

pijnbestrijding bij de zuigeling: wat zijn de opties?

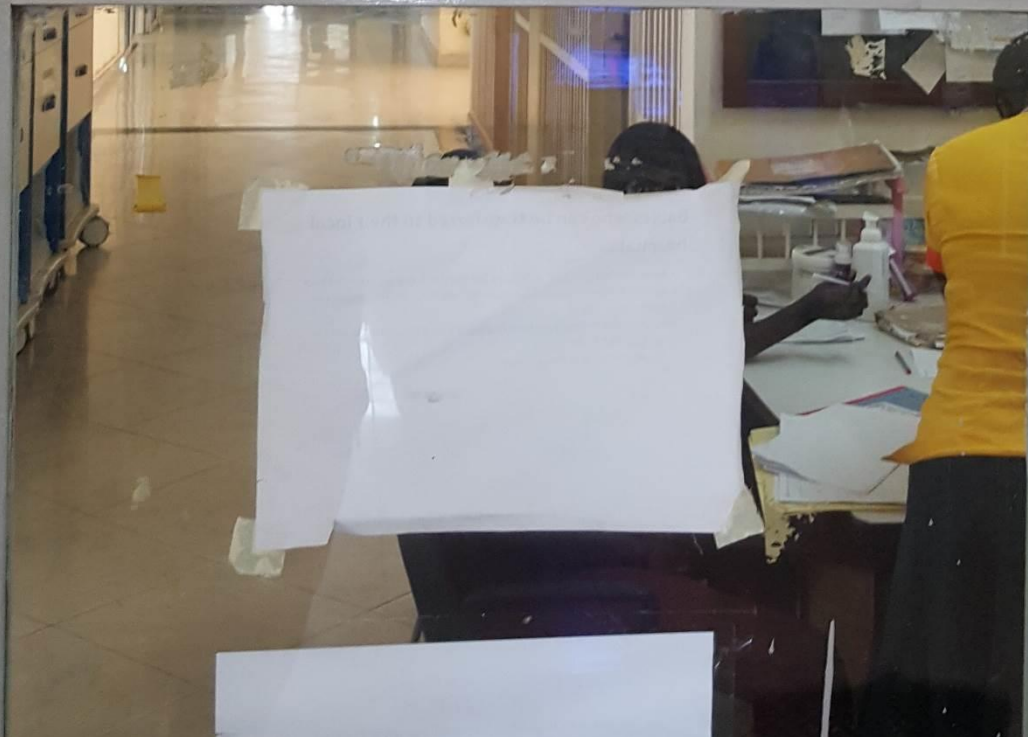


Erasmus MC Rotterdam, the Netherlands
KU Leuven, Belgium

karel allegaert



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



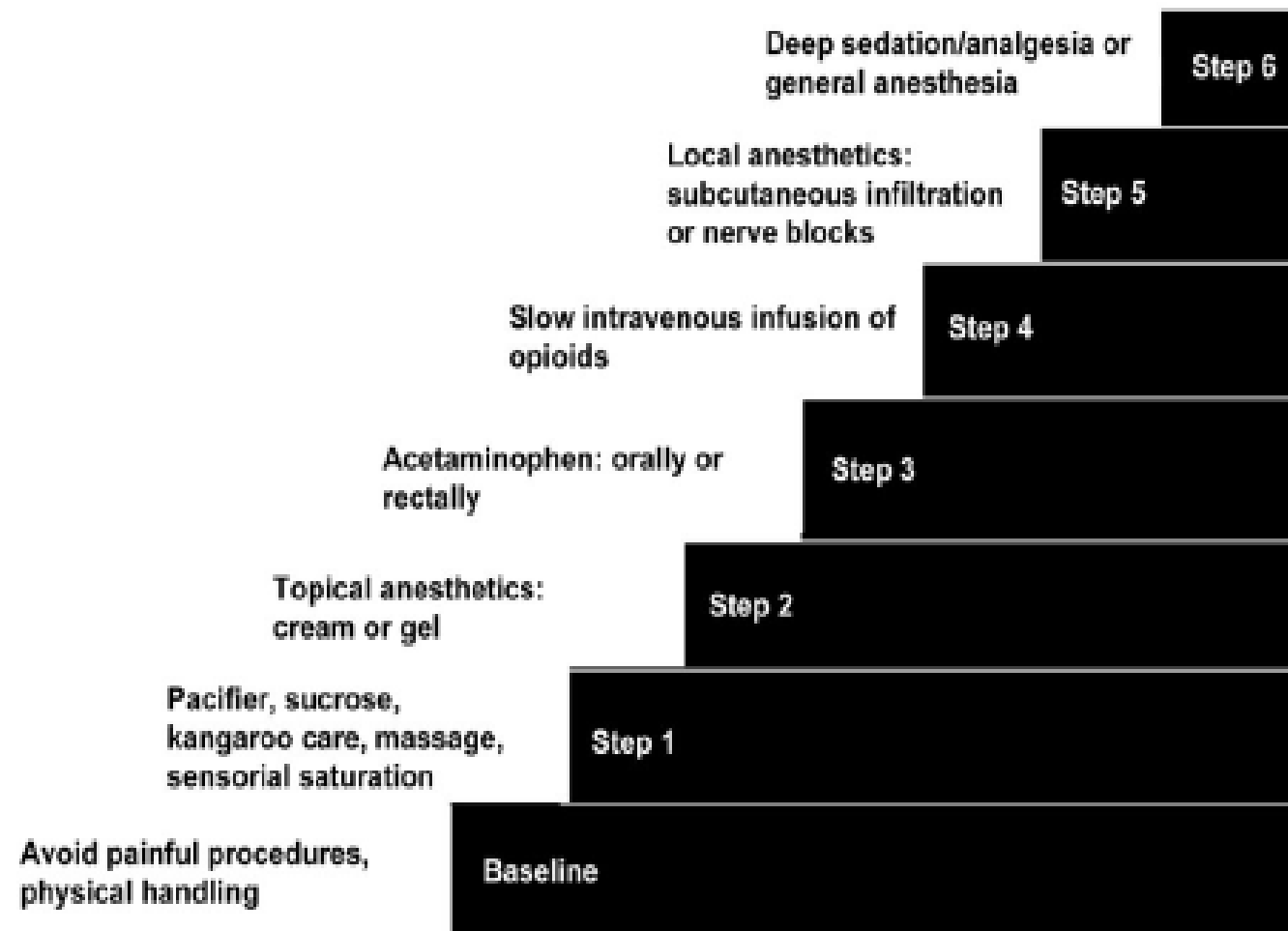
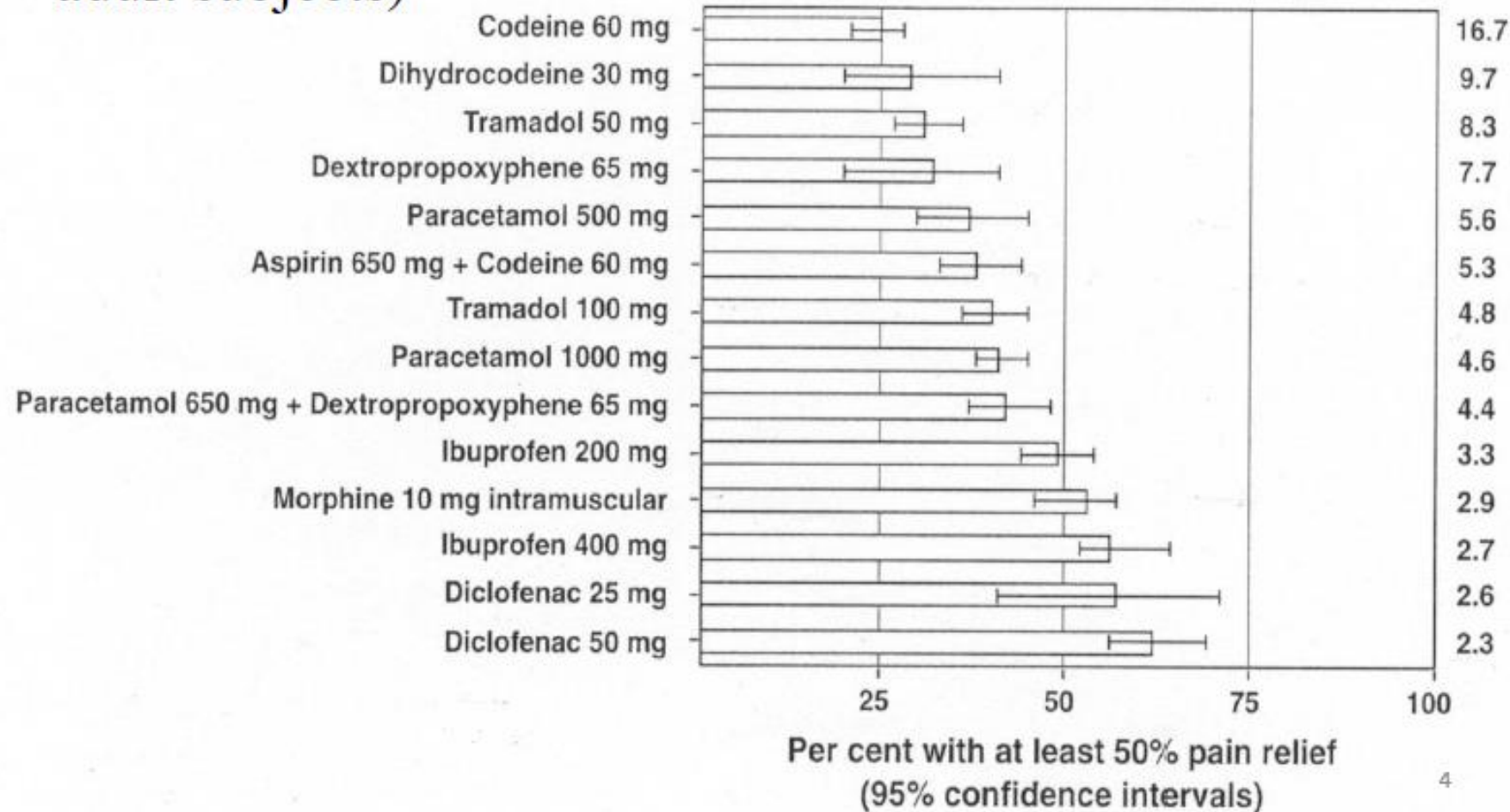
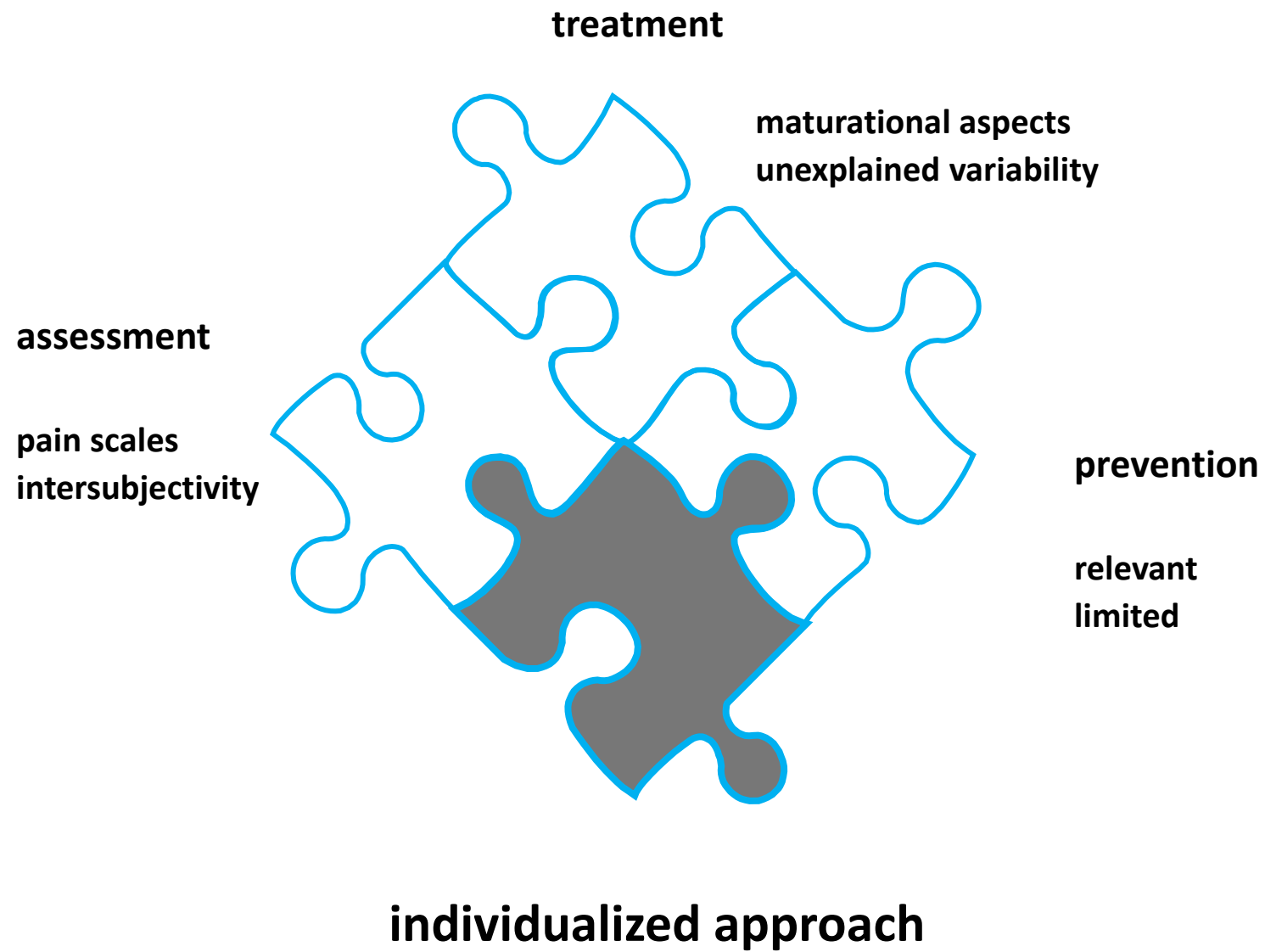


Figure 1. Stepwise approach to neonatal analgesia.

