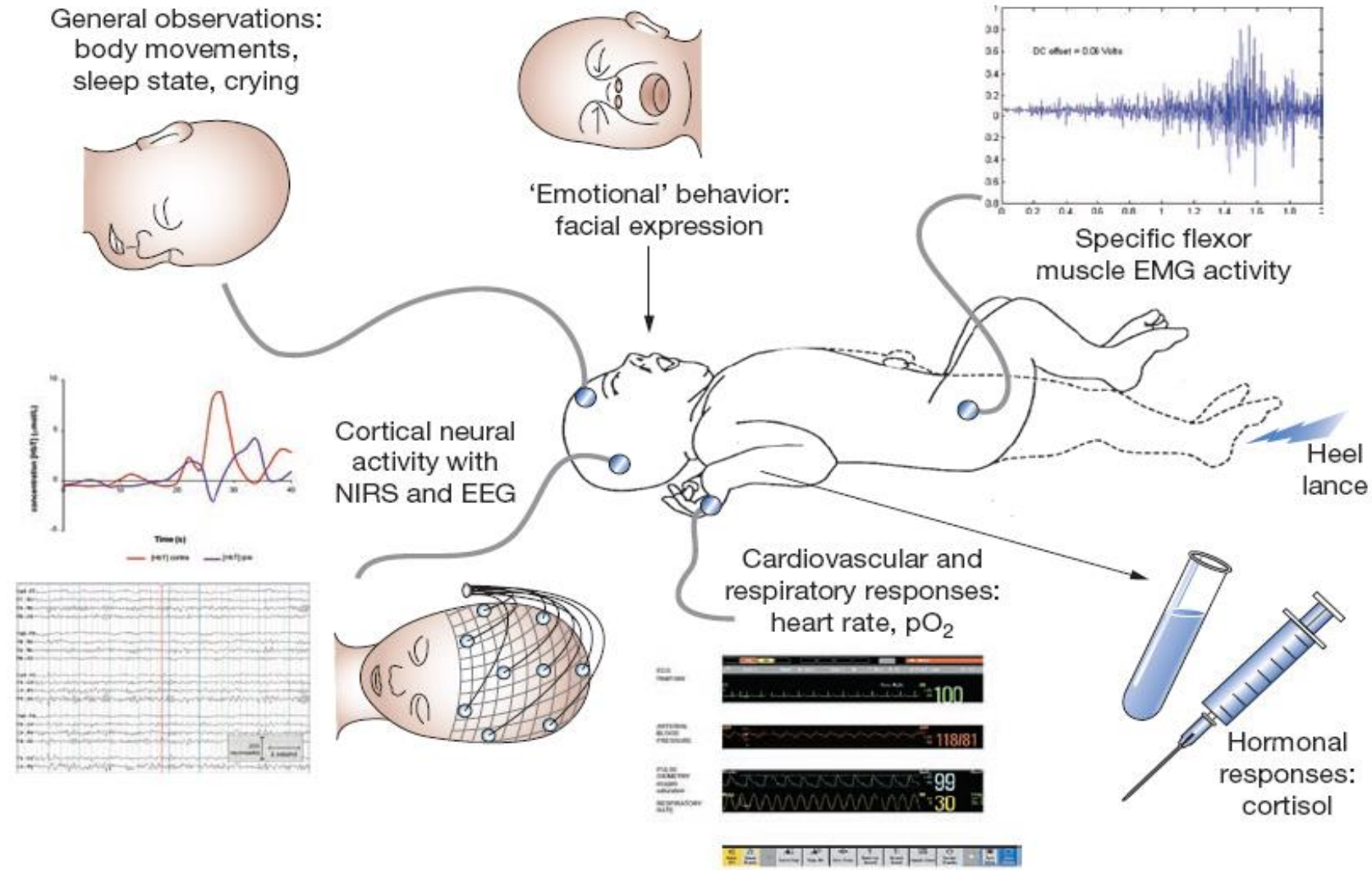
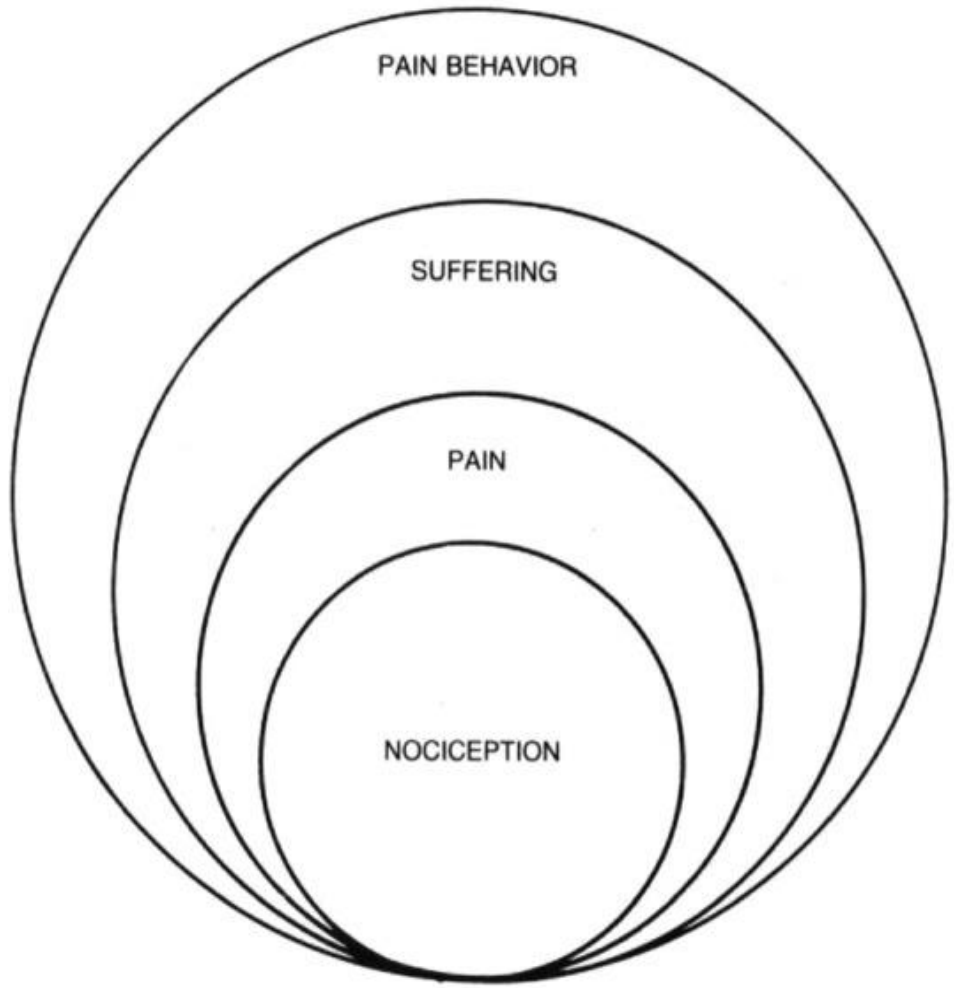


Figure 2 Methods of assessing infant pain. In the absence of language, infant pain is assessed by a number of different physiological methods. Some of these methods are integrated into current clinical pain assessment tools. The neurophysiological techniques EMG, EEG and NIRS are not used for routine 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.

CONCEPTS OF PAIN



A multifaceted model of the components of pain.

PIPP Scale

	0	1	2	3
GA	> / = 36 Wks	32-35 6/7 Wks	28-31 6/7 Wks	< / = 28 Wks
Behavioral State	Active/Awake	Quiet/Awake	Active/Sleep	Quiet/Sleep
HR	0-4 Beats/ Minute Inc	5-14 Beats/ Minute Inc	15-24 Beats/ Minute	25 Beats or > Inc
O2 Sats	0-2.4% Decrease	2.5-4.9% Decrease	5-7.4% Decrease	7.5% or > Decrease
Brow Bulge	None	Minimum	Moderate	Maximum
Eye Squeeze	None	Minimum	Moderate	Maximum
Nasolabial Furrow	None	Minimum	Moderate	Maximum

Comfort assessment

Neo Scale

Date/time 1 | Date/time 2 | Date/time 3 | Date/time 4

Sticker with patient's name

		Place a mark 1 ▼	2 ▼	3 ▼	4 ▼	
Alertness	1.	☐	☐	☐	☐	quiet sleep (eyes closed, no facial movement)
	2.	☐	☐	☐	☐	active sleep (eyes closed, facial movement)
	3.	☐	☐	☐	☐	quietly awake (eyes open, no facial movement)
	4.	☐	☐	☐	☐	actively awake (eyes open, facial movement)
	5.	☐	☐	☐	☐	awake and hyperalert
Calmness/ Agitation	1.	☐	☐	☐	☐	calm (appears lucid and serene)
	2.	☐	☐	☐	☐	slightly anxious (shows slight anxiety)
	3.	☐	☐	☐	☐	anxious (appears agitated but remains in control)
	4.	☐	☐	☐	☐	very anxious (appears very agitated, just able to control)
	5.	☐	☐	☐	☐	panicky (severe distress with loss of control)
Respiratory response (only in mechanically ventilated children)	1.	☐	☐	☐	☐	no spontaneous respiration
	2.	☐	☐	☐	☐	spontaneous respiration on ventilator
	3.	☐	☐	☐	☐	unrest or resistance to ventilator
	4.	☐	☐	☐	☐	actively breathes against ventilator or coughs regularly
	5.	☐	☐	☐	☐	fights ventilator
Crying (only in spontaneously breathing children)	1.	☐	☐	☐	☐	no crying
	2.	☐	☐	☐	☐	faint crying
	3.	☐	☐	☐	☐	soft crying or moaning
	4.	☐	☐	☐	☐	hard crying
	5.	☐	☐	☐	☐	intense crying or screaming
Body movement	1.	☐	☐	☐	☐	no or minimal movement
	2.	☐	☐	☐	☐	up to three slight arm and / or leg movements
	3.	☐	☐	☐	☐	more than three slight arm and / or leg movements
	4.	☐	☐	☐	☐	up to three vigorous arm and / or leg movements
	5.	☐	☐	☐	☐	more than three vigorous arm and / or leg movements, or whole body
Facial tension	1.	☐	☐	☐	☐	facial muscles fully relaxed, relaxed open mouth
	2.	☐	☐	☐	☐	normal facial tension
	3.	☐	☐	☐	☐	intermittent eye squeeze and brow furrow
	4.	☐	☐	☐	☐	continuous eye squeeze and brow furrow
	5.	☐	☐	☐	☐	facial muscles contorted and grimacing (eye squeeze, brow furrow, open mouth, nasal-labial lines)
(Body) muscle tone (observation only)	1.	☐	☐	☐	☐	muscles fully relaxed (open hands, dribbling, open mouth)
	2.	☐	☐	☐	☐	reduced muscle tone; less resistance than normal
	3.	☐	☐	☐	☐	normal muscle tone
	4.	☐	☐	☐	☐	increased muscle tone (clenched hands and/or clenched, bent toes)
	5.	☐	☐	☐	☐	extreme muscle tone (rigidity and flexion of fingers and/or toes)
Total score		☐	☐	☐	☐	
NRS pain*		....	....	....	....	estimate of pain (0 = no pain to 10 = worst possible pain)
NRS distress*		....	....	....	....	estimate of distress (0 = no distress to 10 = worst possible distress)

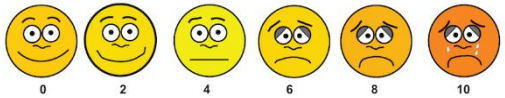
Details sedatives/ analgesics _____

Reason assessment _____

(Before or after medication or standard assessment) *Abbreviation: NRS = Numeric Rating Scale

COMFORTneo Scale version 5, September 2014 Monique van Dijk

Pain management in preterm infants



Recognize it

Measure it

Treat it

Adequate assessment

Evaluate

Adequate therapy:
- Non-pharma
- Pharmacological

Treatment of pain in neonates/infants

- Reduction of painful events
- Altered procedure (venipuncture vs heel lance)*
- Non-pharmacological measures
  - Holding
  - Swaddling
  - Oral sucrose/glucose
  - Breastfeeding
  - Non-nutritive sucking
  - Kangaroo care (skin-to-skin contact)
  - Limiting environmental stimuli

***Shah V. Cochrane Database Syst Rev 2011; CD001452**

SUGGESTIE 4

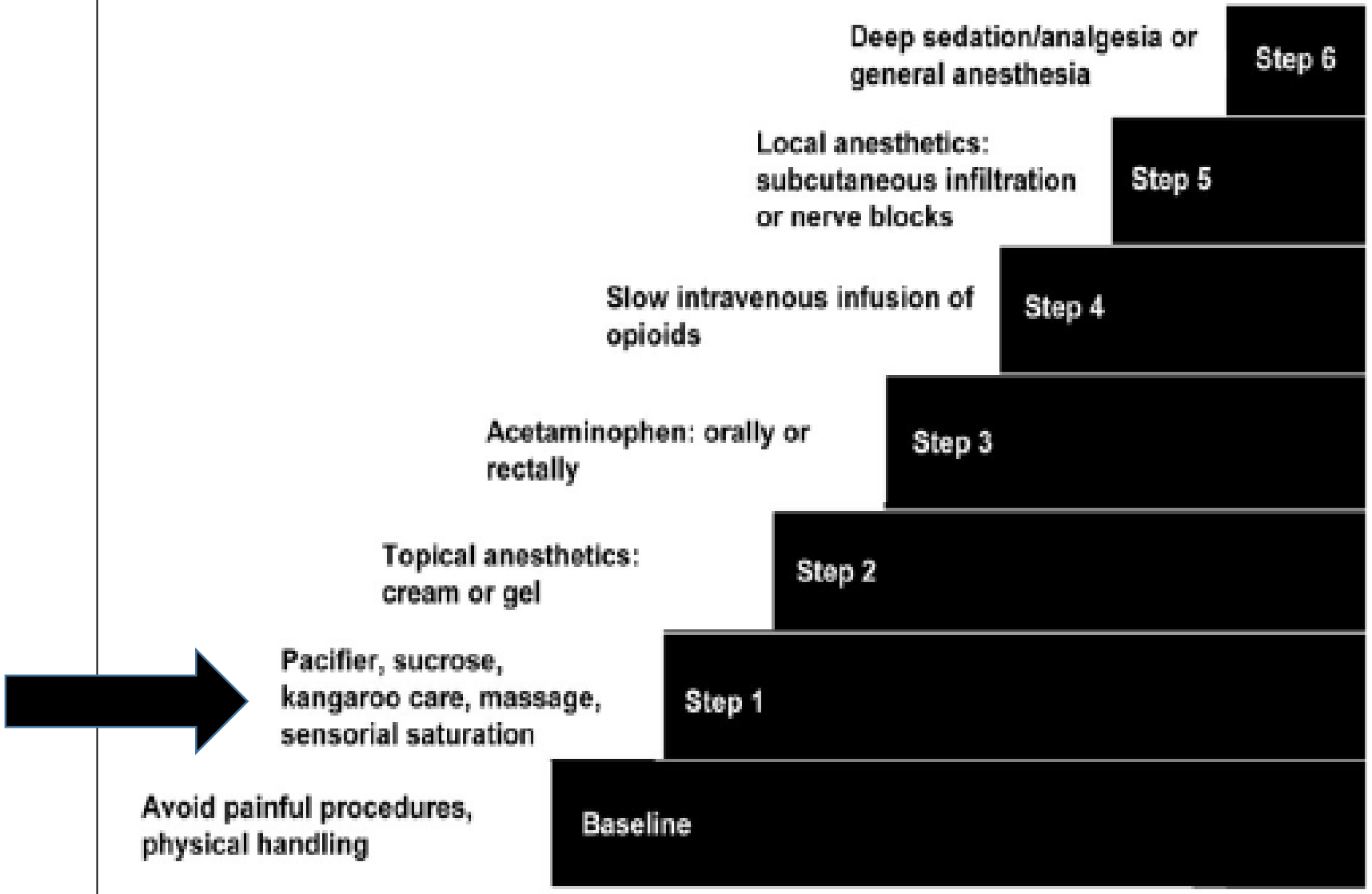


Figure 1. Stepwise approach to neonatal analgesia.

Treatment of pain in neonates

Oral sucrose

Very well studied non-pharmacological intervention

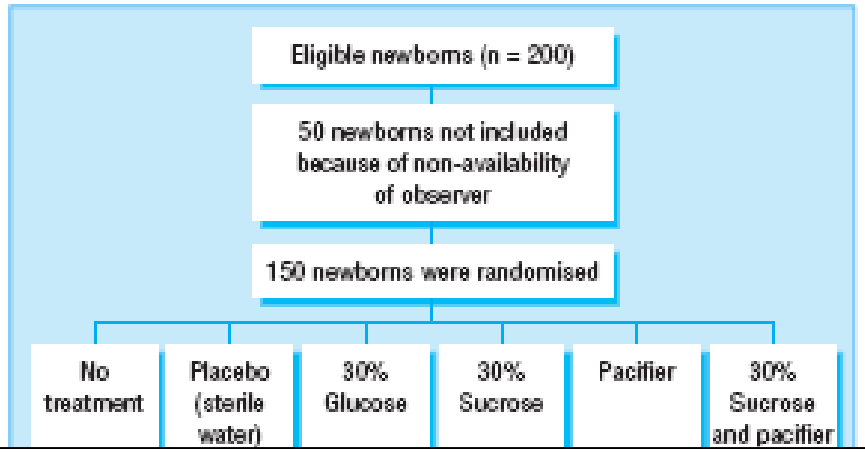
Leads to reduced pain response to painful procedures

Widely implemented in neonatal care

Discussion

Rebecca Slater et al. found that oral sucrose did reduce pain scores (PIPP score) but did not change the nociceptive brain activity

Advice is still to use sucrose in clinical practice. But it is important to realize that sucrose might not protect the newborn infant against pain as good as we thought.



Acta Pædiatr 86: 787–8. 1997

INVITED COMMENTARY

Calming minds or killing pain in newborn infants?

S Lindahl

Department of Anaesthesiology and Intensive Care, Karolinska Hospital and Institute, Stockholm, Sweden

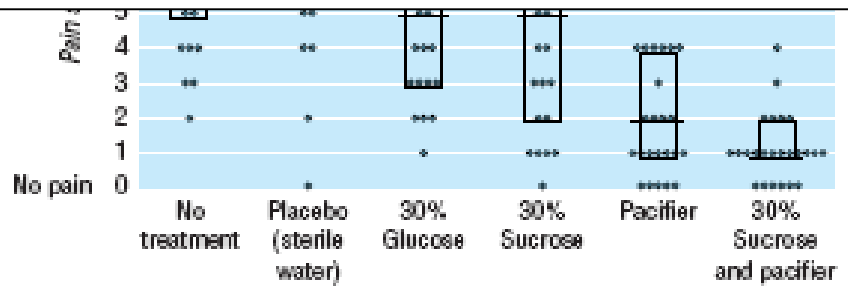


Fig 2 Pain evaluation with DAN scale (0 to 10) during venepuncture in 150 newborns randomised to six equal sized groups, with values for individual infants, median values, and interquartile ranges (for 30% sucrose and pacifier lower quartile coincides with median value)

Randomised trial of analgesic effects of sucrose, glucose, and pacifiers in term neonates

R Carbajal, X Chauvet, S Couderc, M Olivier-Martin

BREASTFEEDING MEDICINE
Volume 2, Number 2, 2007

DOI: 10.1089/bfm.2006.0031

Breastfeeding or Breastmilk to Alleviate Procedural Pain in Neonates: A Systematic Review

PRAKESH S. SHAH, LUCIA ALIWALAS, and VIBHUTI SHAH

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†*

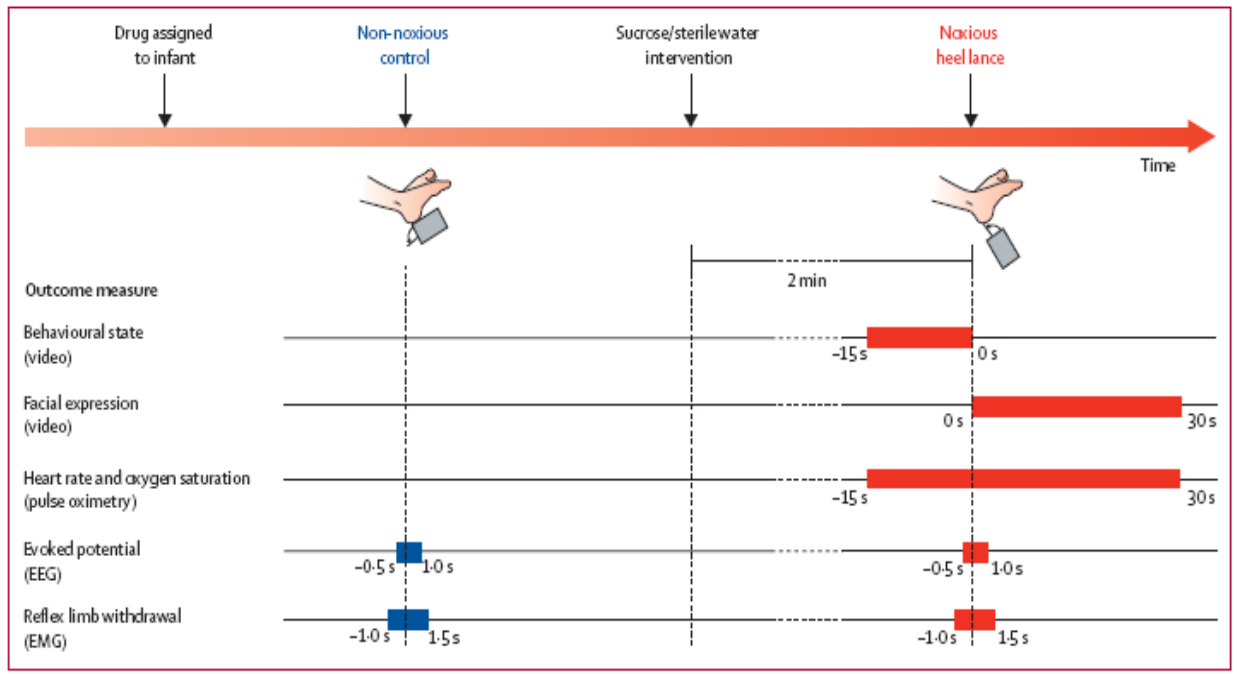


Figure 1: Experimental time line
EEG=electroencephalography. EMG=electromyography.

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

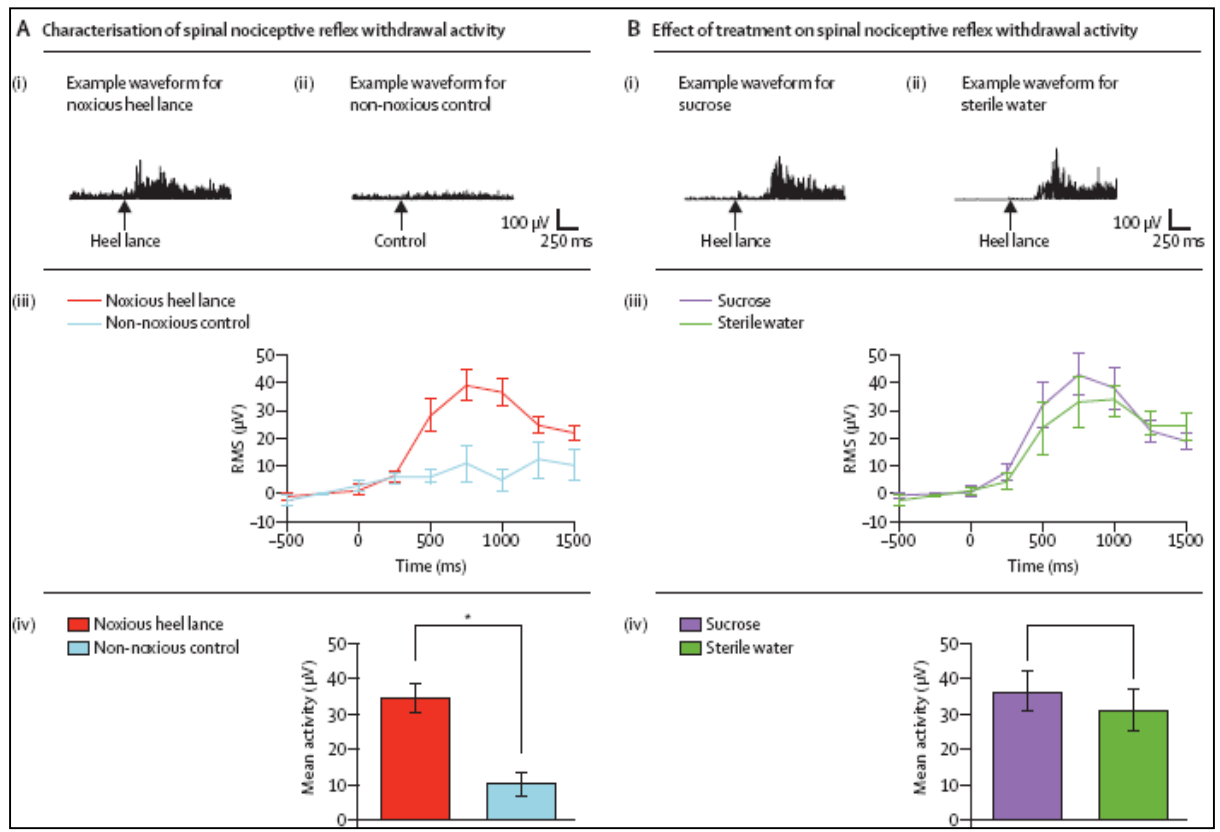
Rebeccah Slater, Laura Cornelissen, Lorenzo Fabrizi*, Debbie Patten, Jan Yoxen, Alan Worley, Stewart Boyd, Judith Meek†, Maria Fitzgerald†*

	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.