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)





SUGGESTIE 1





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Pain in babies may cause later harm



Photodisc file

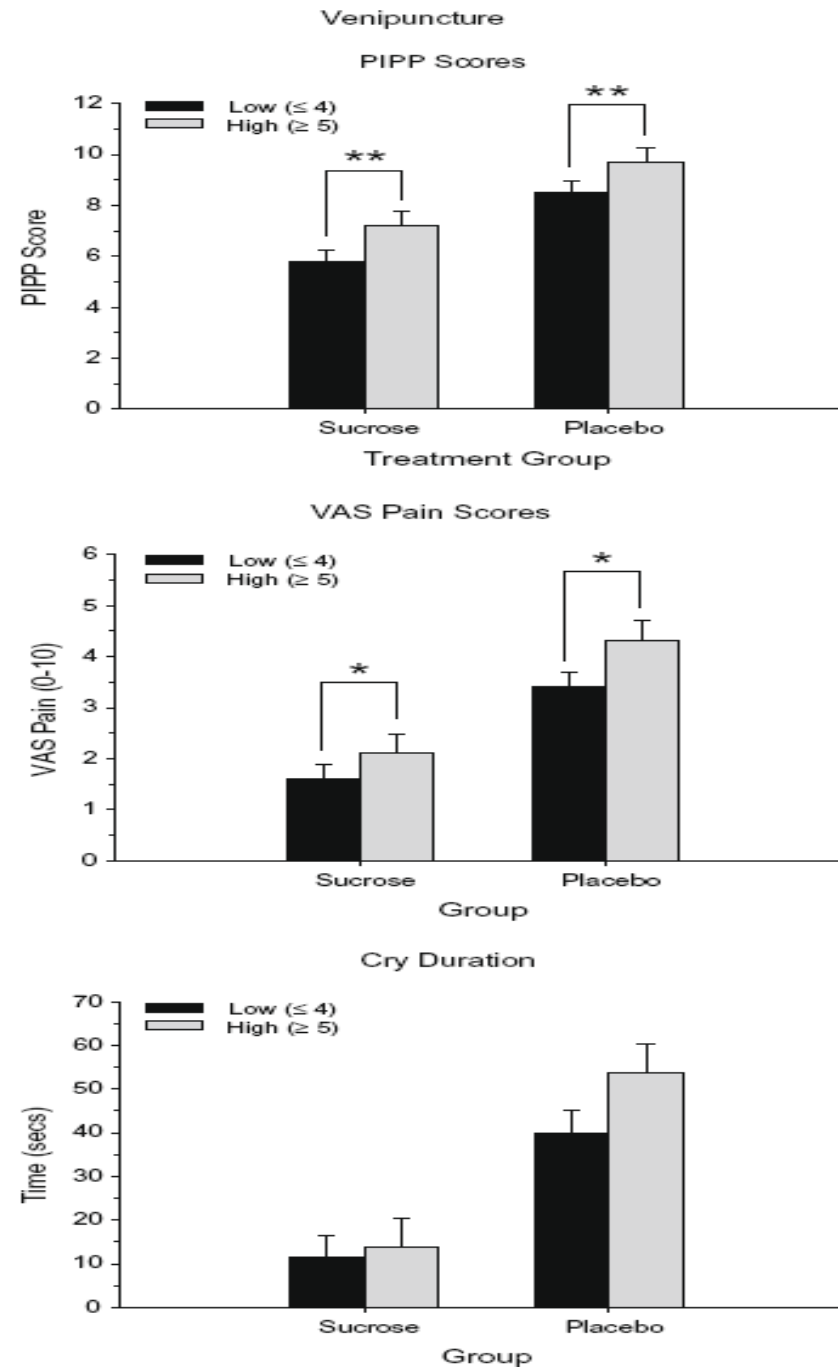
Study in newborn rats suggests early trauma rewires nervous system

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,}



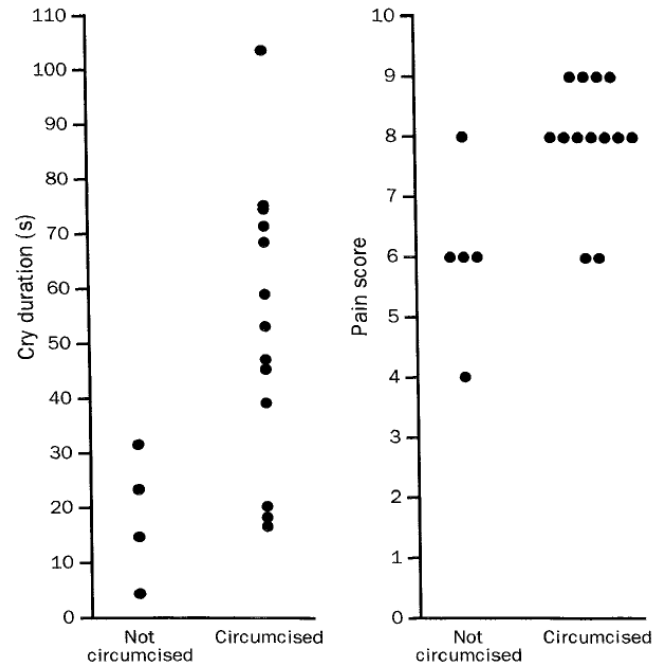
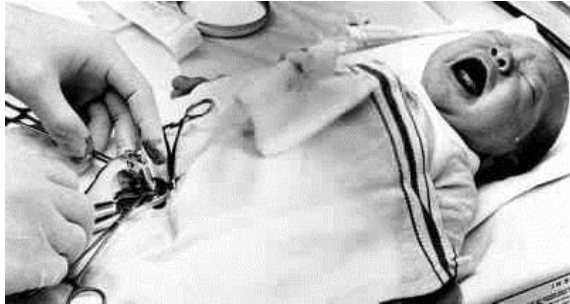
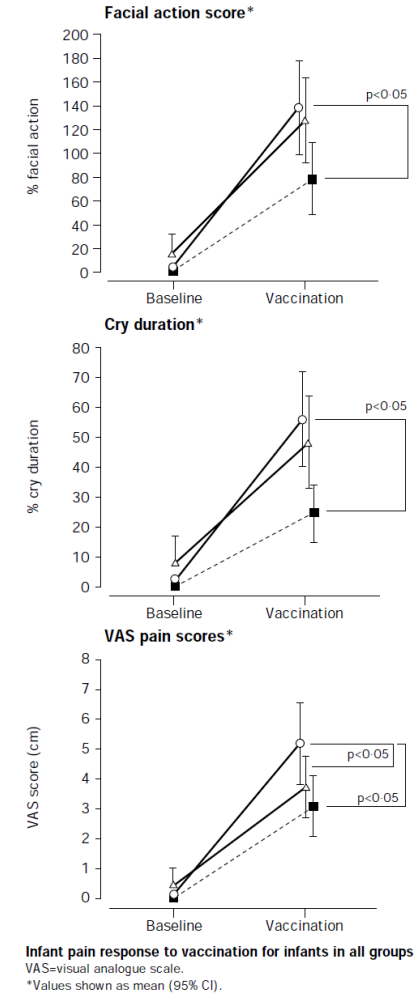


Figure: Pain response during HIB injection in circumcised and uncircumcised boys
 Data not available for cry on 1 infant. $p=0.02$ for cry, $p=0.01$ for behavioural pain score.



Anand *et al.* New Engl J Med 1987

Taddio *et al.* JAMA 2002

Taddio *et al.* Lancet 1995 and 1997

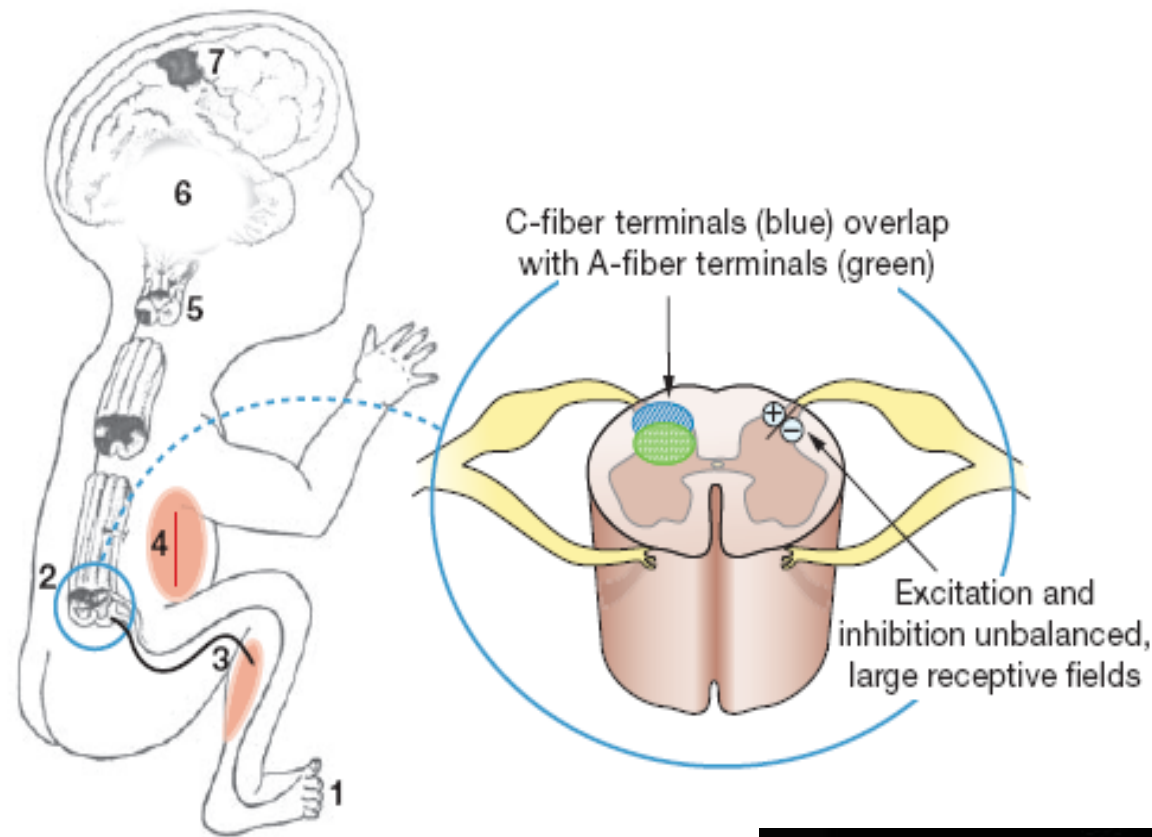
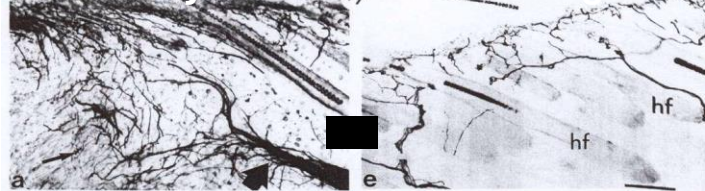


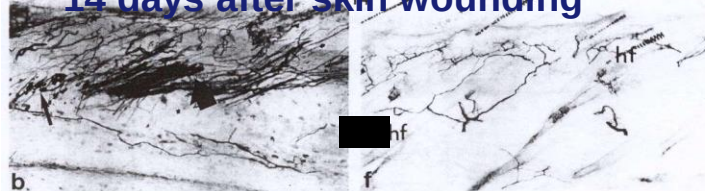
Figure 1 Key sites of developmental transition in pain pathways. Areas of the nervous system are indicated where developmental plasticity impact pain detection and treatment in this system. (1) Peripheral innervation is vulnerable and sensitive to tissue injury. (2) Pain pathways undergo considerable postnatal reorganization. (3) Reflex pathways are diffuse and poorly tuned. (4) Primary somatosensory cortex before secondary hyperalgesia. (5) Endogenous descending modulation of pain pathways is unbalanced. (6) Extensive cortical development but little is known of the development of intracortical networks. (7) The somatosensory cortex is activated by pain from early age, but little is known of activation in other cortical regions.



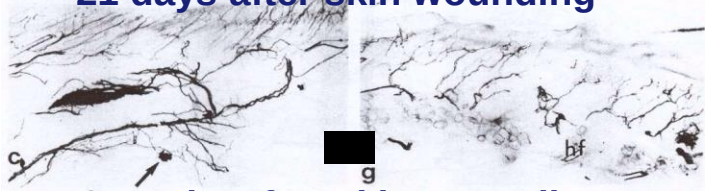
Wounded Control
7 days after skin wounding



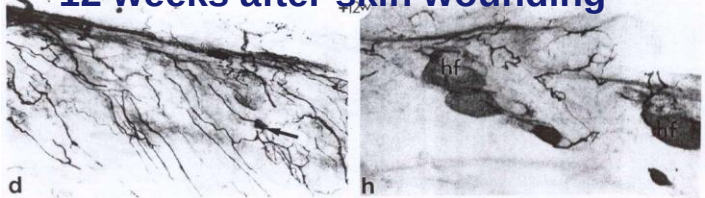
14 days after skin wounding



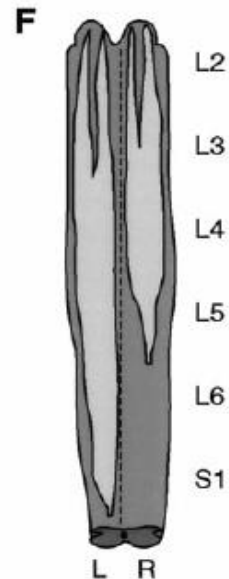
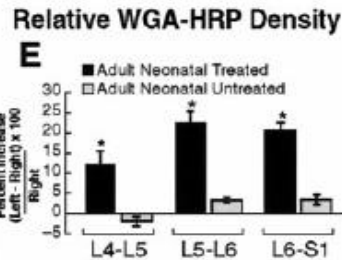
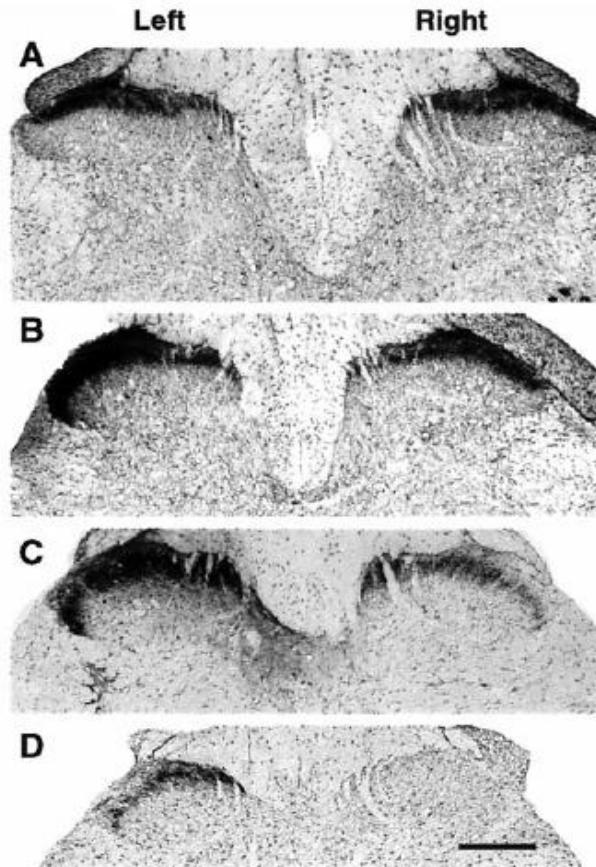
21 days after skin wounding



12 weeks after skin wounding



Reynolds & Fitzgerald. J Comp Neurol 1995; 358: 628-31
hyper(re-)innervation following neonatal skin laesions



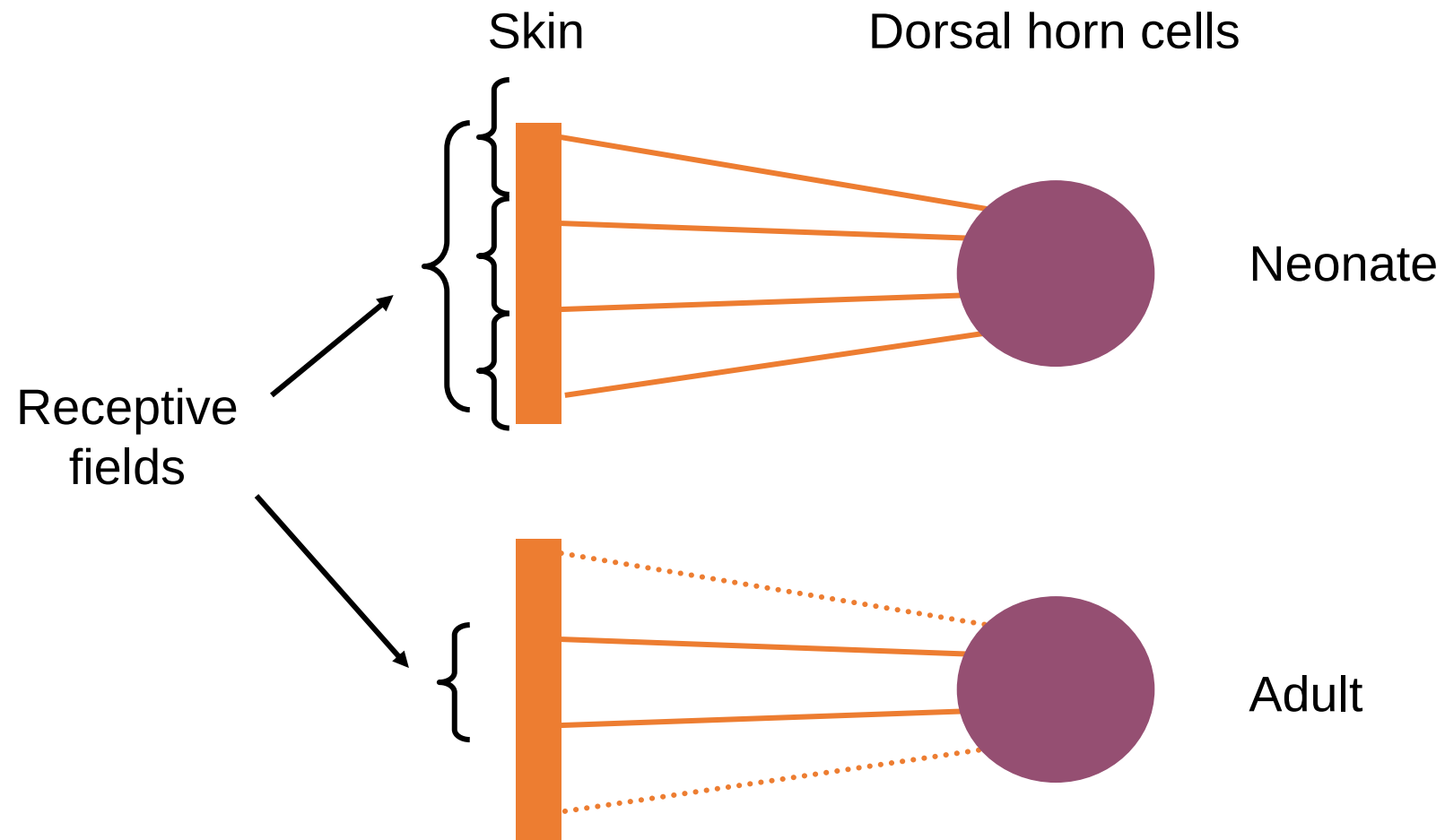
Maximal effect in rats: 6-9 days (*Anand & Scalzo 2000*)

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

<u>Rat</u>	-	<u>Human</u>
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



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*

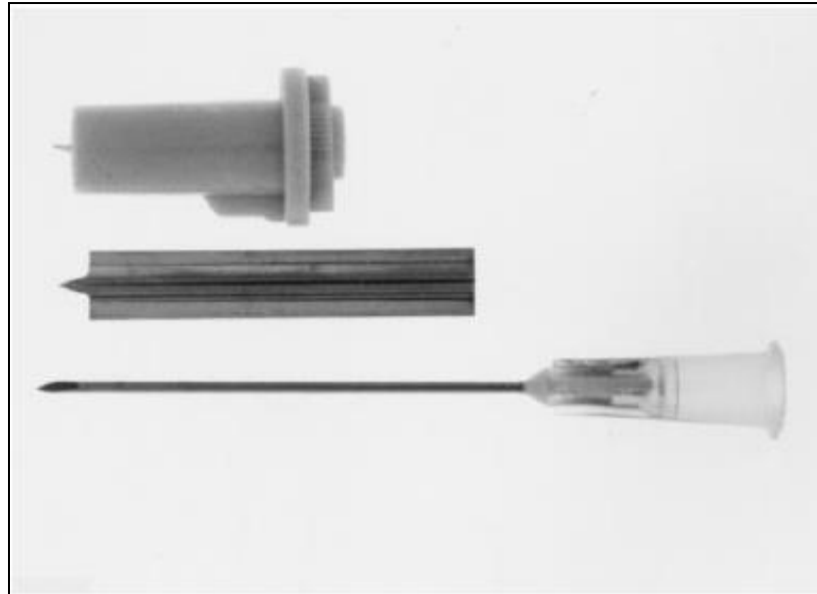


Fig 1. Three devices used for the PKU test. From the top: the CCS Minilancet used in the SL group, the Microlance used in the LL group, and the Microlance needle (0.9 × 40 mm) used in the VP group.





The 3 P's of Helping your Baby during Vaccinations

A Parent's Guide: Babies up to 1 year old



Plan Ahead

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

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)



Apply topical anaesthetics

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.



Give sugar water

SUGAR WATER

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

During Vaccine Injection

STEP 2: PHYSICAL (BODY POSITION AND ACTIVITY)



Hold upright

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.



Breastfeed

STEP 3: PSYCHOLOGICAL (THOUGHTS AND BEHAVIOURS)



Deep breaths

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.

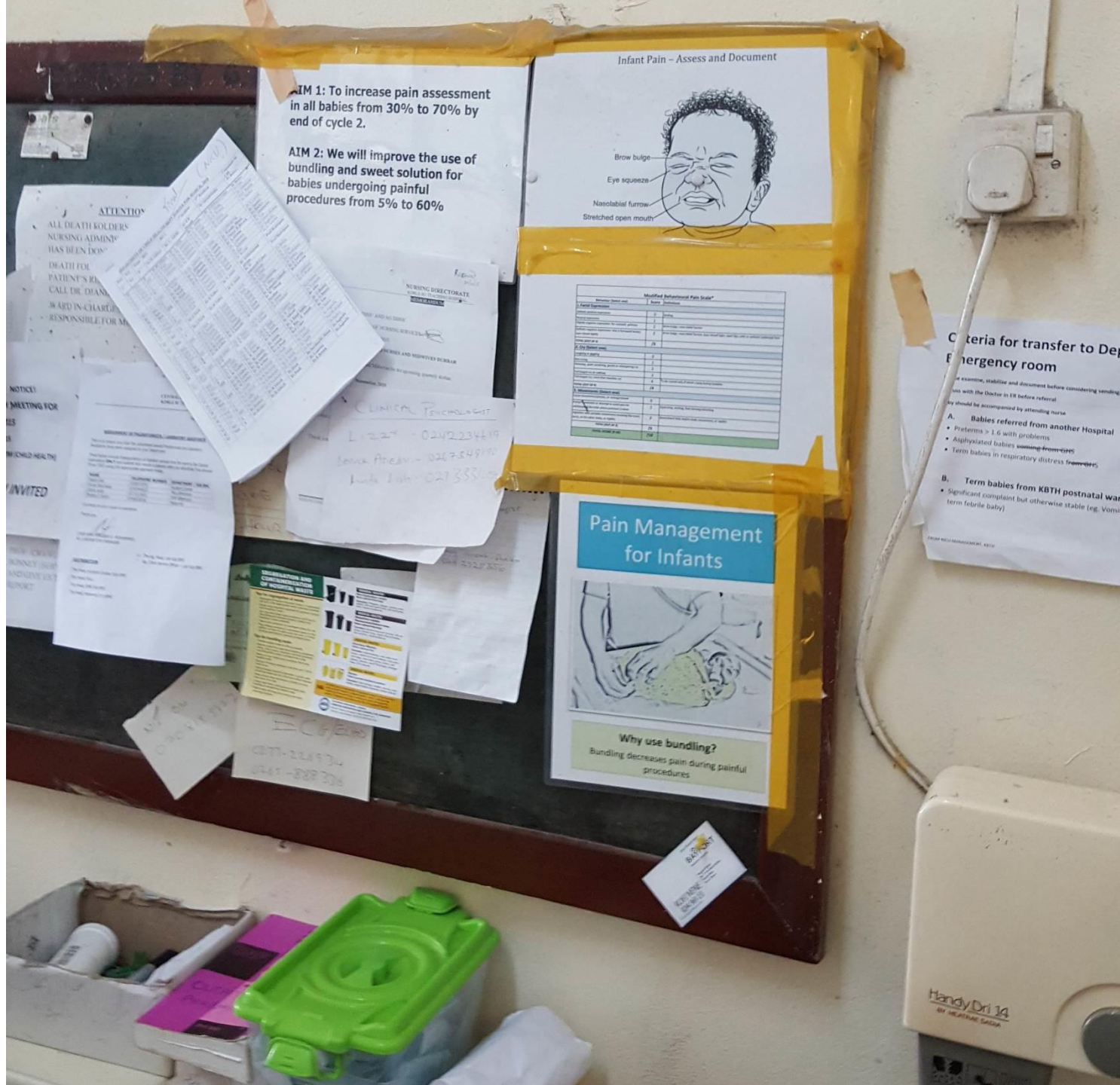


DISTRACT

- Help keep your baby's attention away from the injection.
- Distractions you can use: rocking, cuddling, singing, talking, sucking (breastfeeding 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.



Distract



AIM 1: To increase pain assessment in all babies from 30% to 70% by end of cycle 2.

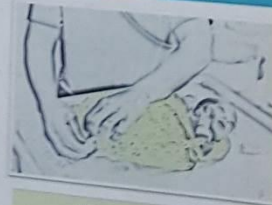
AIM 2: We will improve the use of bundling and sweet solution for babies undergoing painful procedures from 5% to 60%

Infant Pain - Assess and Document



Modified Behavioral Pain Scale*	
Behavioral Signs	Score
1. Facial Expression	0-2
2. Cry Sound	0-2
3. Cry Duration	0-2
4. Grimace	0-2
5. Body Language	0-2
6. Heart Rate	0-2
7. Blood Pressure	0-2
8. Respiratory Rate	0-2
9. Oxygen Saturation	0-2
10. Temperature	0-2
11. Heart Rate	0-2
12. Blood Pressure	0-2
13. Respiratory Rate	0-2
14. Oxygen Saturation	0-2
15. Temperature	0-2
16. Heart Rate	0-2
17. Blood Pressure	0-2
18. Respiratory Rate	0-2
19. Oxygen Saturation	0-2
20. Temperature	0-2

Pain Management for Infants



Criteria for transfer to Dep Emergency room

- Preterm > 1.6 with problems
 - Asphyxiated babies ~~sending from ER~~
 - Term babies in respiratory distress ~~from ER~~
- B. Term babies from KBTH postnatal ward
- Significant complaint but otherwise stable (eg. Vomiting term febrile baby)

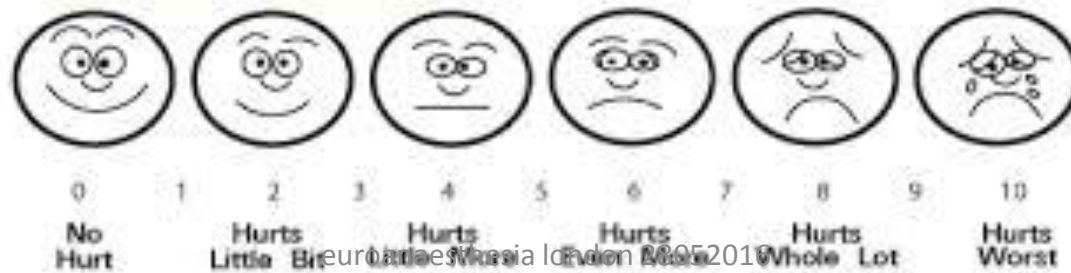
Handy Dri 14
BY HEATHCOTE CLINICAL

SUGGESTIE 3





Wong Baker Face Scale



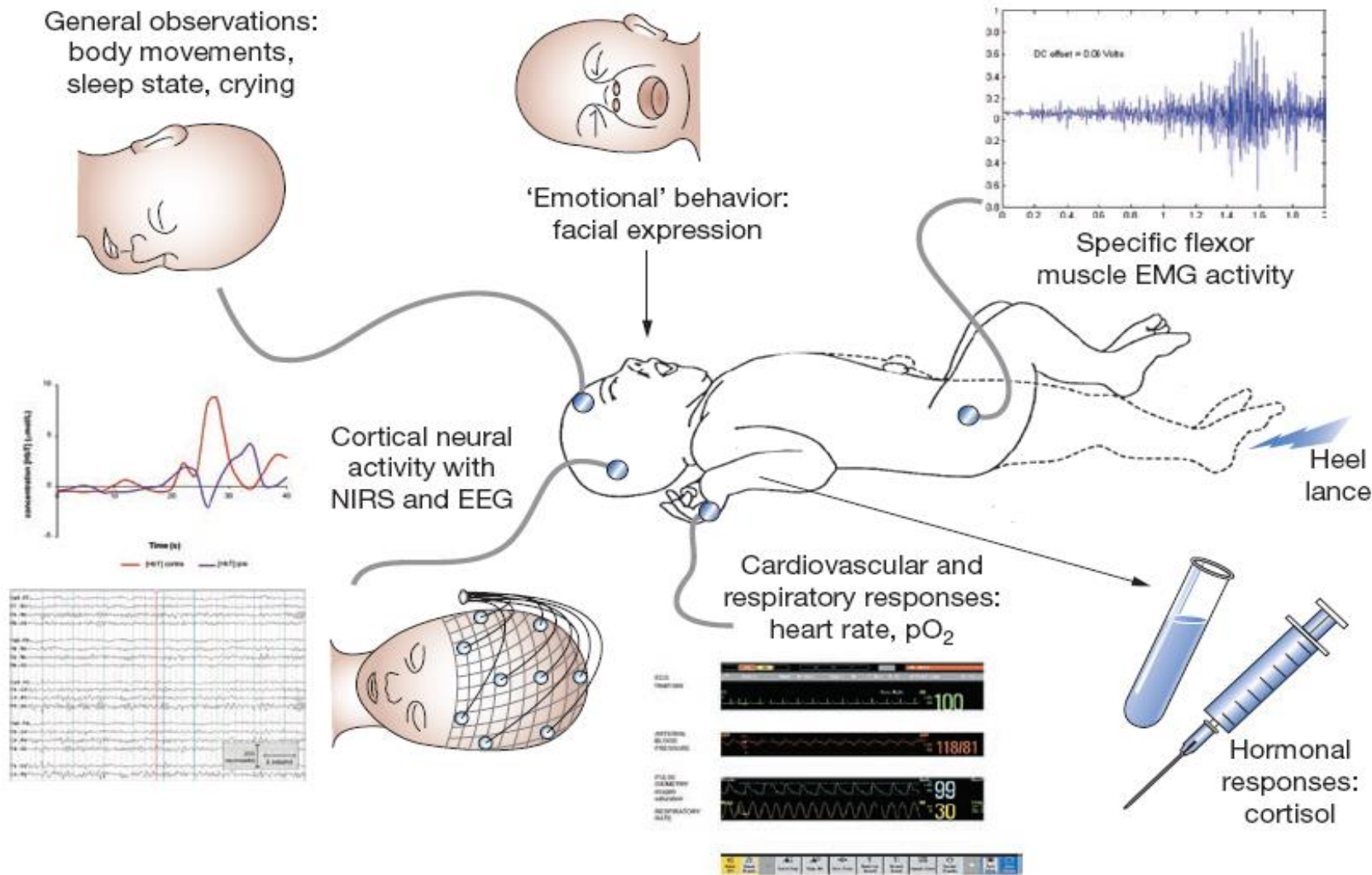
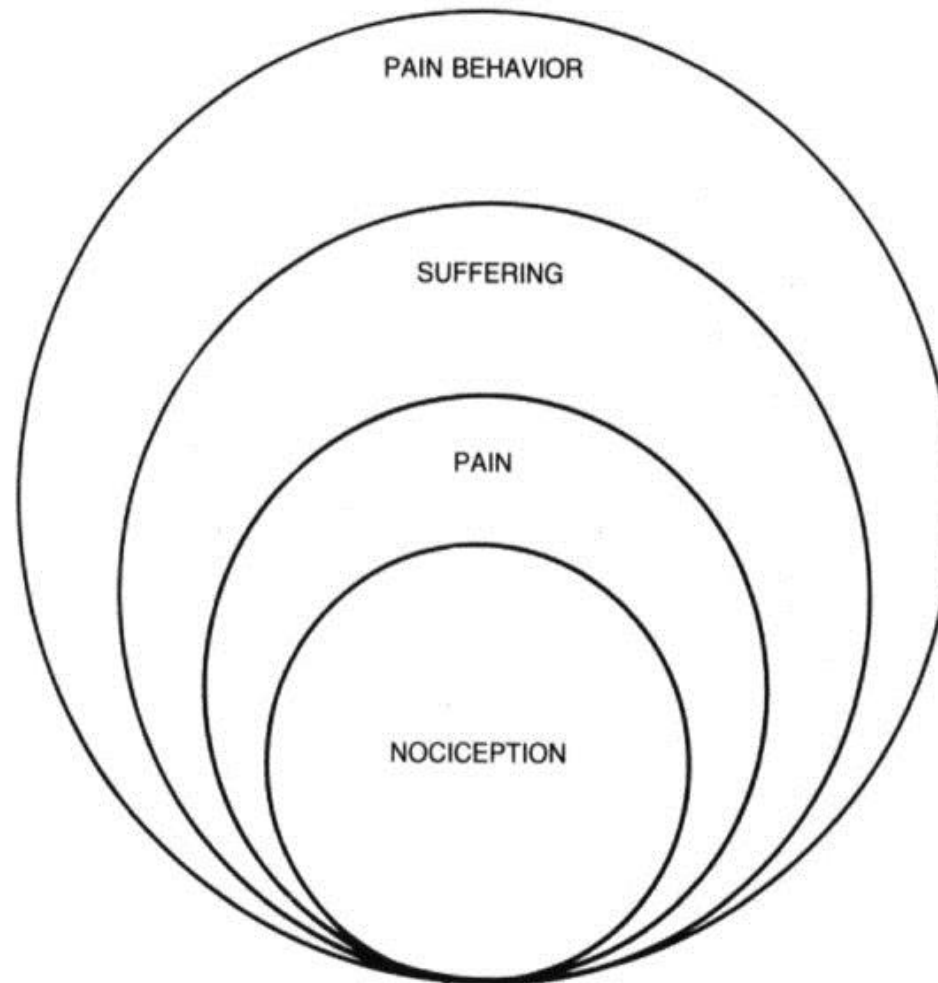