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†*



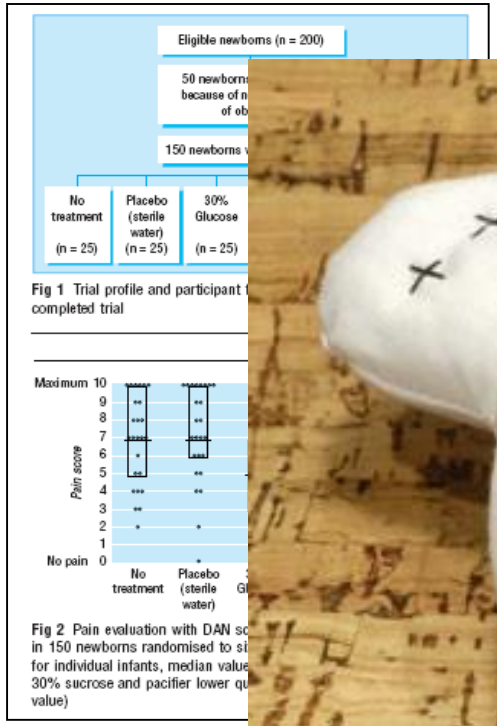
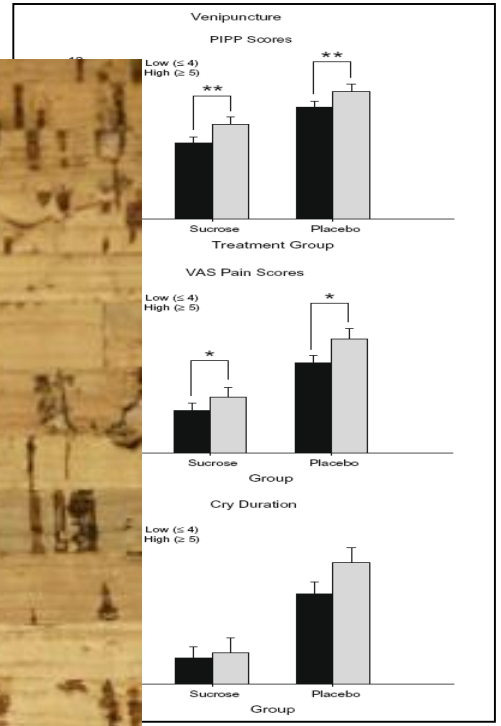


Fig 1 Trial profile and participant
completed trial

Fig 2 Pain evaluation with DAN sc
in 150 newborns randomised to si
for individual infants, median value
30% sucrose and pacifier lower qu
value)

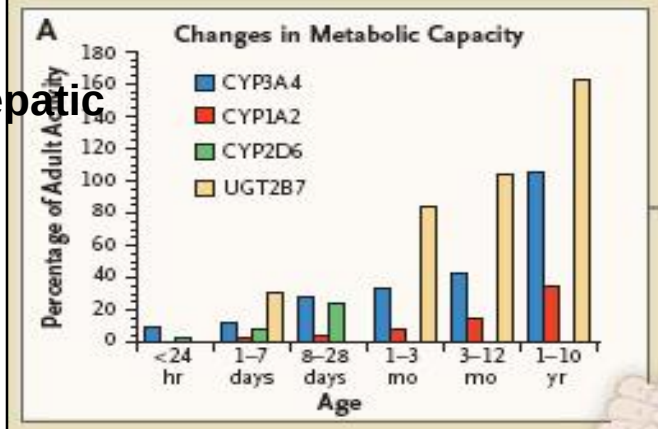


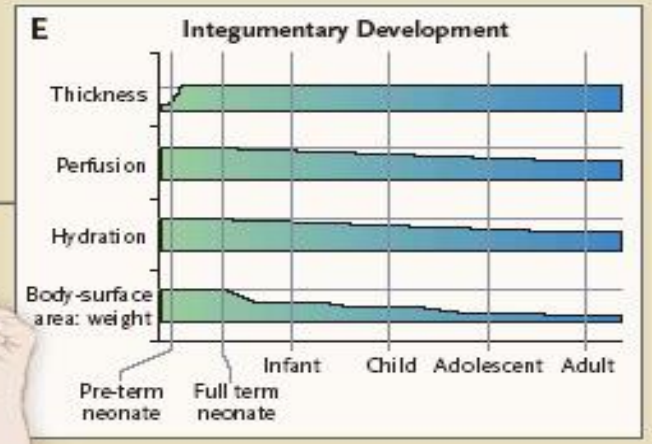
suggestie 4: beperkt effect – if any – in neonates, proven in infants

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

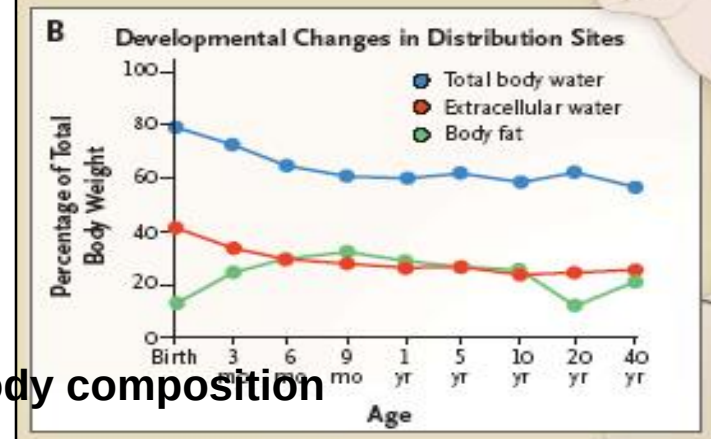
Reference	Study design and results
Shah et al. [88]	Randomized, double-blind, placebo-controlled trial, *intramuscular injection* (vitamin K) in 110 term neonates, topical amethocaine gel 4 %. There were no differences in crying duration, in pain score and only the latency to cry was somewhat longer 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

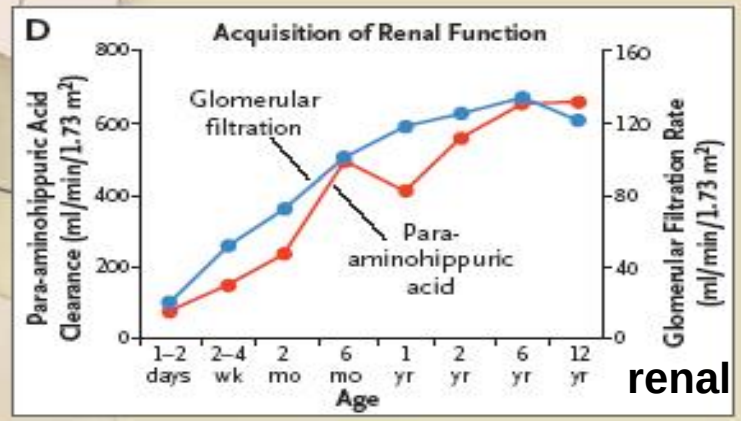
hepatic



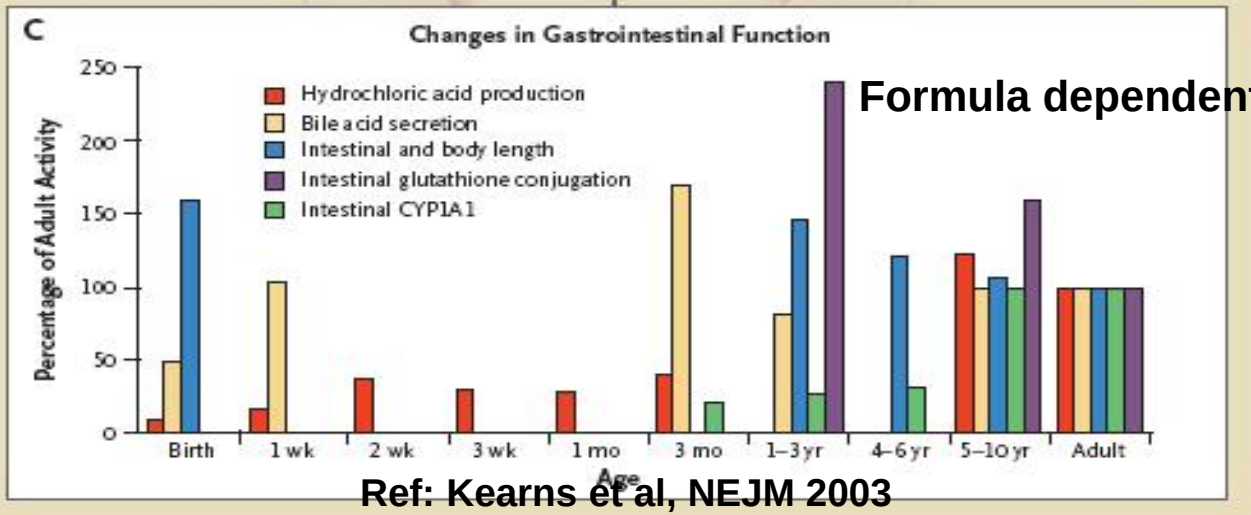


Body composition





renal



Formula dependent

Ref: Kearns et al, NEJM 2003

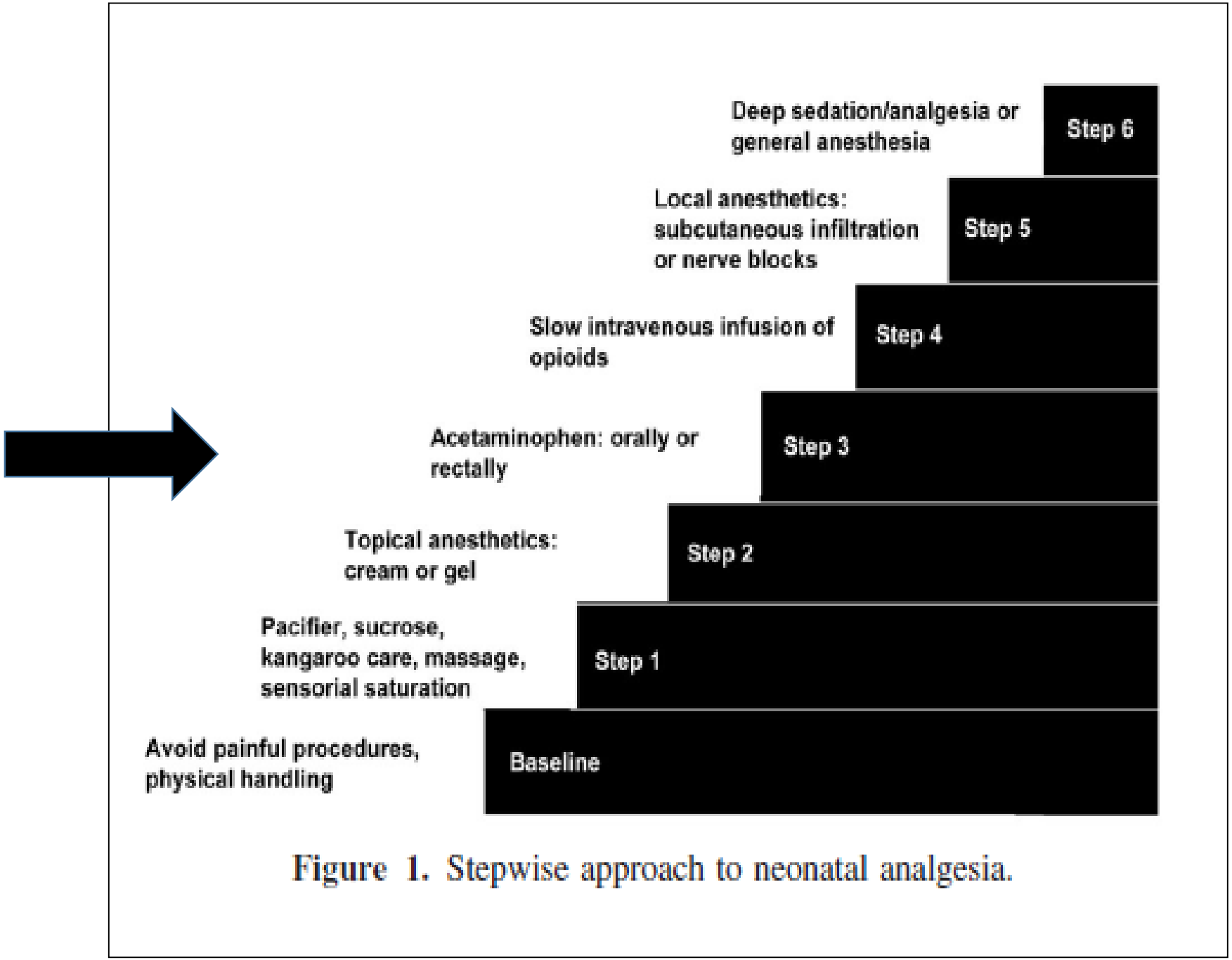


Figure 1. Stepwise approach to neonatal analgesia.