Figure 2 Methods of assessing infant pain. In the absence of language, infant pain is assessed by a number of different physiological methods. Some of these methods are integrated into current clinical pain assessment tools. The neurophysiological techniques EMG, EEG and NIRS are not used for routine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

SUGGESTIE 4

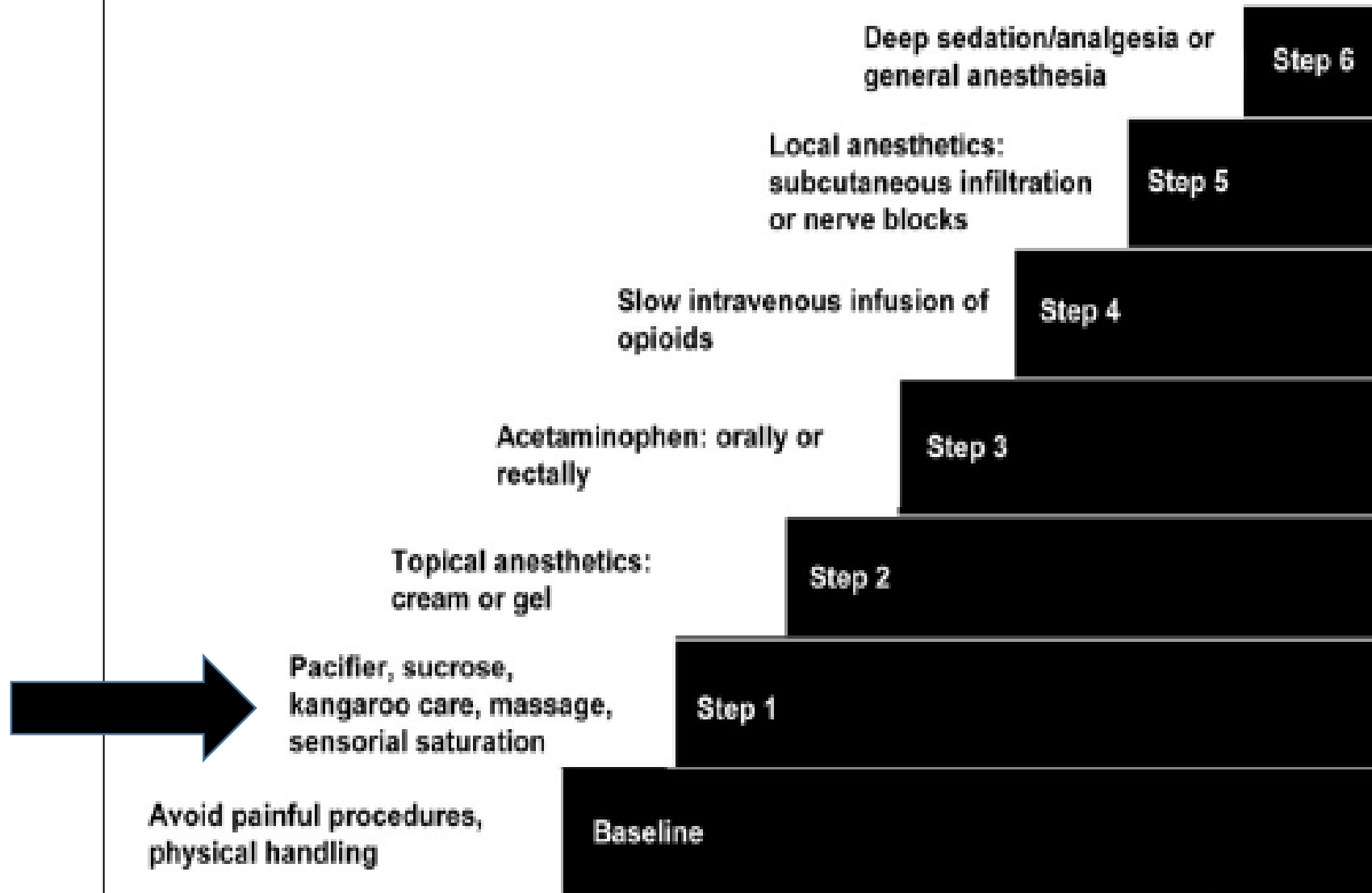
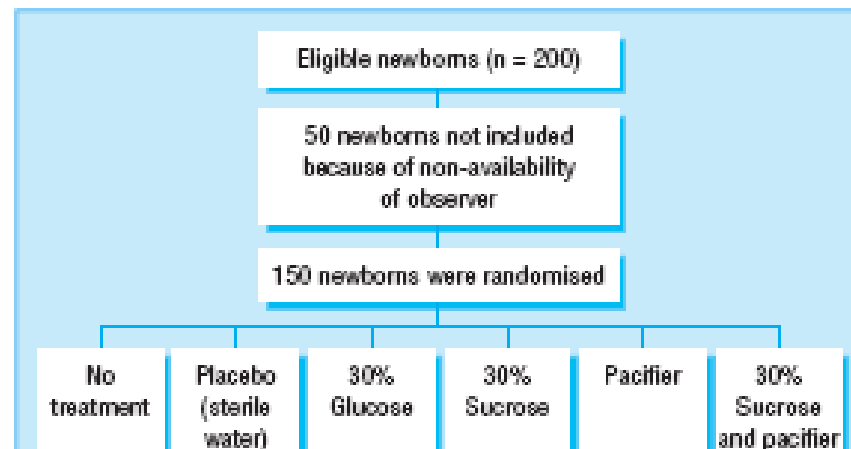


Figure 1. Stepwise approach to neonatal analgesia.



Acta Paediatr 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

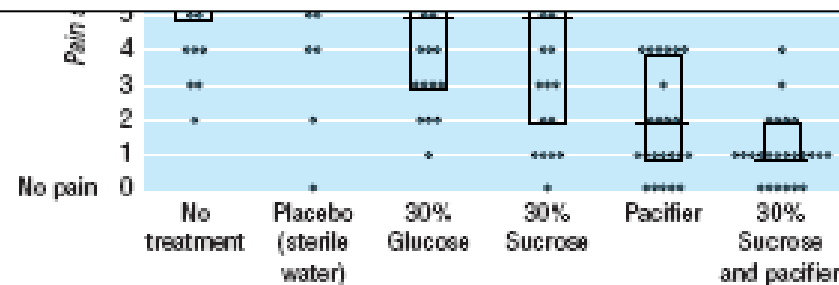


Fig 2 Pain evaluation with DAN scale (0 to 10) during venepuncture in 150 newborns randomised to six equal sized groups, with values for individual infants, median values, and interquartile ranges (for 30% sucrose and pacifier lower quartile coincides with median value)

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

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

BREASTFEEDING MEDICINE
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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



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

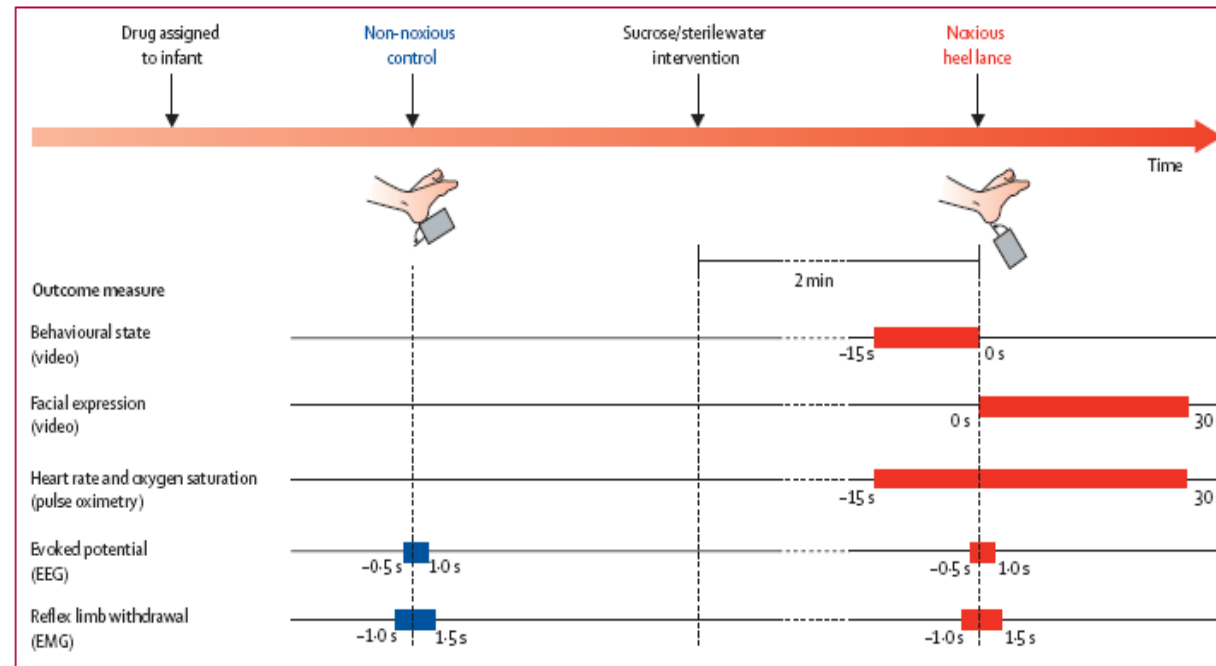


Figure 1: Experimental time line

EEG=electroencephalography. EMG=electromyography.

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



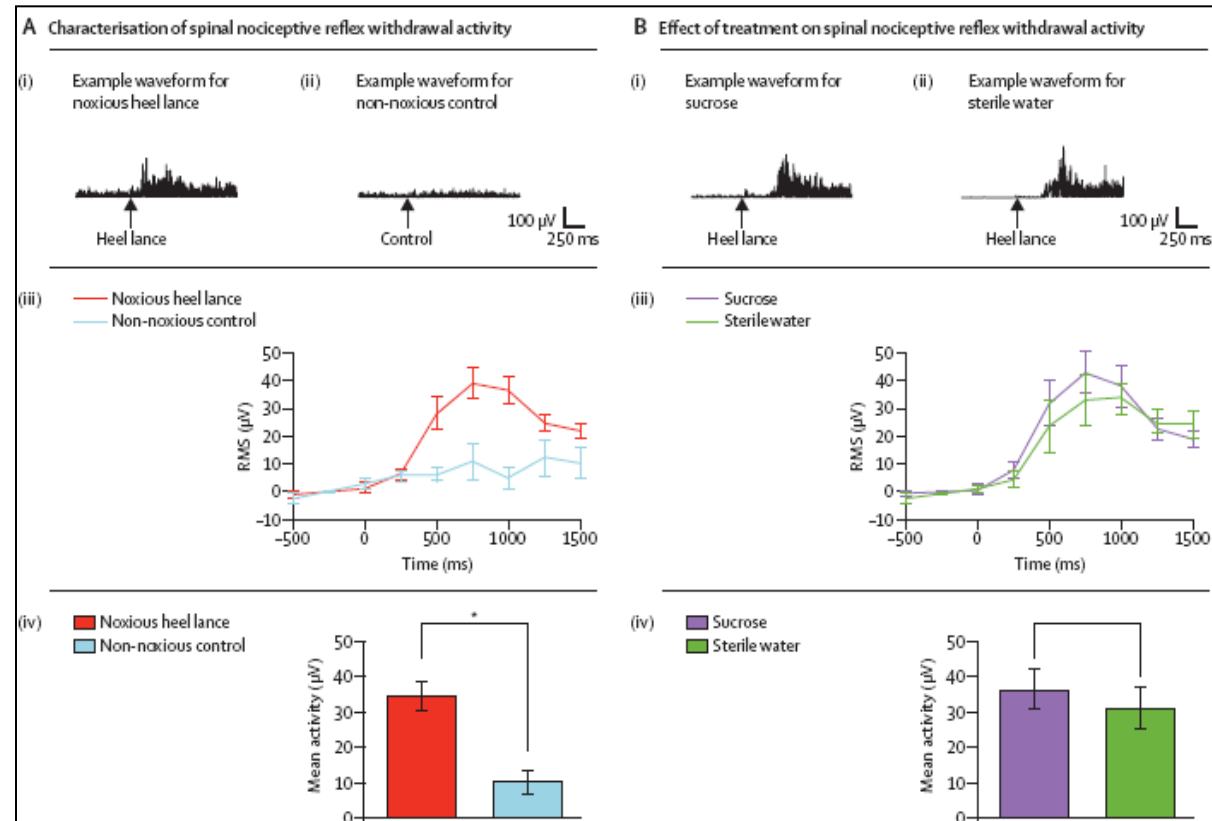
Rebecca Slater, Laura Cornelissen*, Lorenzo Fabrizi*, Debbie Patten, Jan Yoxen, Alan Worley, Stewart Boyd, Judith Meek†, Maria Fitzgerald†