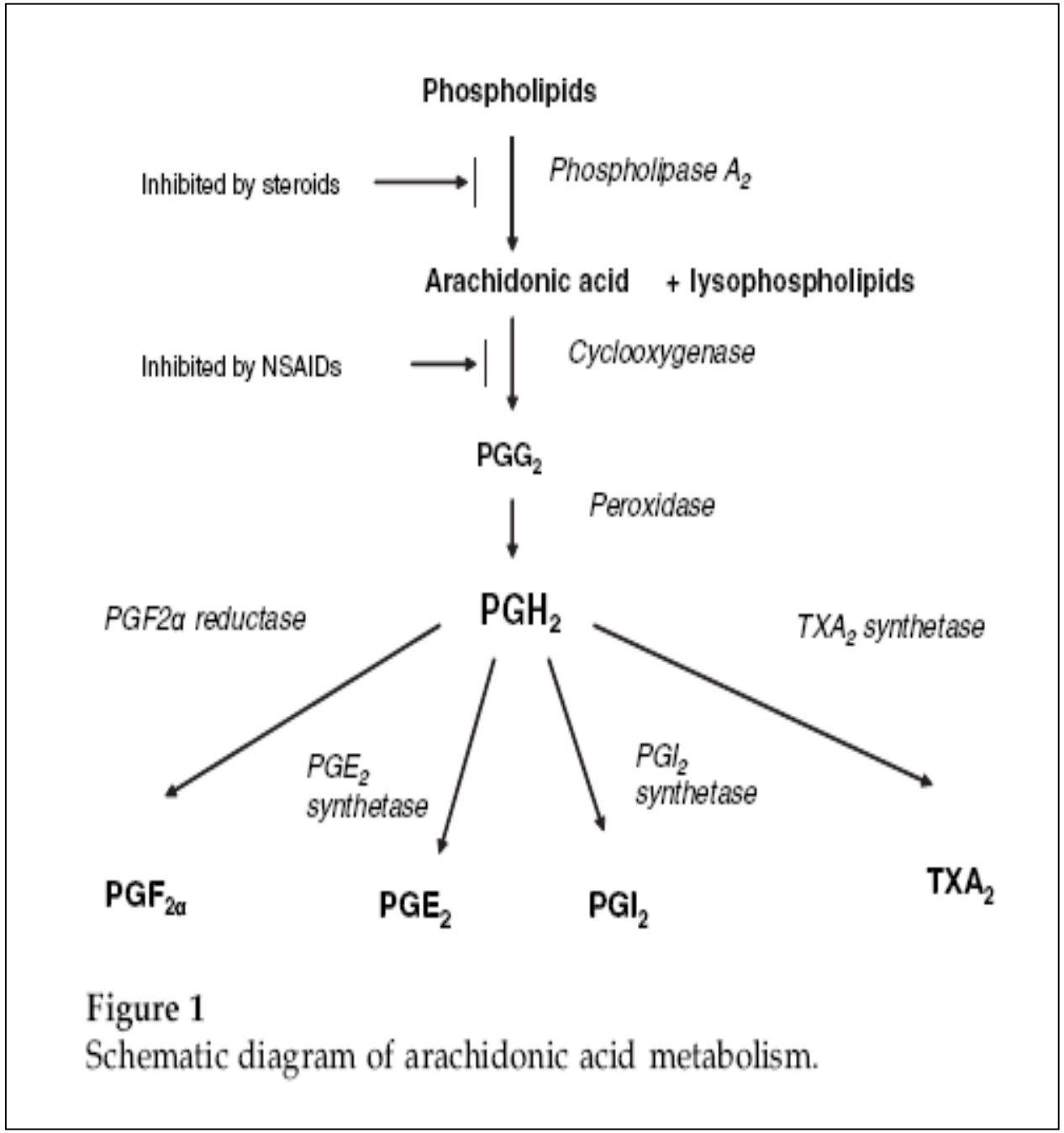


Figure 1
Schematic diagram of arachidonic acid metabolism.

L-arginine-nitric oxide (NO) pathway

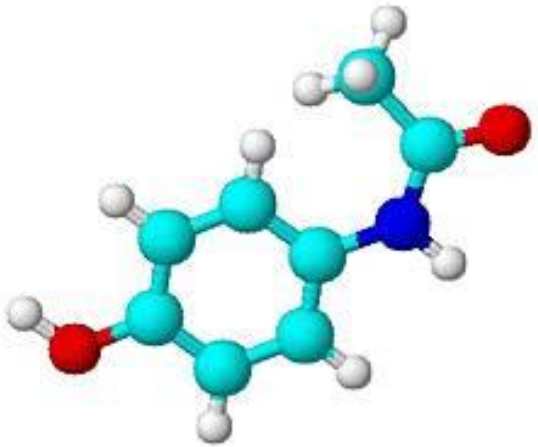
Substance P mediated

NMDA (N-methyl D-aspartate)

Serotonergic pain pathways

cannabinoid pathways, through paracetamol metabolite
(p-amino phenol + arachnidonic acid, Subsequent cannabinoid receptor activation (through vanillin receptor – act as ligand)

how does paracetamol 'work' (pharmacodynamics)



mg/l, plasma

— **10**

— **20**

antipyretic ? lower

— **> 25**

analgesic ceiling or not ?
any type of pain syndrome ?
median conc 10 mg/l

Dutch formulary[13]		
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		Off label in preterm neonates
	Loading dose	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).