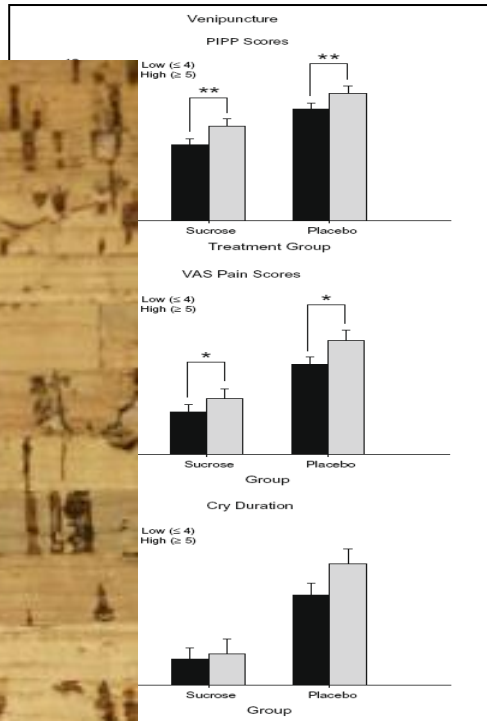
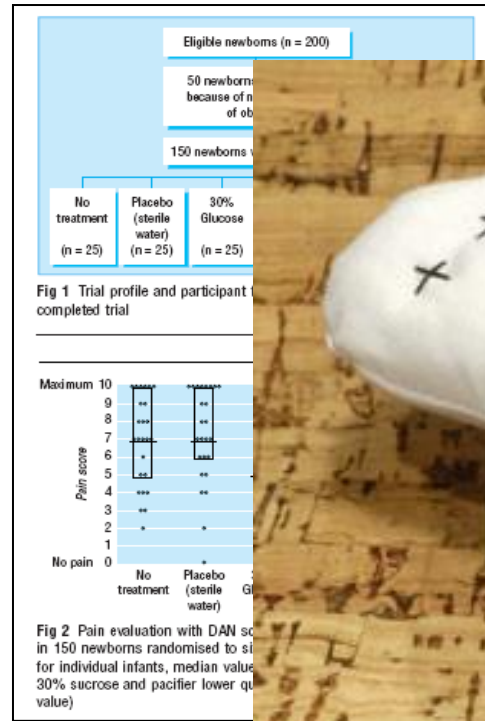
	Sucrose (N=20)	Sterile water (N=24)	p value
Primary outcome			
Nociceptive-specific brain activity (mean weight)	0.10 (0.04-0.16)	0.08 (0.04-0.12)	0.46
Secondary outcomes			
Mean baseline heart rate (bpm)	132.6 (124.3-140.9)	131.8 (122.2-141.5)	0.90
Mean baseline oxygen saturation (%)	99.4% (98.8-100.1)	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 (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



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



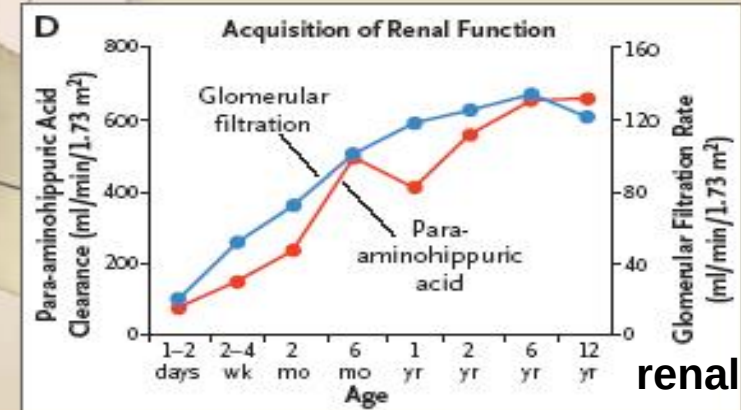
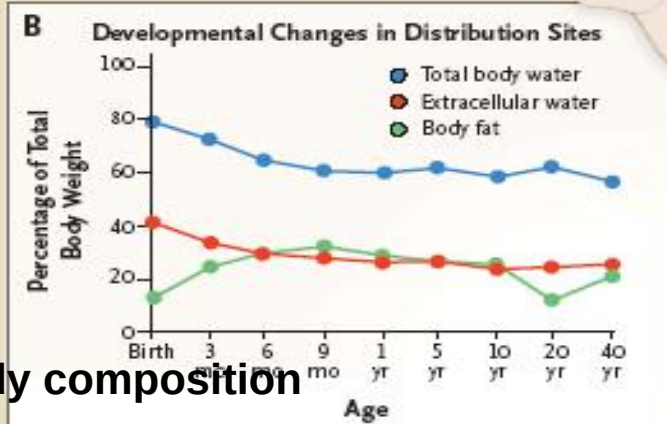
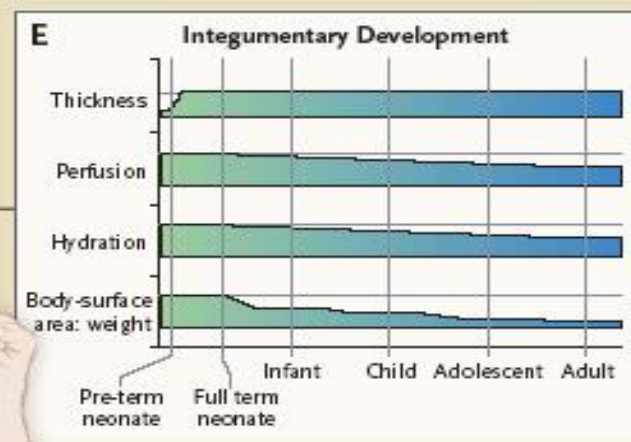
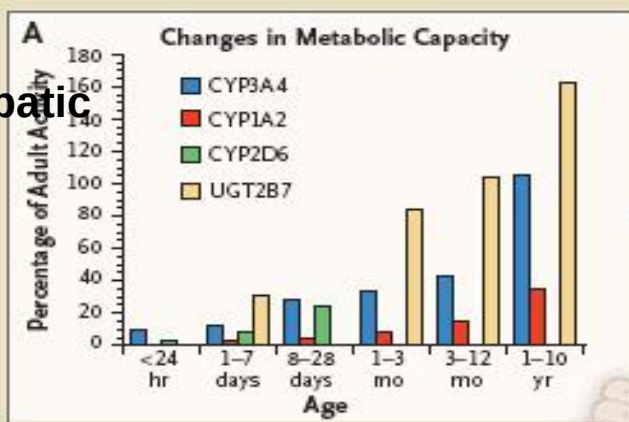


suggestie 4: beperkt effect – if any – in neonates, proven in infants

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

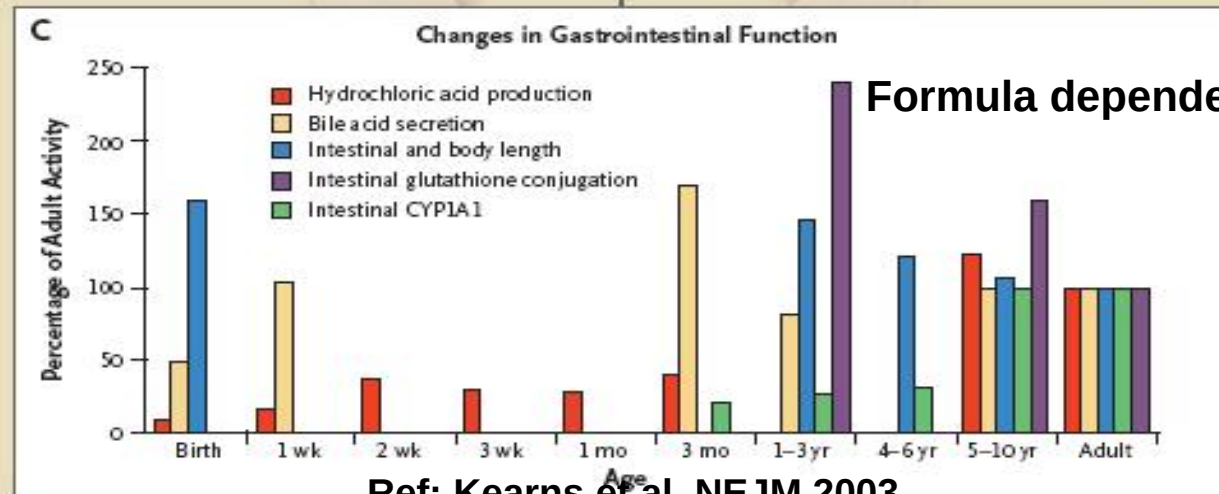
Reference	Study design and results
Shah et al. [88]	Randomized, double-blind, placebo-controlled trial, <i>intramuscular injection</i> (vitamin K) in 110 term neonates, topical amethocaine gel 4 %. There were no differences in crying duration, in pain score and only the latency to cry was somewhat longer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

hepatic



Body composition

renal



Formula dependent

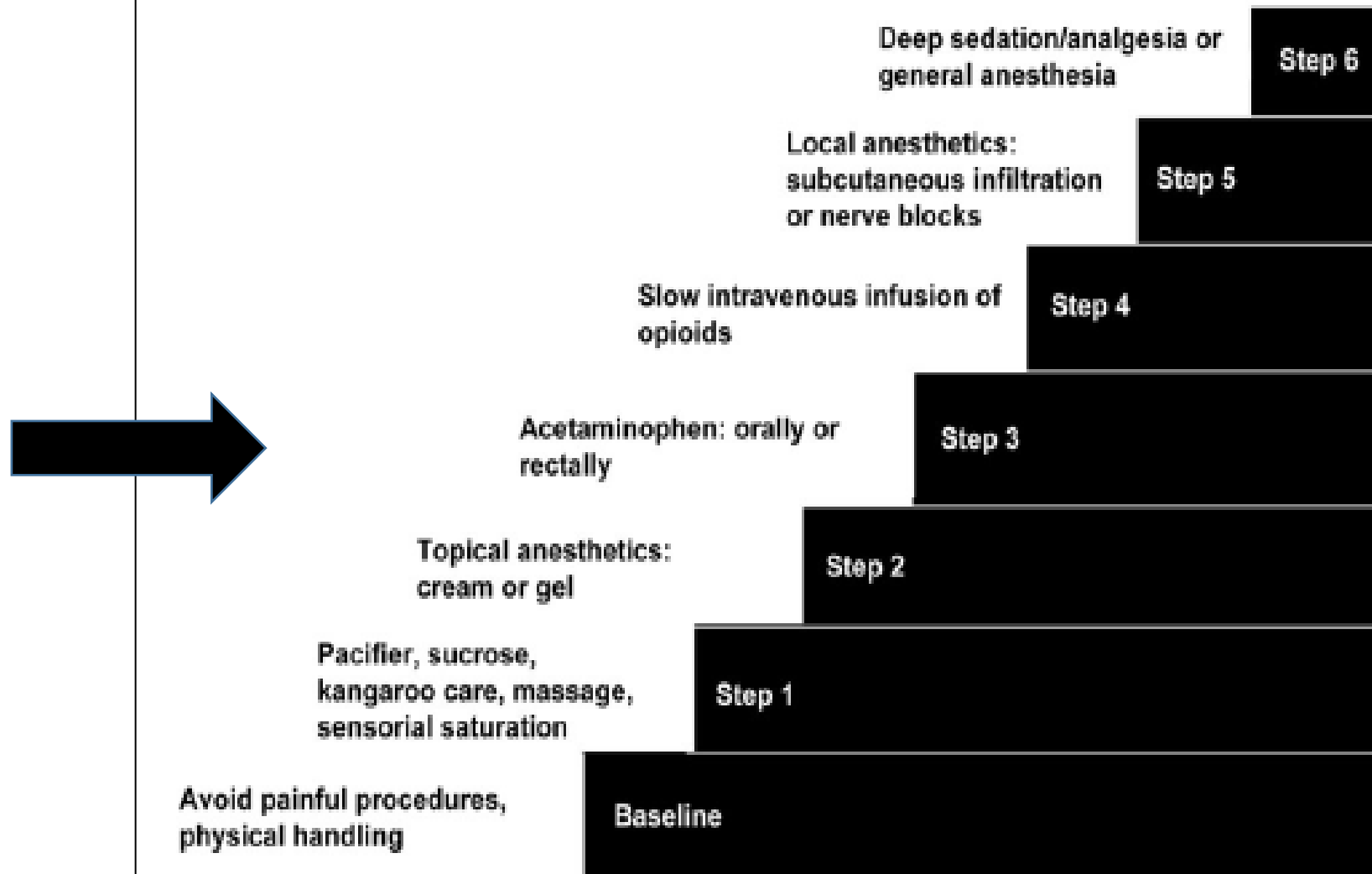


Figure 1. Stepwise approach to neonatal analgesia.

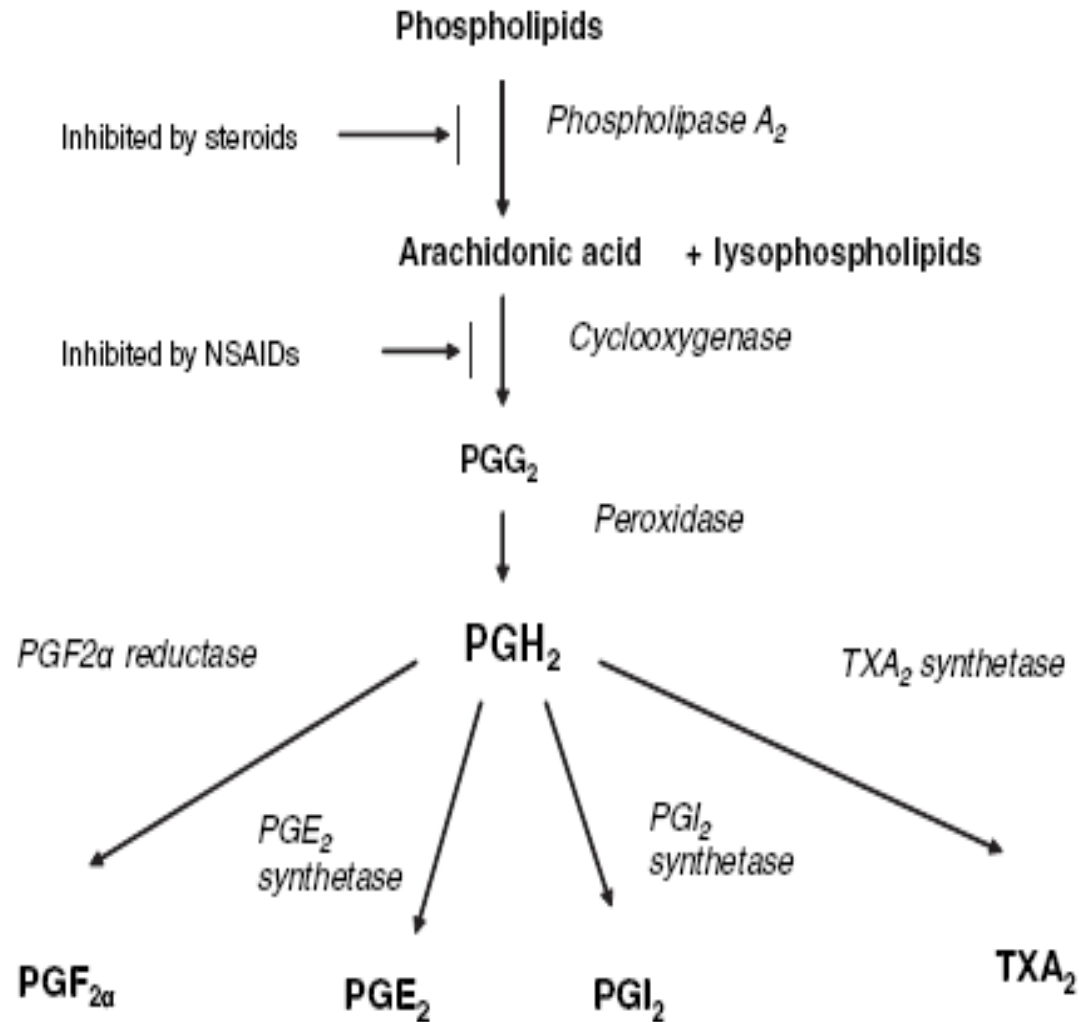


Figure 1
Schematic diagram of arachidonic acid metabolism.