Pacifici, Curr Ther Research 2015

Treatment of pain in neonates
Example dose suggestions for term newborn

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

suggestie 5: paracetamol werkt, soms…

standard rectale dosis paracetamol is onvoldoende

lagere bio-availabiliteit

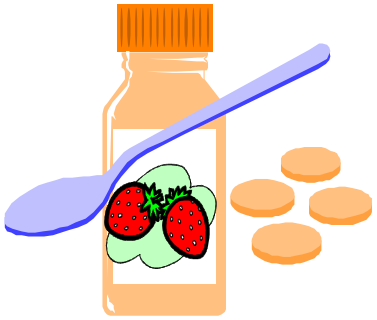
vertraagde absorptie

belangrijke variabiliteit

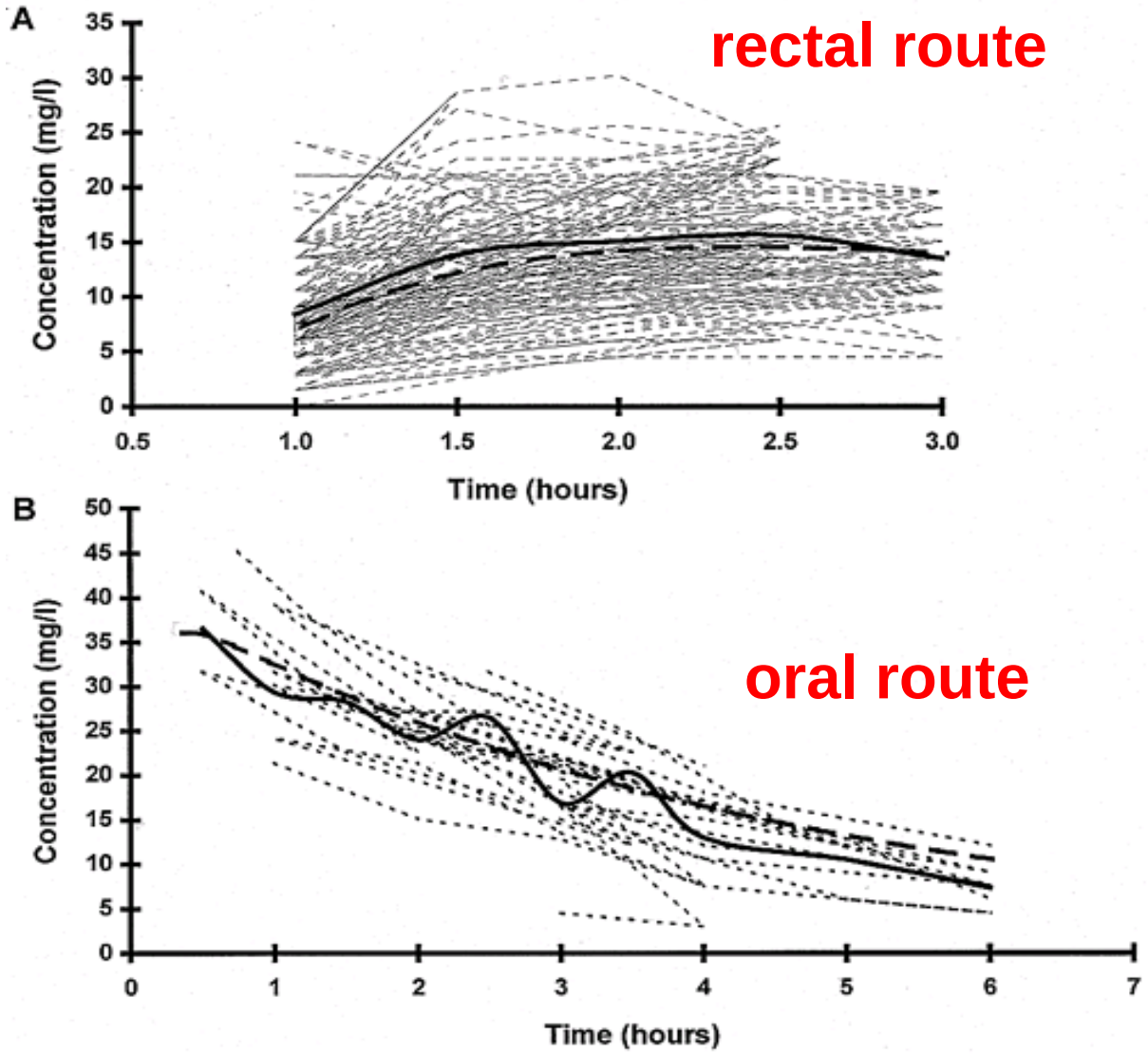
oral > iv > rectal

denk aan een oplaaddosis: distributie volume

leeftijd gerelateerde veranderingen in klaring zijn eerder beperkt

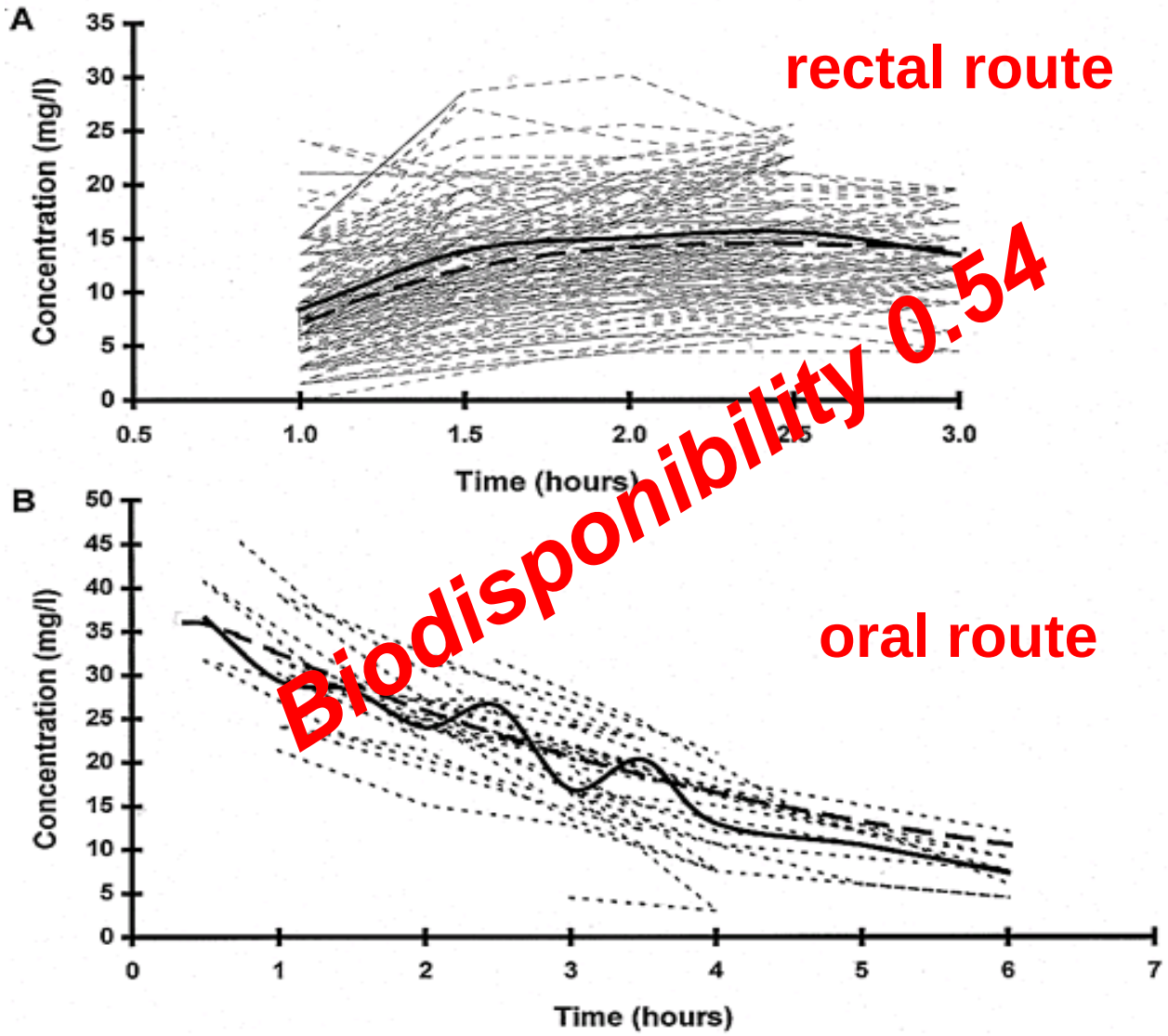


rectaal of oraal, 20 mg/kg single dose na NKO heelkunde



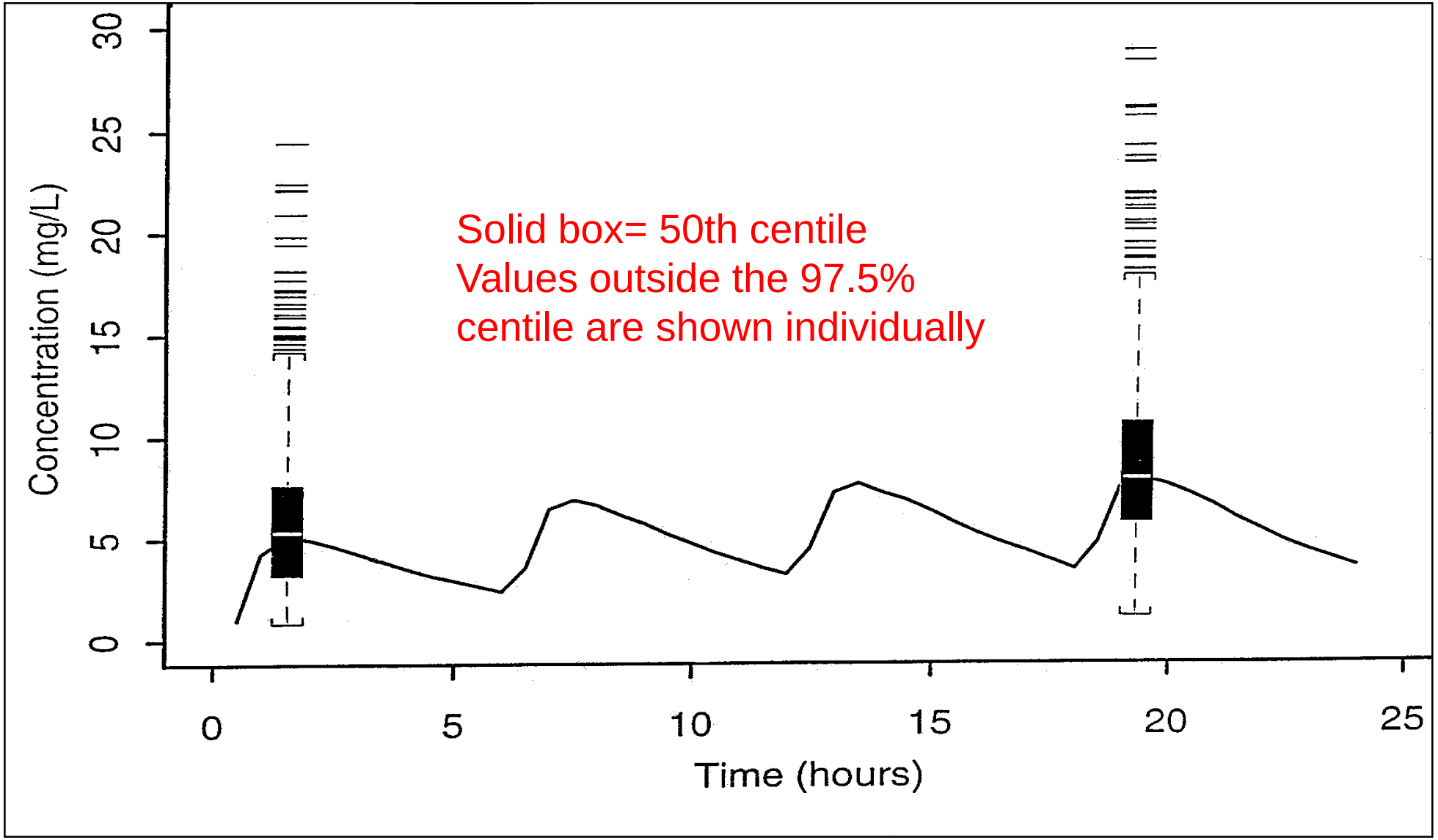
Anderson et al. Anesthesiology 1999

rectaal of oraal, 20 mg/kg single dose na NKO heelkunde



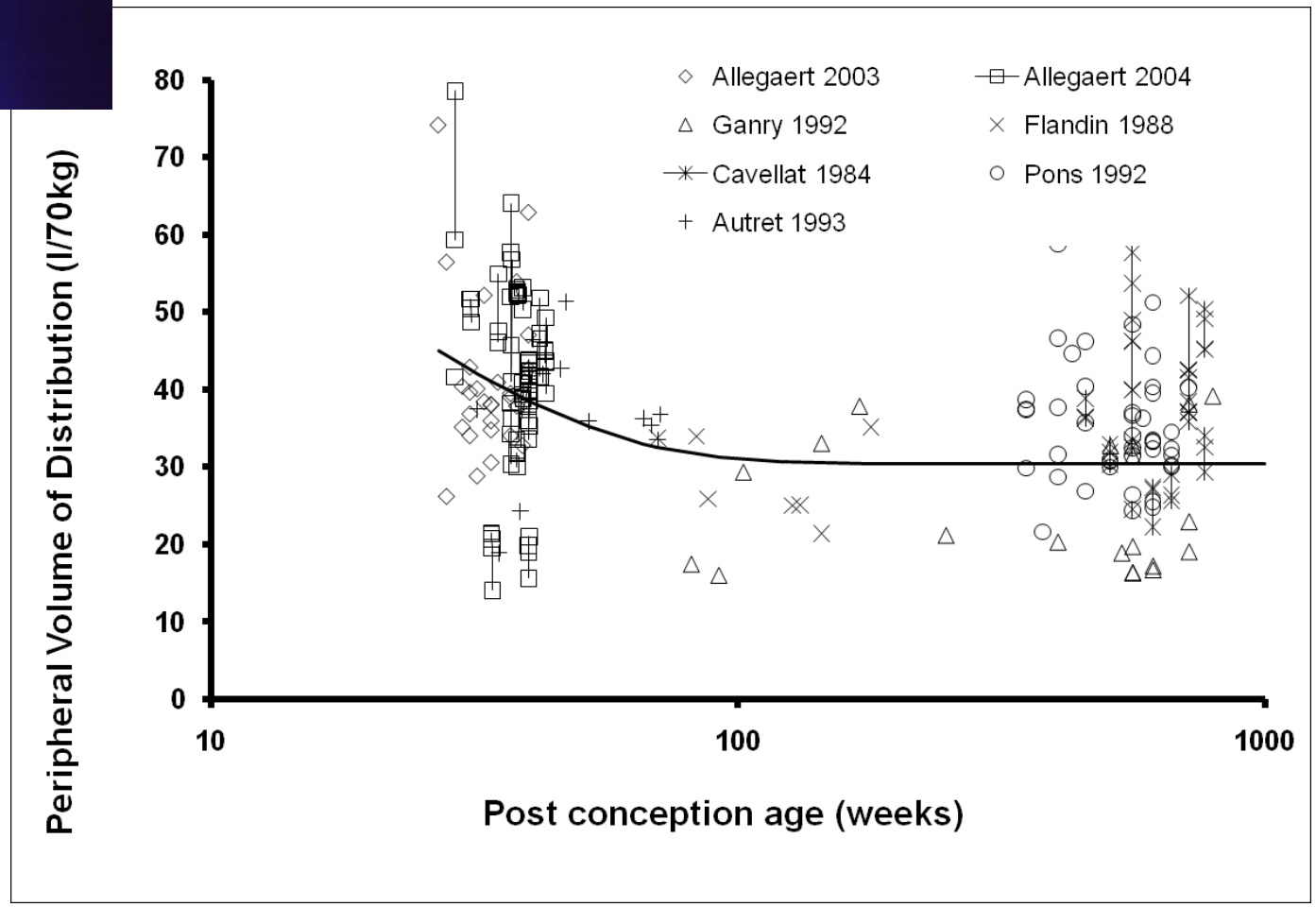
Anderson et al. Anesthesiology 1999

hogere doseringen rectaal ?



Anderson et al. Anesthesiology 1999

body water/paracetamol distribution



Anderson BJ *et al*, Paediatr Anaesth 2004

body water/paracetamol distribution

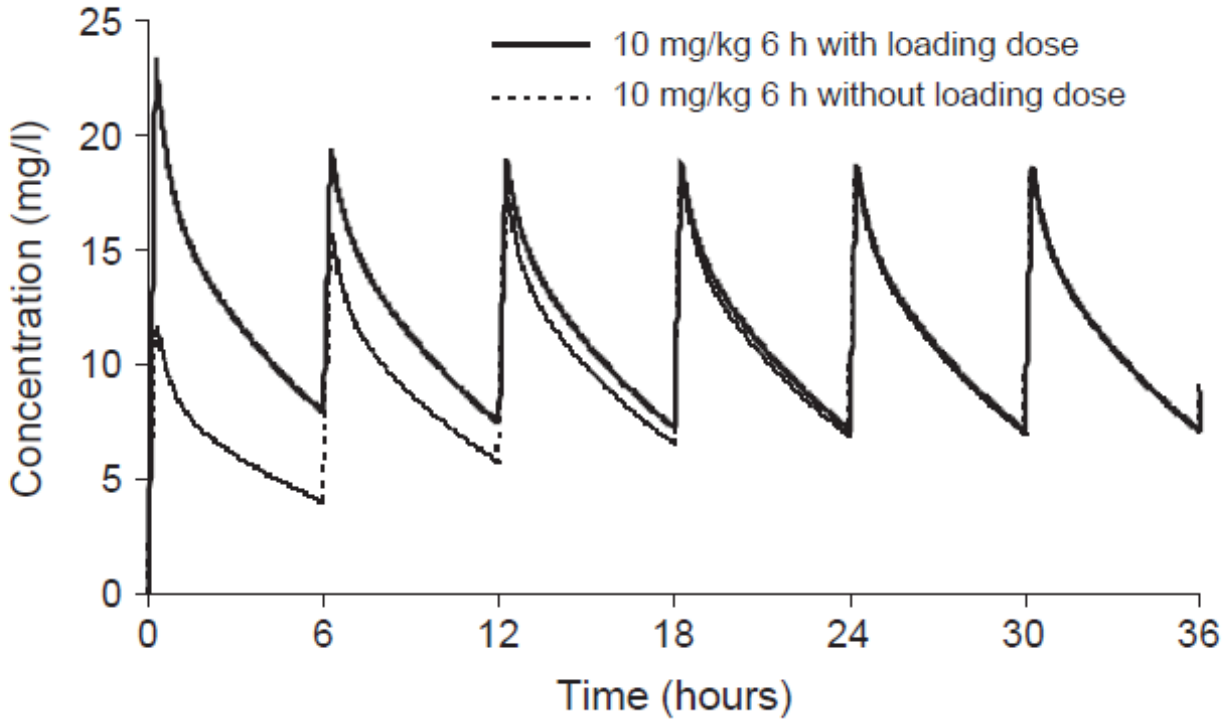
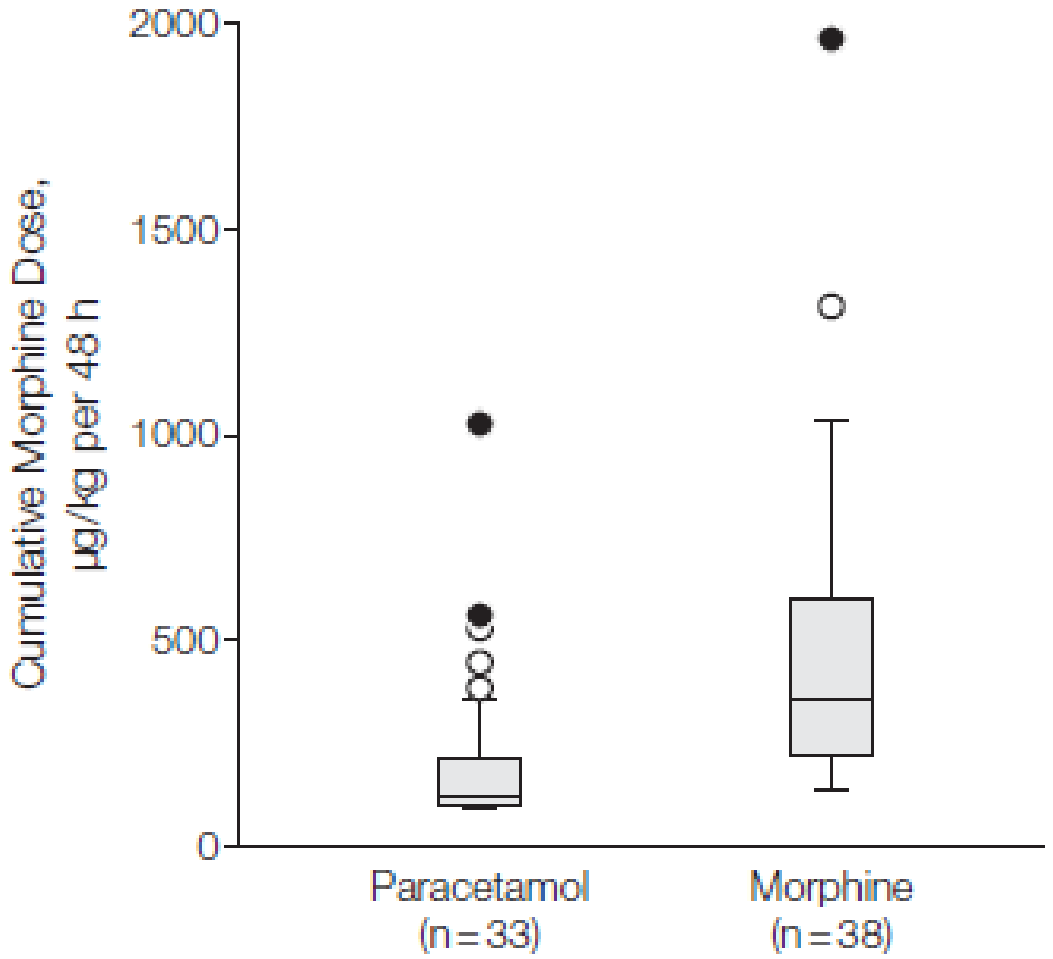


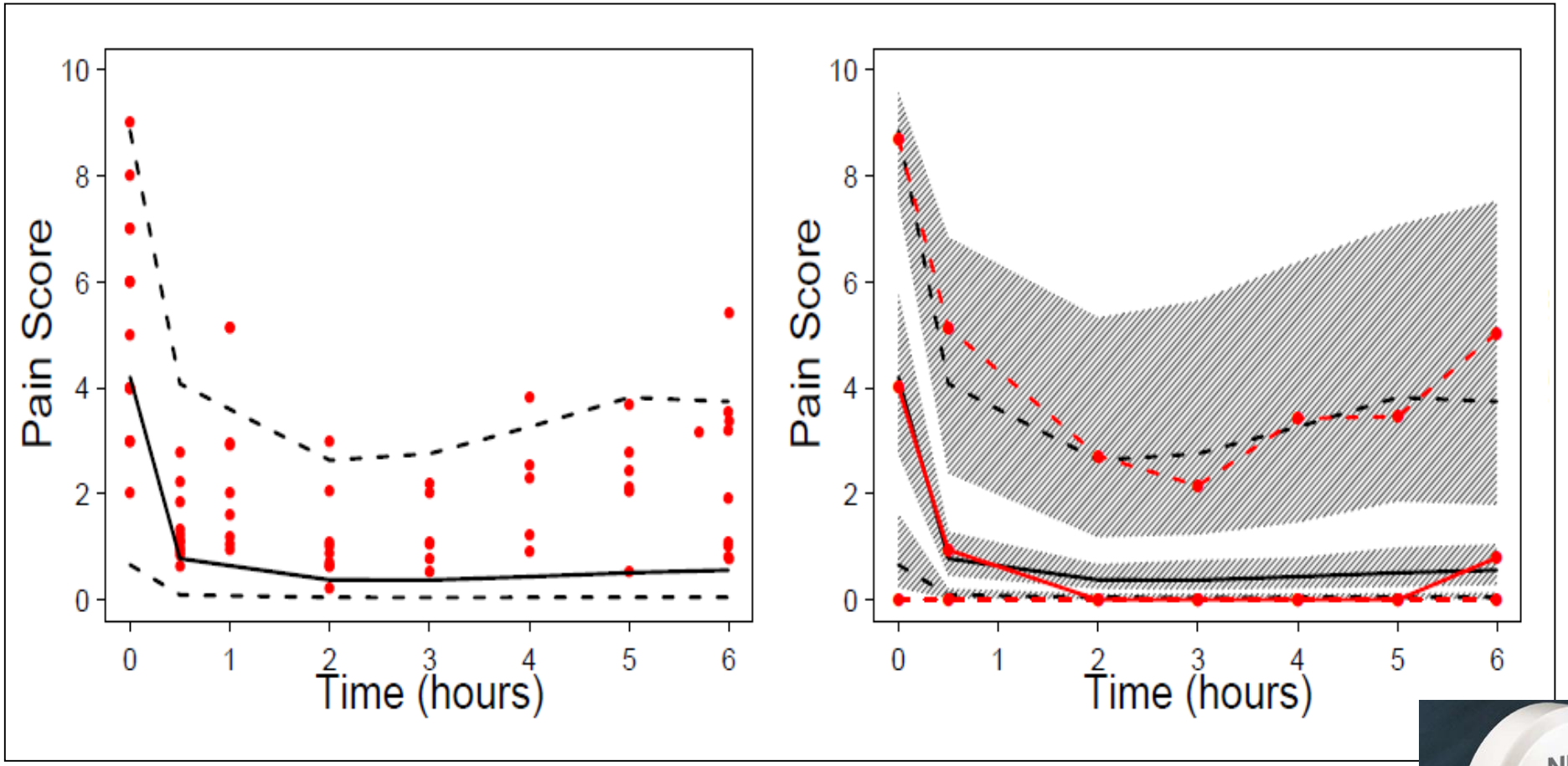
Figure 3 A typical concentration profile for neonates of 28–44 weeks' premenstrual age given a paracetamol loading dose of 20 mg/kg (black continuous line) or not given a loading dose (grey continuous line), followed by a maintenance dose of 10 mg/kg every 6 h. A mean concentration of 11 mg/l is achieved.

pooled iv paracetamol in neonates. Arch Dis Child 2011

Figure 2. Cumulative Morphine Dose for Morphine and Paracetamol Study Groups Over 48 Postoperative Hours



Ceelie et al. JAMA 2013



Pediatr Anesth, 2014

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)

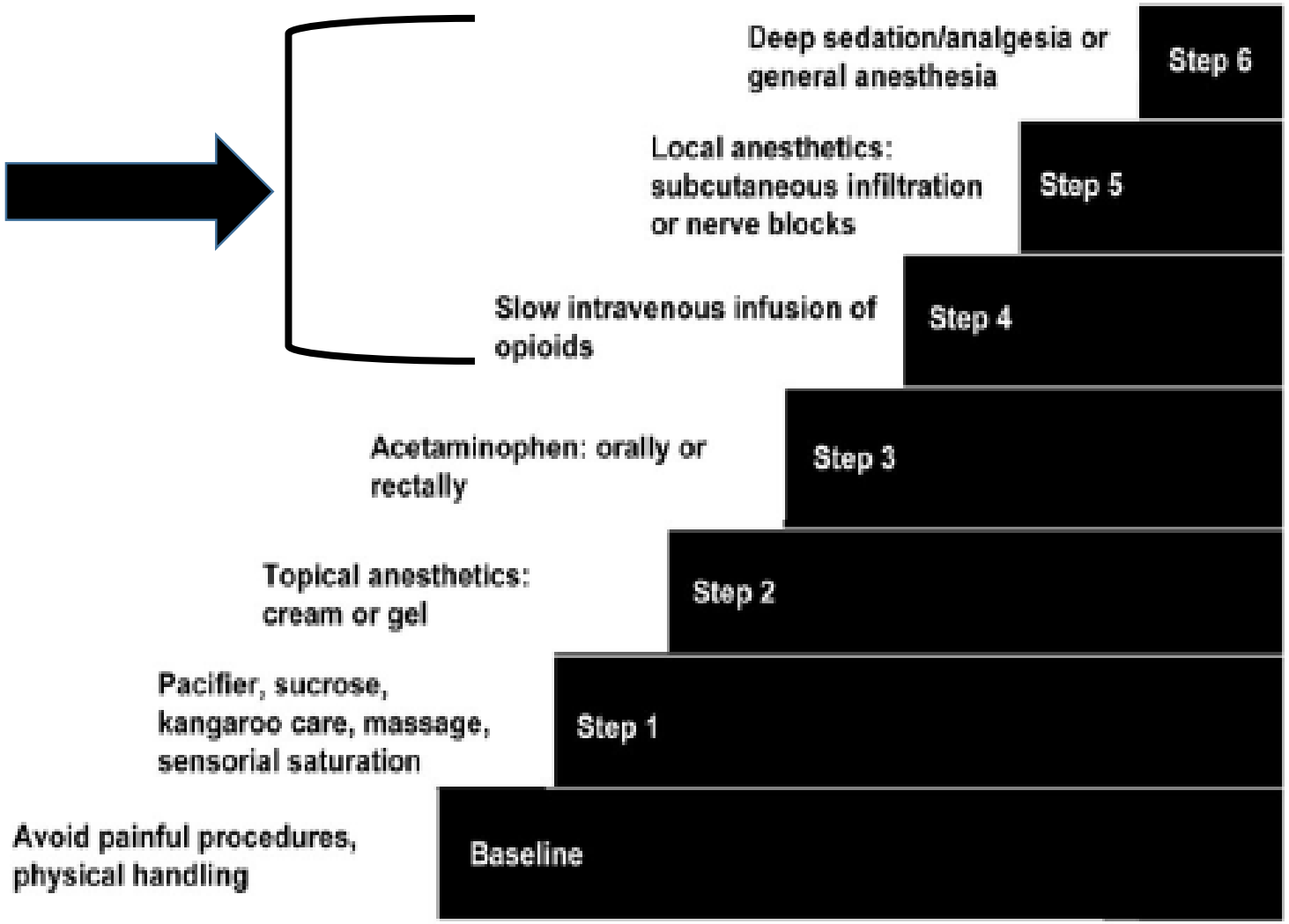
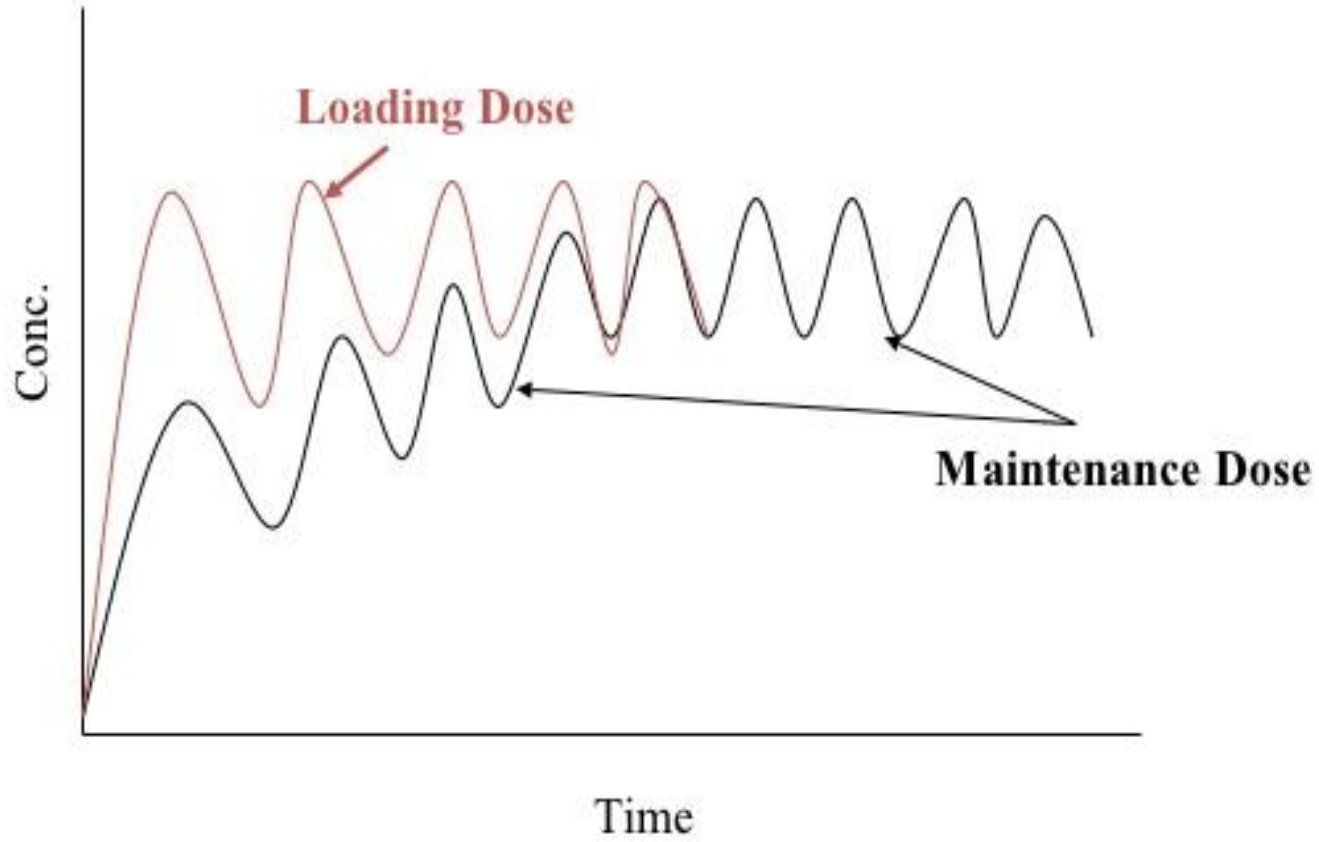


Figure 1. Stepwise approach to neonatal analgesia.