L-arginine-nitric oxide
(NO) pathway

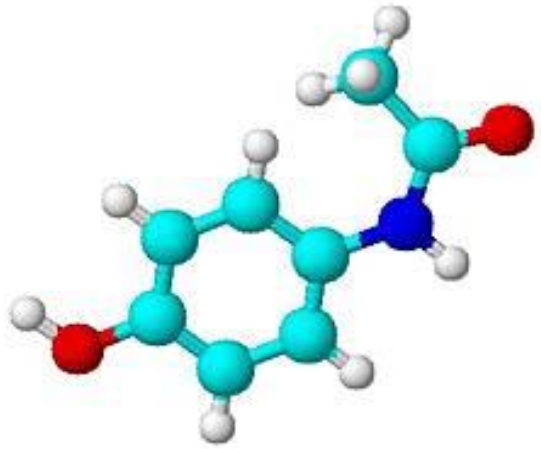
Substance P mediated

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



antipyretic ? lower

—

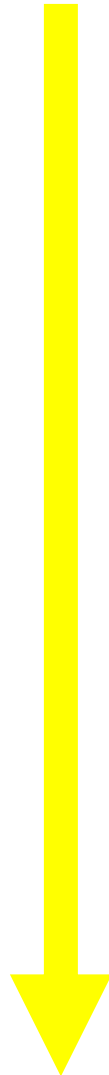
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> 25



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



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).

suggestie 5: paracetamol werkt, soms...

standard rectale dosis paracetamol is onvoldoende

lagere bio-availabiliteit

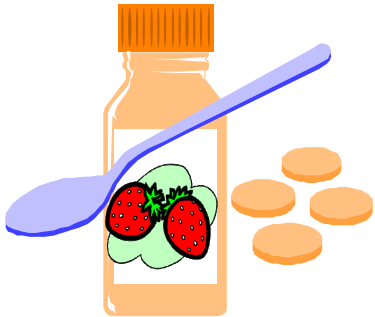
vertraagde absorptie

belangrijke variabiliteit

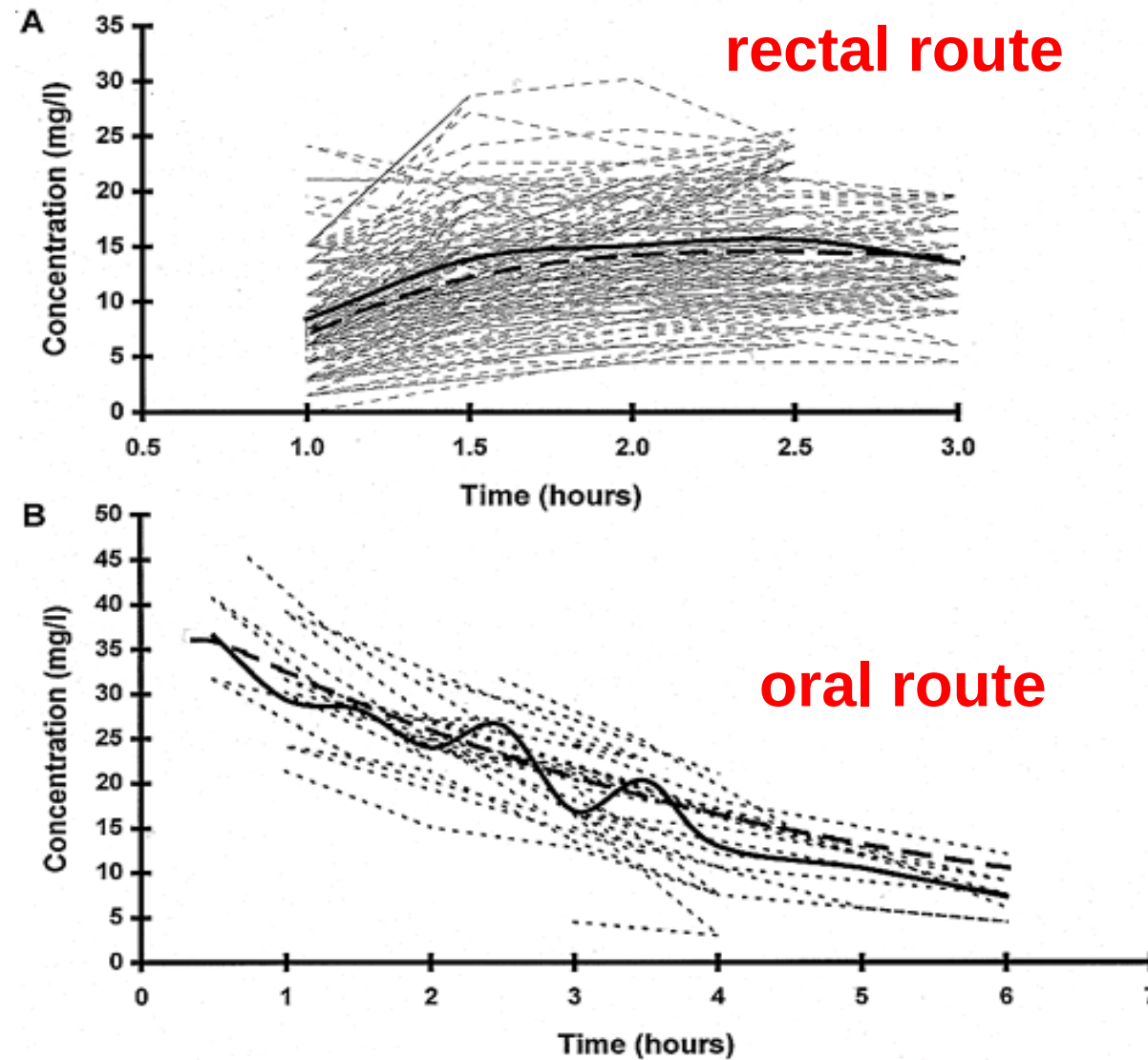
oral > iv > rectal

denk aan een oplaaddosis: distributie volume

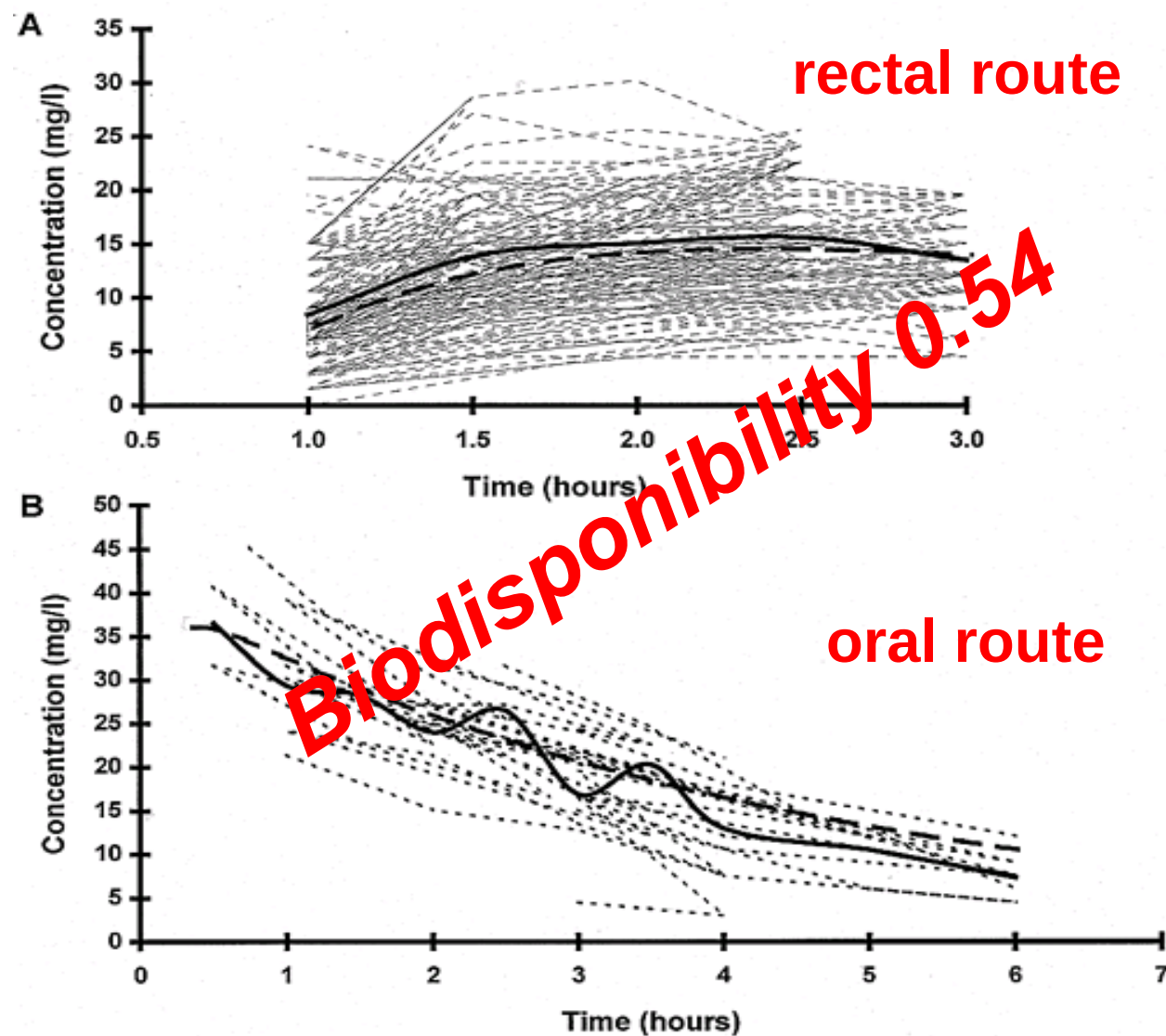
leeftijd gerelateerde veranderingen in klaring zijn eerder beperkt



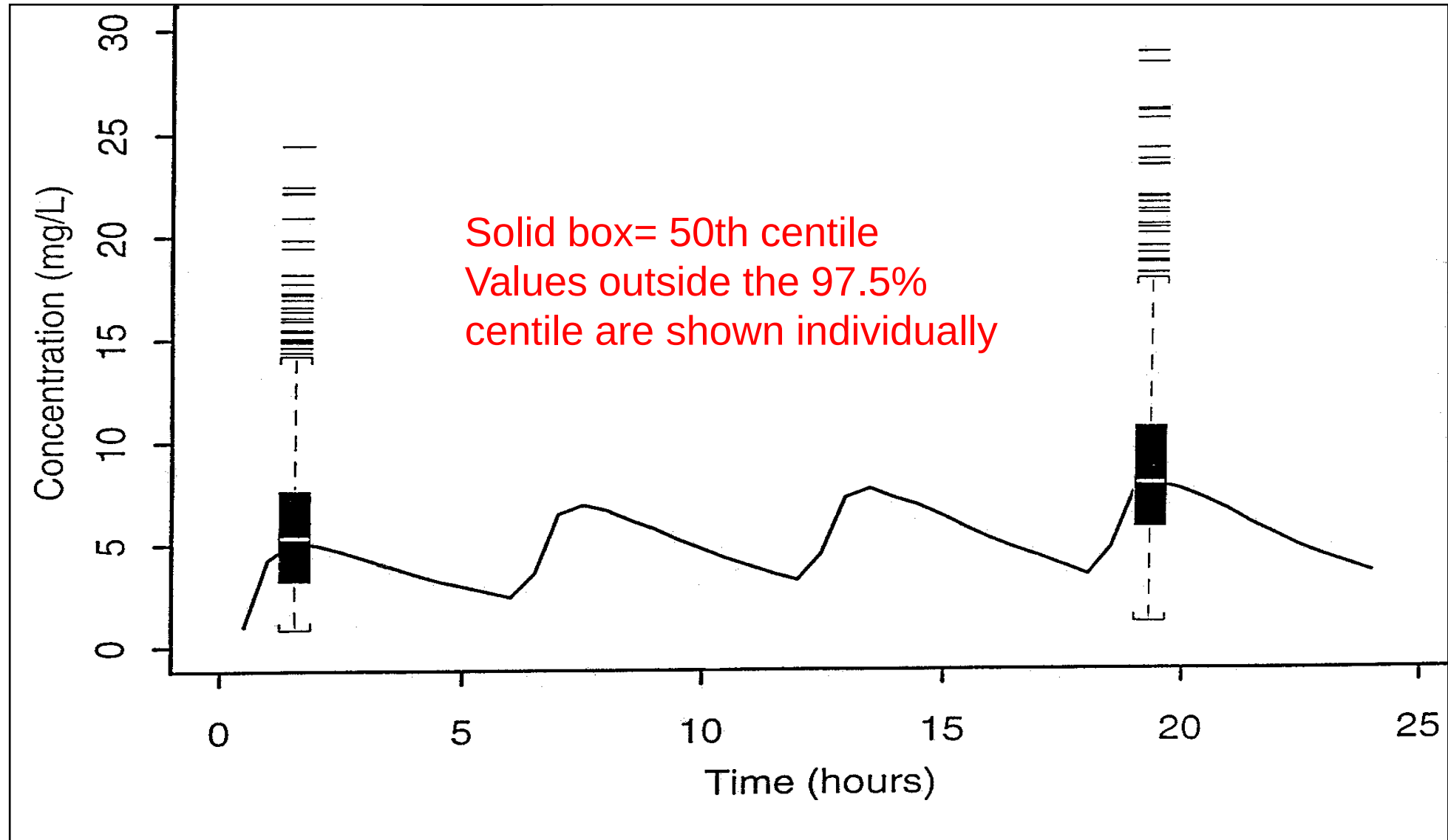
rectaal of oraal, 20 mg/kg single dose na NKO heilkunde