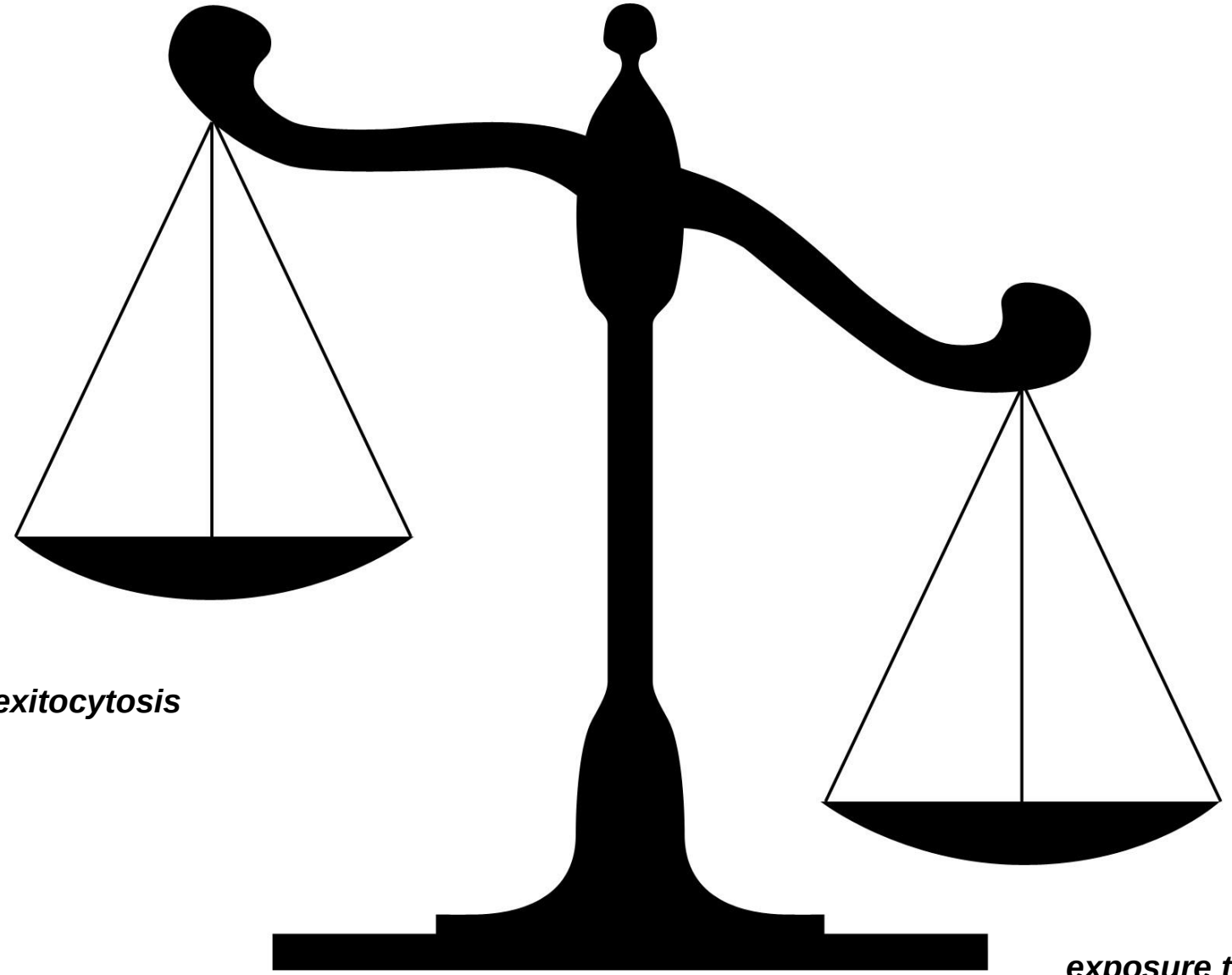
SUGGESTIE 6



OPLADEN IS VAN BELANG, NOG MEER BIJ PASGEBORENEN

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]

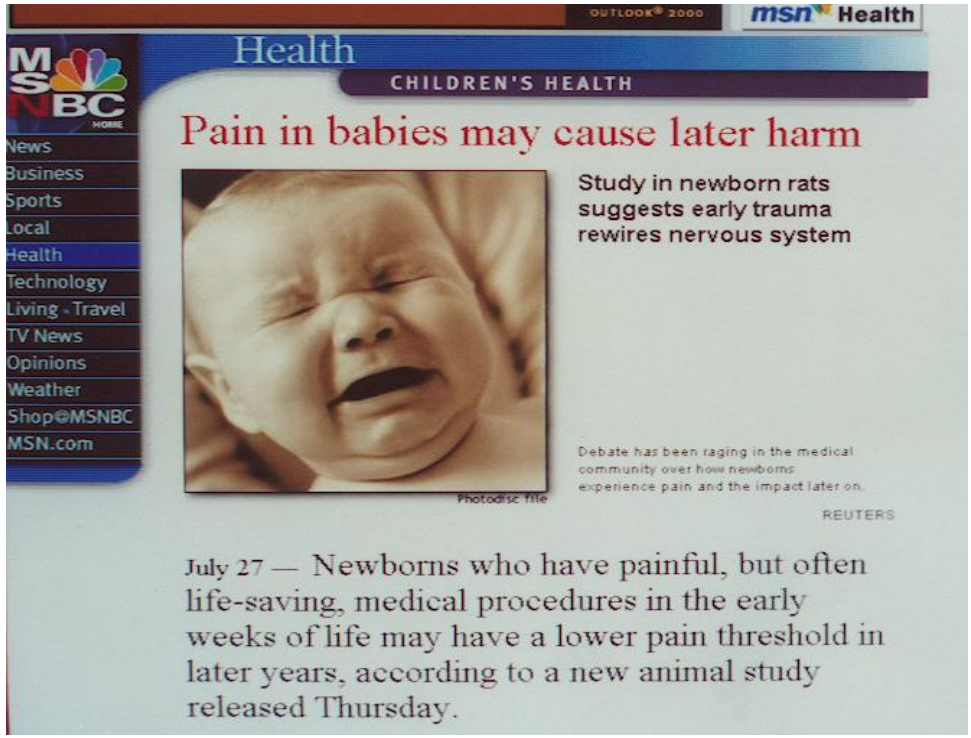
	Route	Loading dose	Maintenance dose
Morphine	iv	50–100μg/kg	10–30μg/kg/h
Fentanyl	iv	1–3μg/kg	1–5μg/kg/h
Tramadol	iv	2 mg/kg/30 min	6–8 mg/kg/day
Paracetamol	Oral	20 mg/kg	4×10 mg/kg/day
	Rectal	40 mg/kg	4×20 mg/kg/day
	iv	20 mg/kg	4×10 mg/kg/day



pain/exitocytosis

exposure to analgesics
apoptosis-synaptogenesis

SUGGESTIE 7



OUTLOOK® 2000 msn Health

MSNBC HOME

Health

CHILDREN'S HEALTH

News
Business
Sports
Local
Health
Technology
Living + Travel
TV News
Opinions
Weather
Shop@MSNBC
MSN.com

Pain in babies may cause later harm

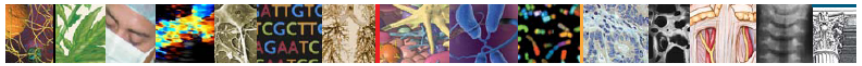
Study in newborn rats suggests early trauma rewires nervous system

Photodisc file

Debate has been raging in the medical community over how newborns experience pain and the impact later on.

REUTERS

July 27 — Newborns who have painful, but often life-saving, medical procedures in the early weeks of life may have a lower pain threshold in later years, according to a new animal study released Thursday.



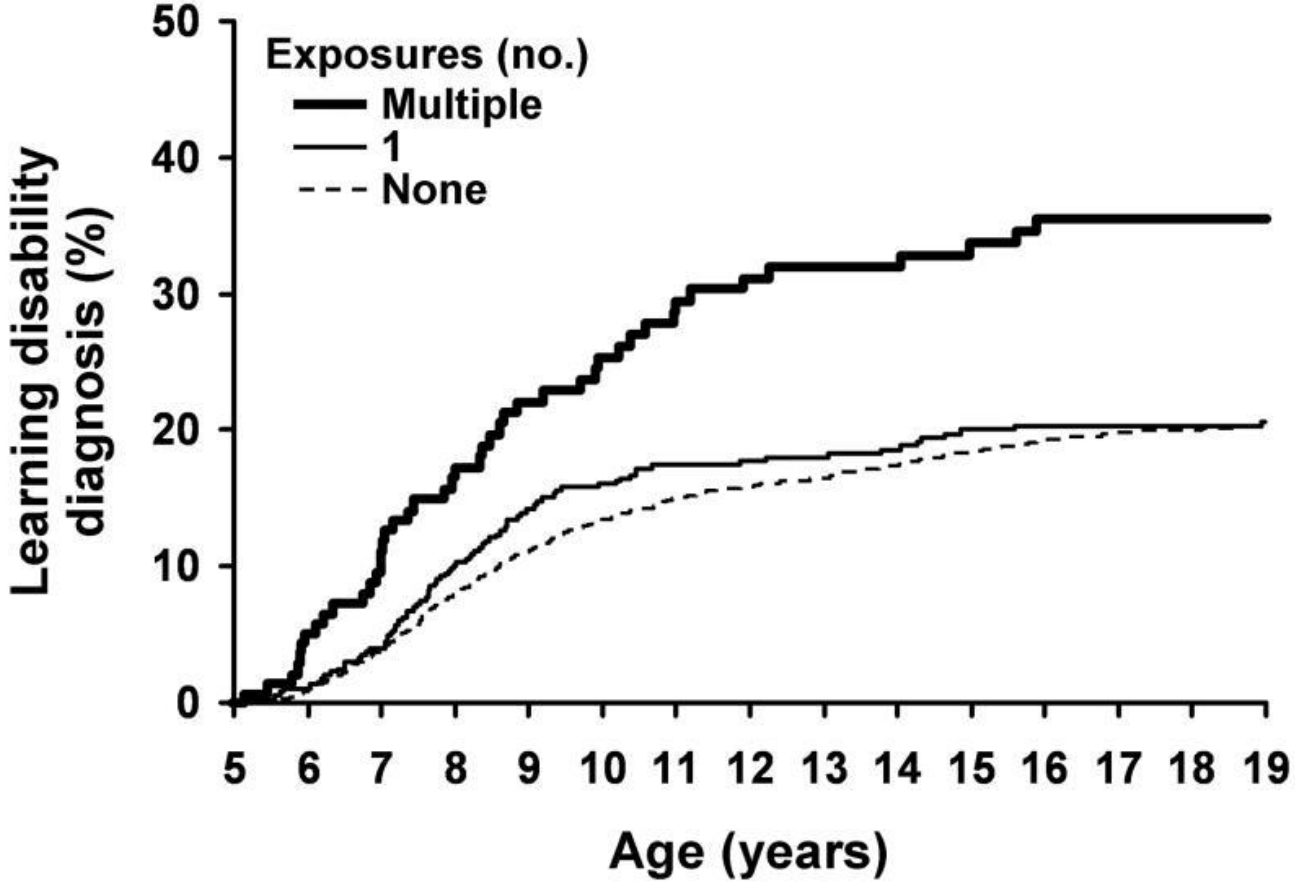
The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Defining Safe Use of Anesthesia in Children

Bob Rappaport, M.D., R. Daniel Mellon, Ph.D., Arthur Simone, M.D., Ph.D., and Janet Woodcock, M.D.


Mind numbing: Anesthesia in baby rats stunts brain development.
Common general anesthetics given at an early age may cause brain damage and other neurologic problems



Wilder *et al*. Anesthesiology 2009

Ongoing Clinical Trials Assessing the Effects of Anesthetics on Neurocognitive Development.

Odense University Hospital (Denmark) and the Danish Registry Study Group	A nationwide epidemiologic study comparing the educational achievement of all children who have undergone a surgical procedure before the age of 1 with that of a general-population control group.
Columbia University	A prospective cohort study of children who had exposure to an anesthetic before the age of 3 and their siblings who were not exposed. The two groups will be followed for neurodevelopmental outcomes.
International collaboration of institutions from Australia, the United States, Canada, Italy, the United Kingdom, and the Netherlands	Prospective, randomized, investigator-blinded, controlled clinical trial to assess the effects of general anesthesia using sevoflurane versus neuraxial anesthesia using bupivacaine on neurocognitive function in infants over 26 weeks' gestational age. Children will be followed with evaluations of neurocognitive development at 2 and 5 years of age.

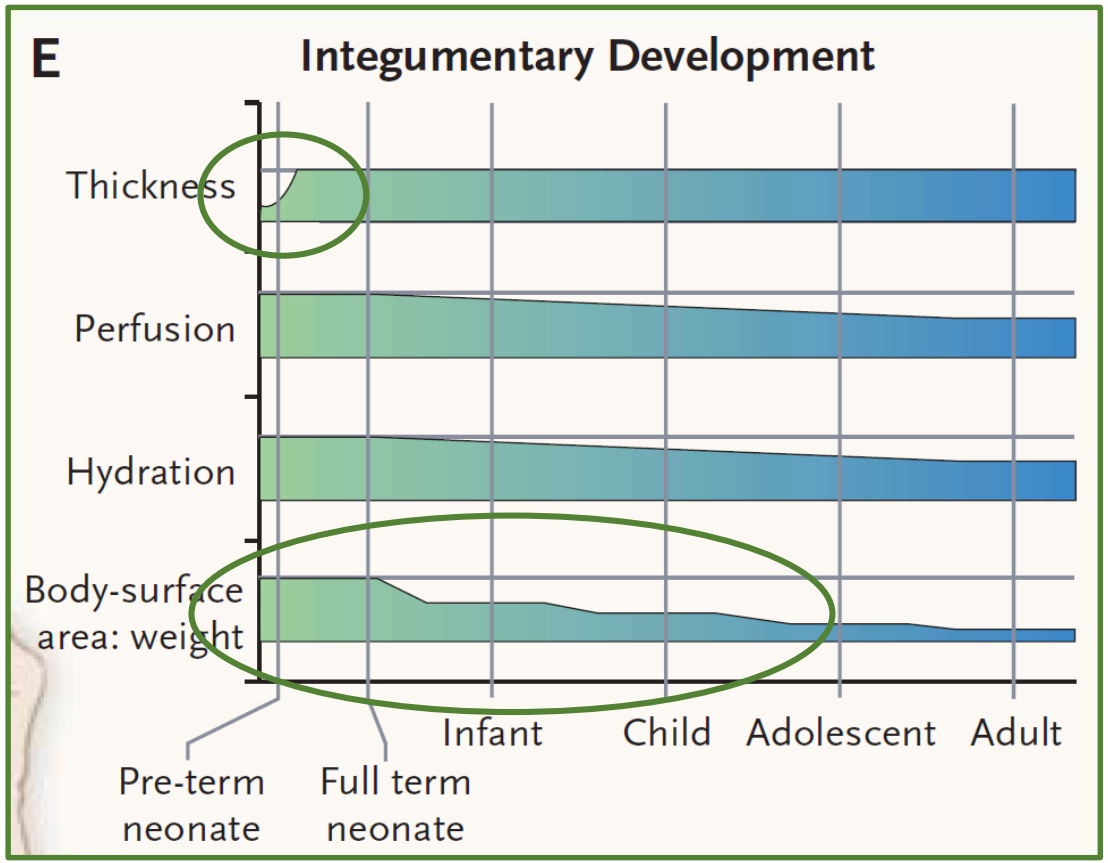
Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial

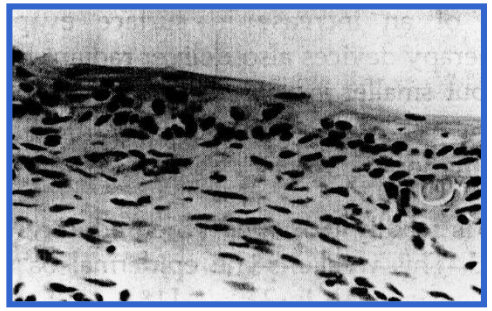
*Andrew J Davidson, Nicola Disma, Jurgen C de Graaff, Davinia E Withington, Liam Dorris, Graham Bell, Robyn Stargatt, David C Bellinger, Tibor Schuster, Sarah J Arnup, Pollyanna Hardy, Rodney W Hunt, Michael J Takagi, Gaia Giribaldi, Penelope L Hartmann, Ida Salvo, Neil S Morton, Britta S von Ungern Sternberg, Bruno Guido Locatelli, Niall Wilton, Anne Lynn, Joss J Thomas, David Polaner, Oliver Bagshaw, Peter Szmuk, Anthony R Absalom, Geoff Frawley, Charles Berde, Gillian D Ormond, Jacki Marmor, Mary Ellen McCann, for the GAS consortium**

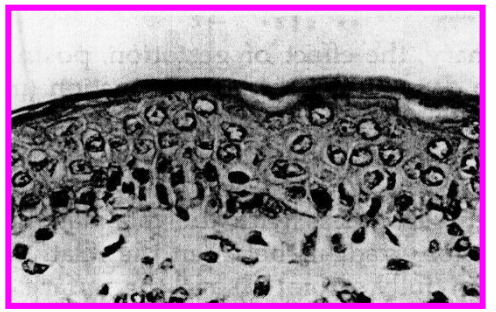
Findings Between Feb 9, 2007, and Jan 31, 2013, 363 infants were randomly assigned to receive awake-regional anaesthesia and 359 to general anaesthesia. Outcome data were available for 238 children in the awake-regional group and 294 in the general anaesthesia group. In the as-per-protocol analysis, the cognitive composite score (mean [SD]) was 98·6 (14·2) in the awake-regional group and 98·2 (14·7) in the general anaesthesia group. There was equivalence in mean between groups (awake-regional minus general anaesthesia 0·169, 95% CI –2·30 to 2·64). The median duration of anaesthesia in the general anaesthesia group was 54 min.

Interpretation For this secondary outcome, we found no evidence that just less than 1 h of sevoflurane anaesthesia in infancy increases the risk of adverse neurodevelopmental outcome at 2 years of age compared with awake-regional anaesthesia.

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.

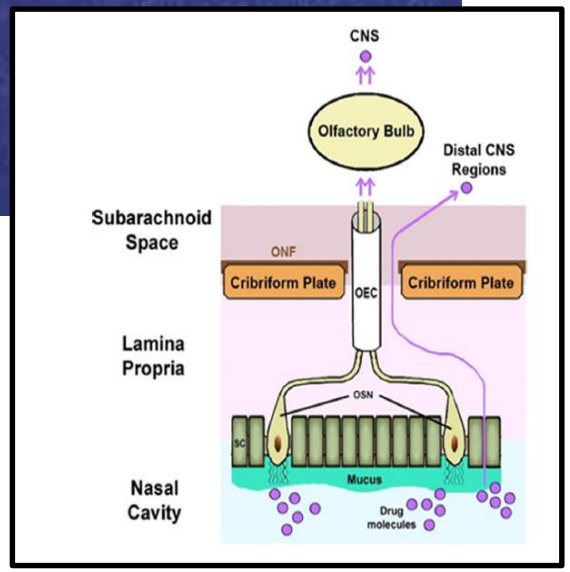
Preterm neonates are exposed to a range of painful procedures and topical anesthetics as EMLA are used routinely for pain management. Because premature neonates are low weight and consequently they are easily overdosed, routinely use of EMLA should be carefully evaluated.

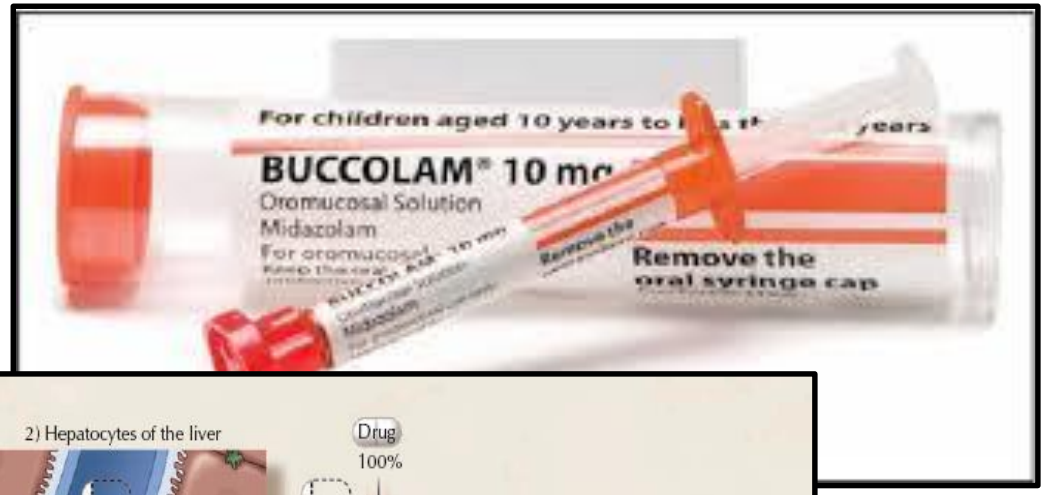
absorption, skin: BSA > permeability

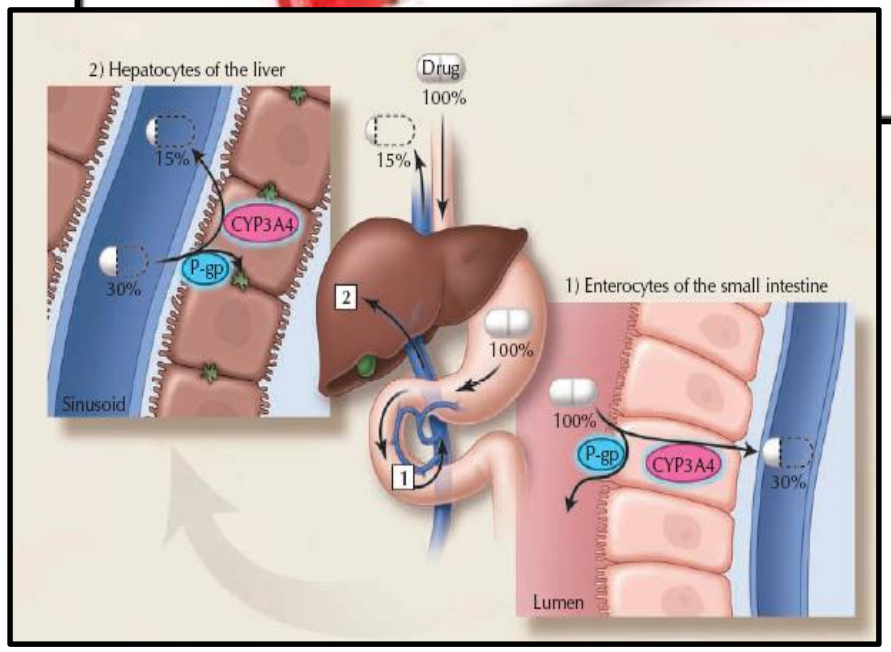
Table 15.3 Reported papers on the analgesic effects of tetracaine/amethocaine in neonates (type of procedure highlighted)

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







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

NIKS DOEN IS GEEN OPTIE

PREVENTIEVE MAATREGELEN BESTAAT EN WERKEN

METEN IS WETEN ?

PROCEDURALE PIJNSTILLING

PRO EN CO VAN SUCROSE EN DE VARIANTEN
PRO EN CO VAN TOPISCHE LOCALE ANALGETICA

PARACETAMOL WERKT, SOMS

MILDE PIJNBEELDEN
MORPHINE SPAREND
PROCEDURALE PIJNSTILLING

OPLADEN IS VAN BELANG, NOG MEER BIJ PASGEBORENEN

TEVEEL IS OOK NIET GOED