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

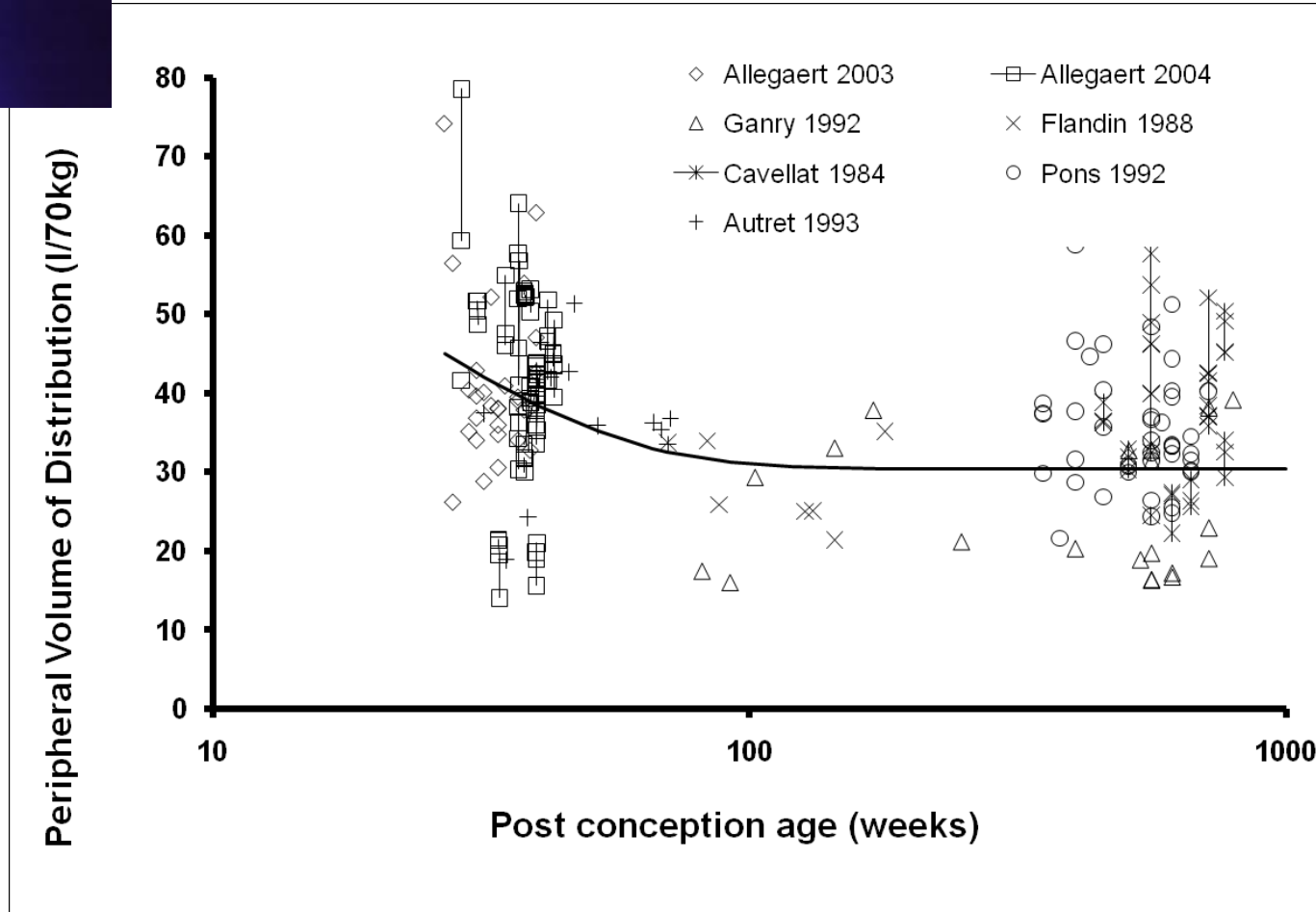


hogere doseringen rectaal ?





body water/paracetamol distribution



body water/paracetamol distribution

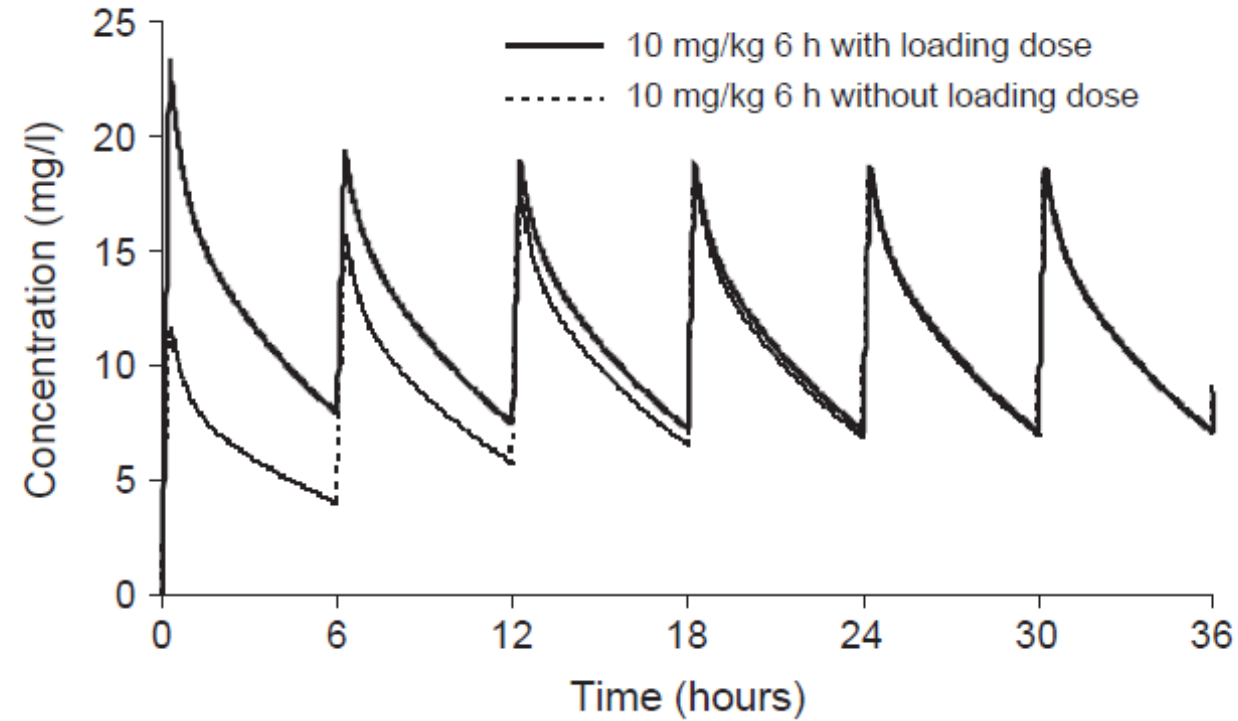


Figure 3 A typical concentration profile for neonates of 28–44 weeks' premenstrual age given a paracetamol loading dose of 20 mg/kg (black continuous line) or not given a loading dose (grey continuous line), followed by a maintenance dose of 10 mg/kg every 6 h. A mean concentration of 11 mg/l is achieved.

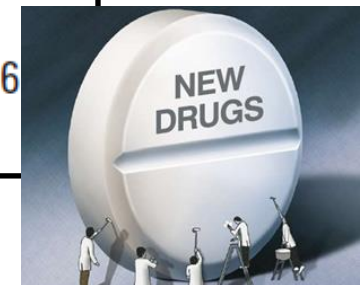
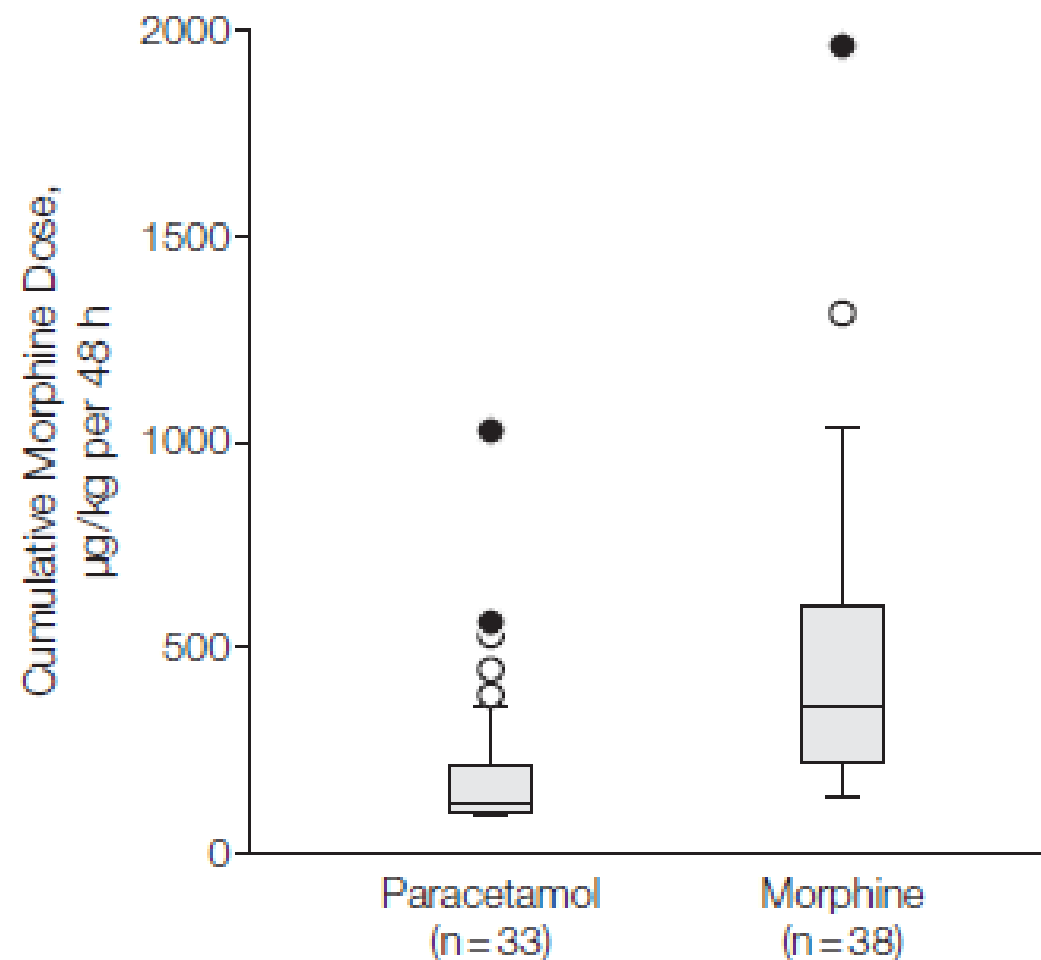
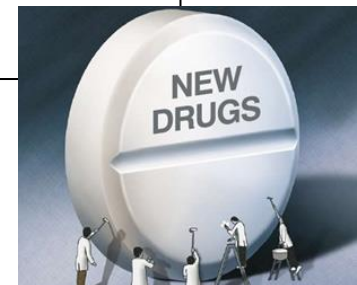
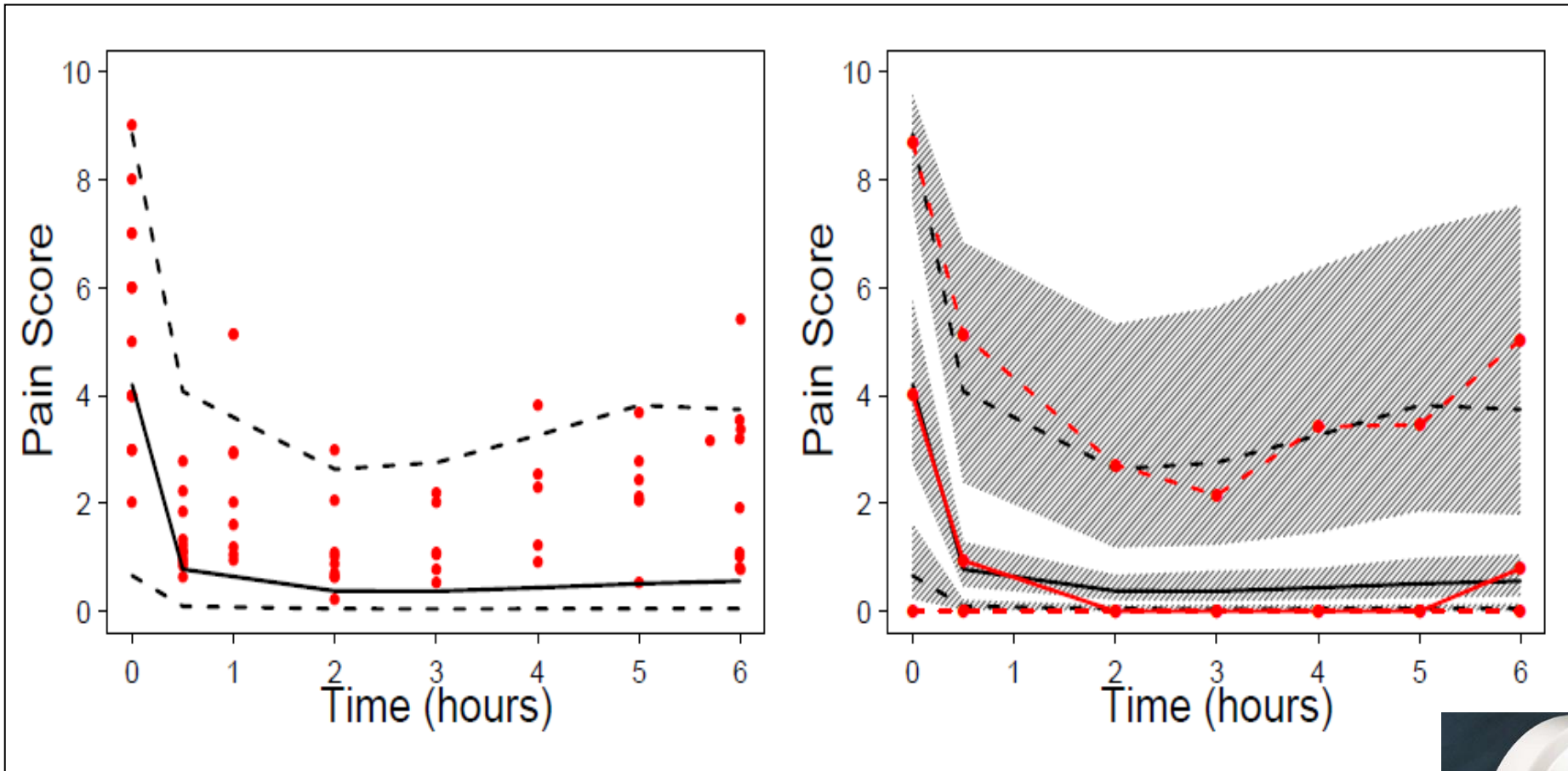


Figure 2. Cumulative Morphine Dose for Morphine and Paracetamol Study Groups Over 48 Postoperative Hours





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)

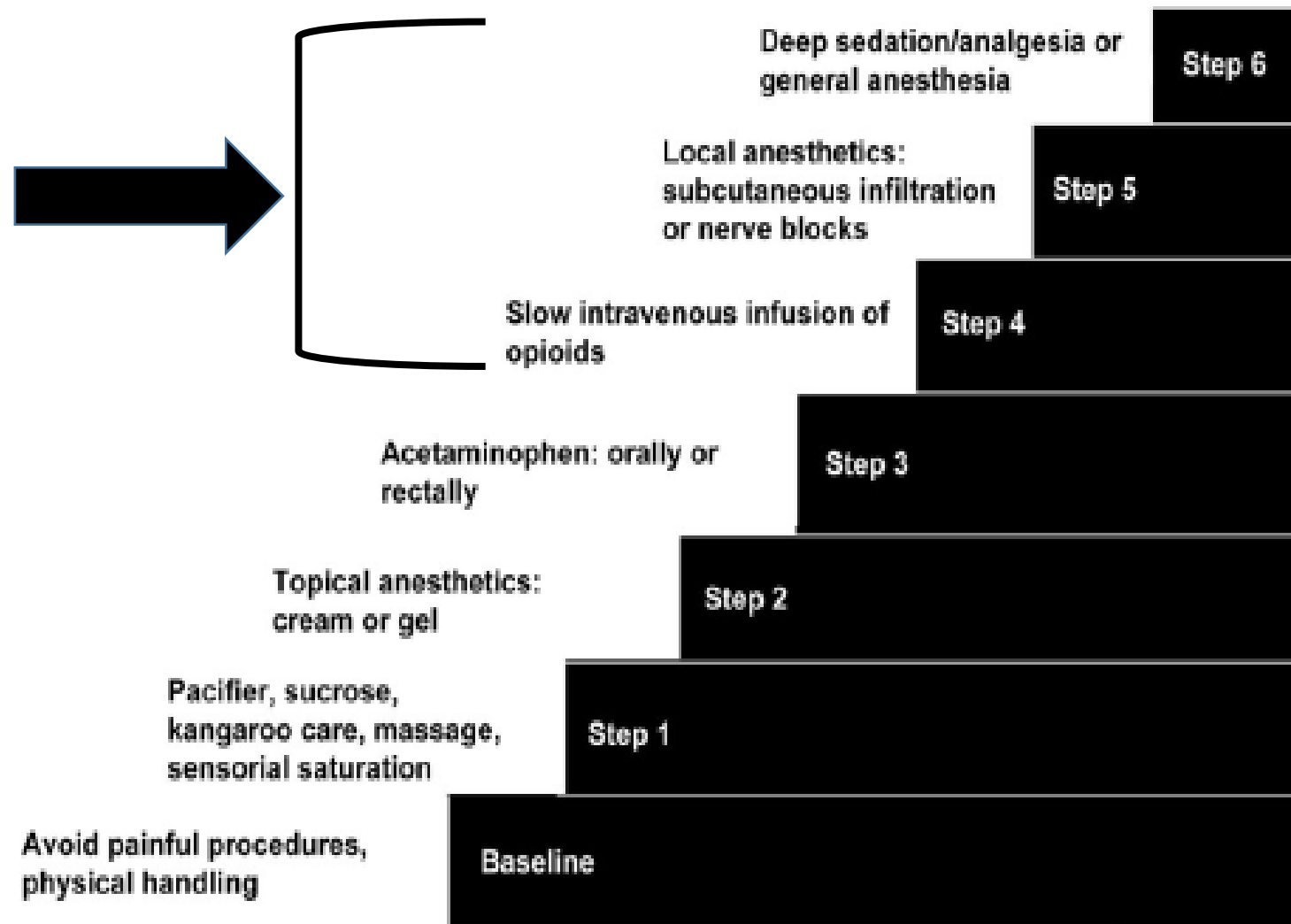
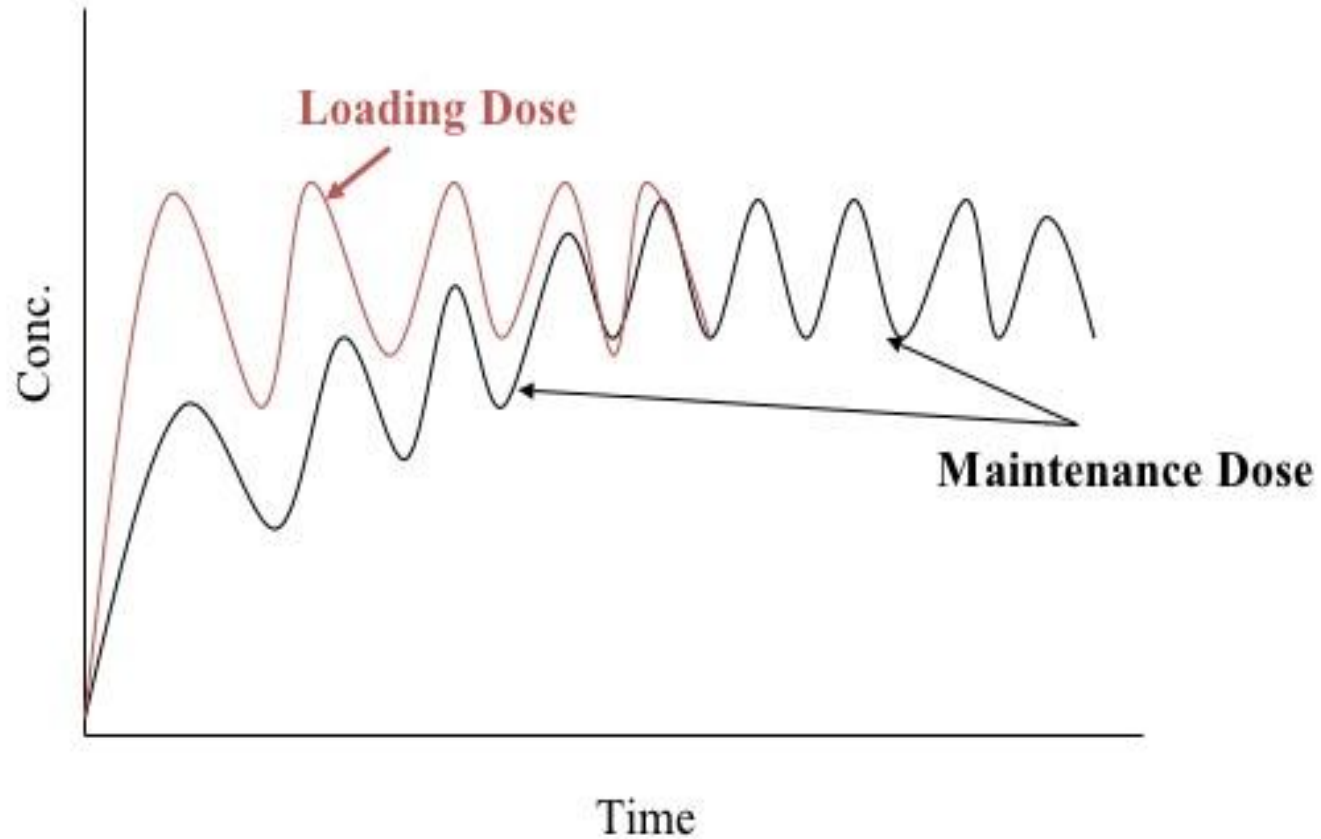


Figure 1. Stepwise approach to neonatal analgesia.

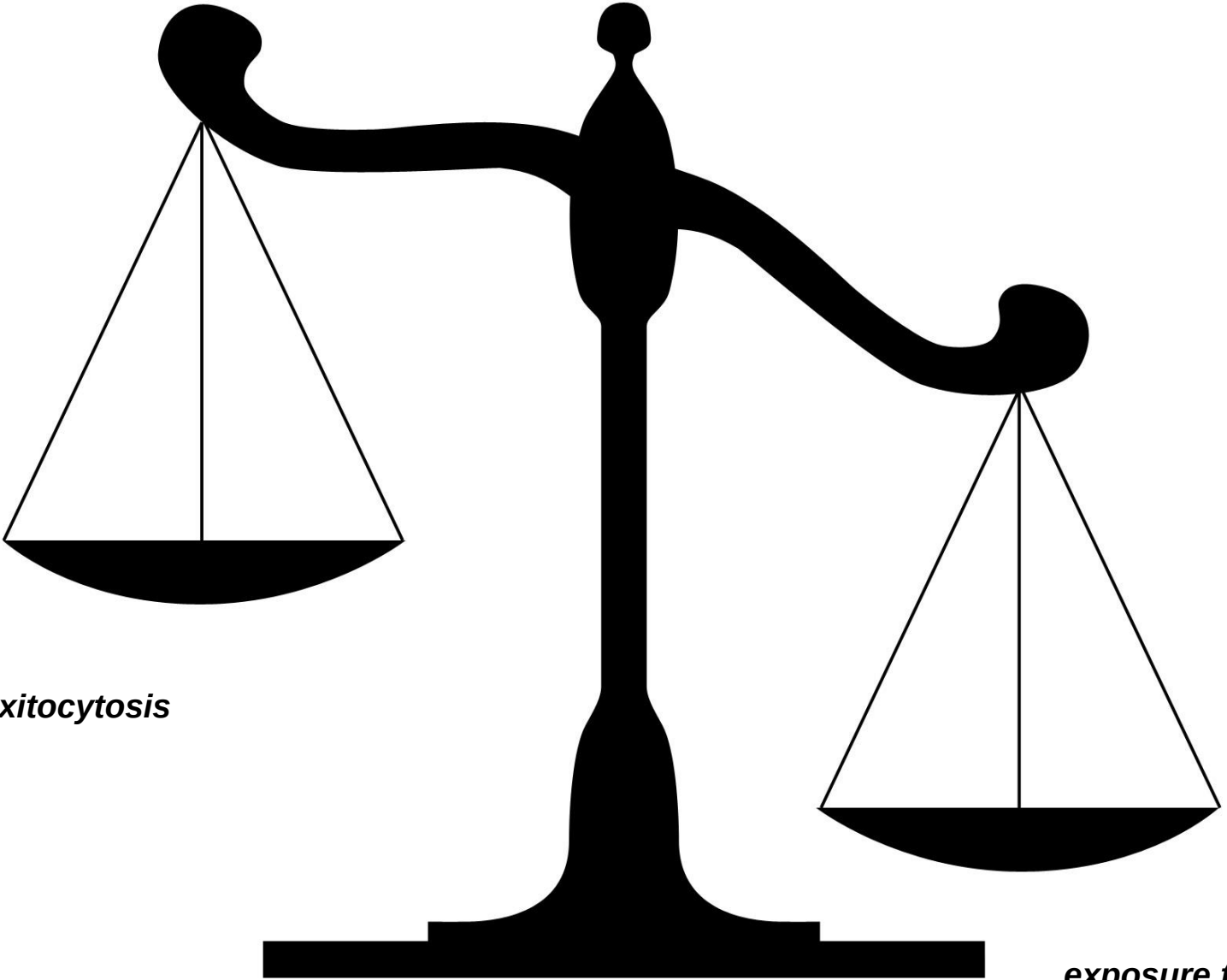
SUGGESTIE 6



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]

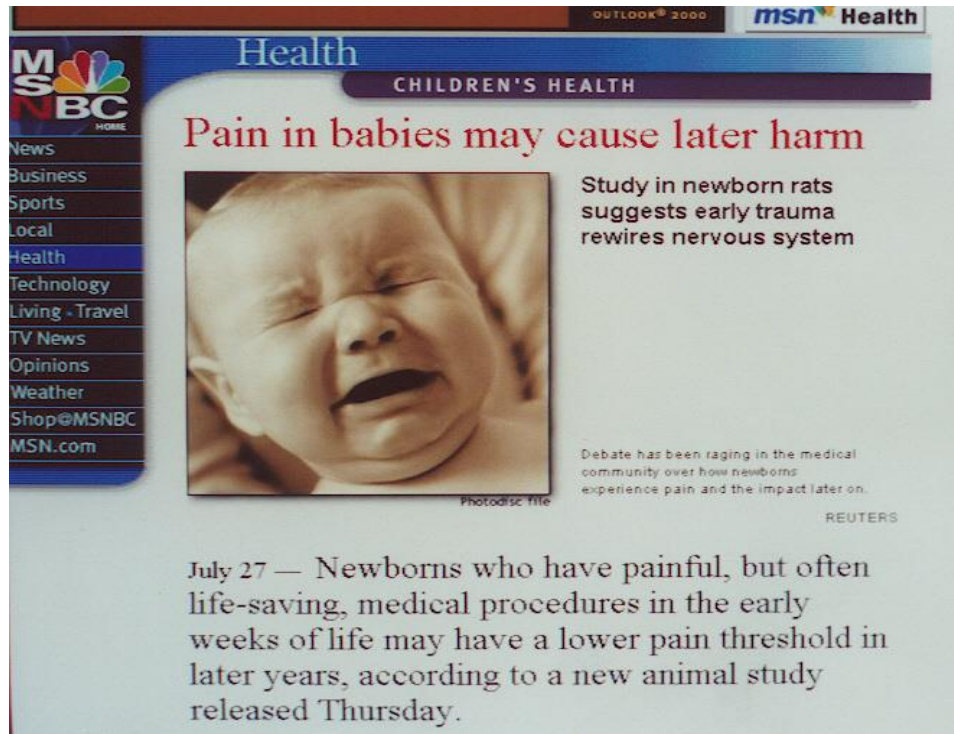
	Route	Loading dose	Maintenance dose
Morphine	iv	50–100µg/kg	10–30µg/kg/h
Fentanyl	iv	1–3 µg/kg	1–5µg/kg/h
Tramadol	iv	2 mg/kg/30 min	6–8 mg/kg/day
Paracetamol	Oral	20 mg/kg	4×10 mg/kg/day
	Rectal	40 mg/kg	4×20 mg/kg/day
	iv	20 mg/kg	4×10 mg/kg/day



pain/exitocytosis

***exposure to analgesics
apoptosis-synaptogenesis***

SUGGESTIE 7



The NEW ENGLAND JOURNAL of MEDICINE

Perspective

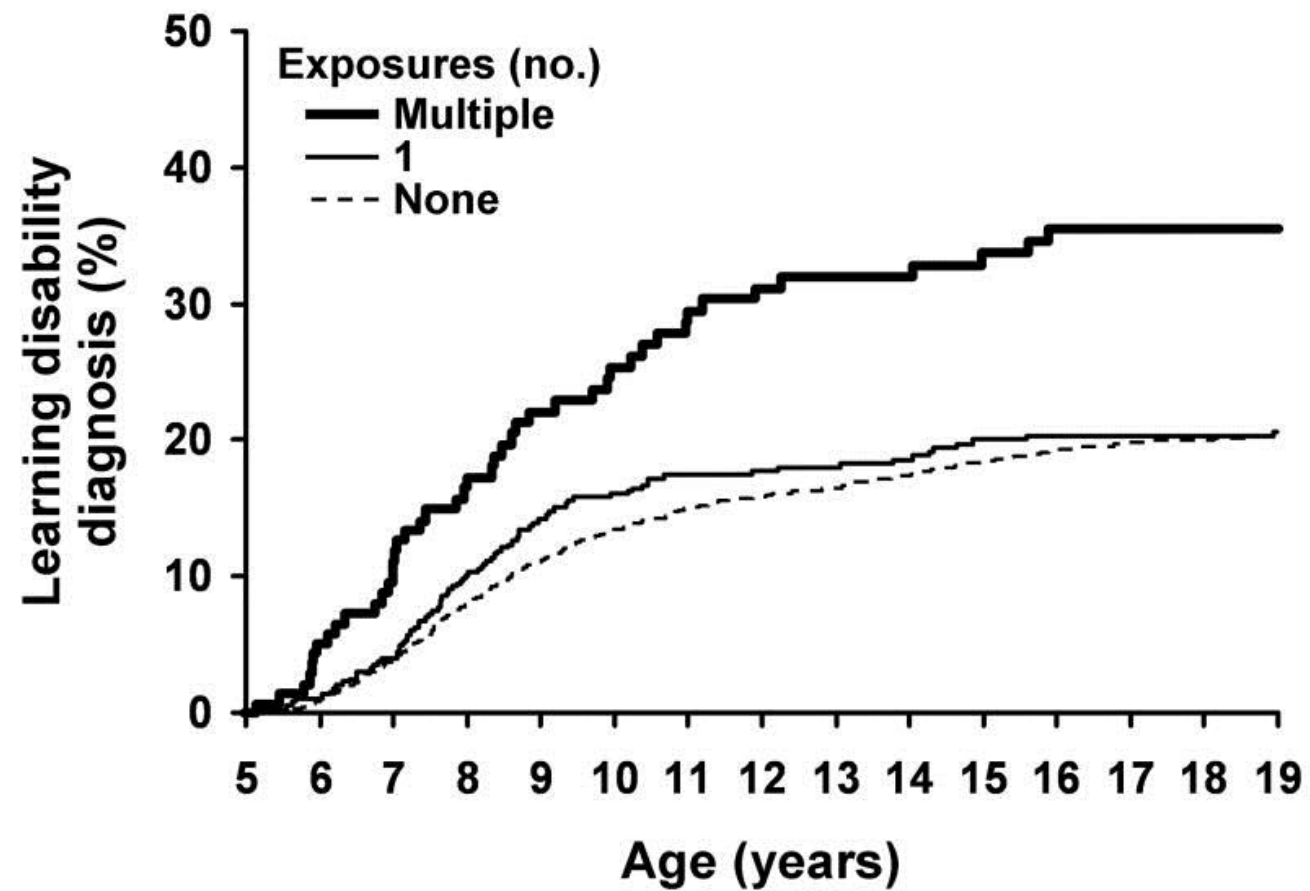
Defining Safe Use of Anesthesia in Children

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

A white rat is seen from the side, clinging to the vertical bars of a wire cage. The rat has large, pinkish ears and its body is pressed against the metal. The background is dark and out of focus, showing more of the cage structure.

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



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, MaryEllen 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.

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

