farmacologische aspecten van procedurale (analgo)sedatie bij pasgeborenen, zuigelingen en kinderen

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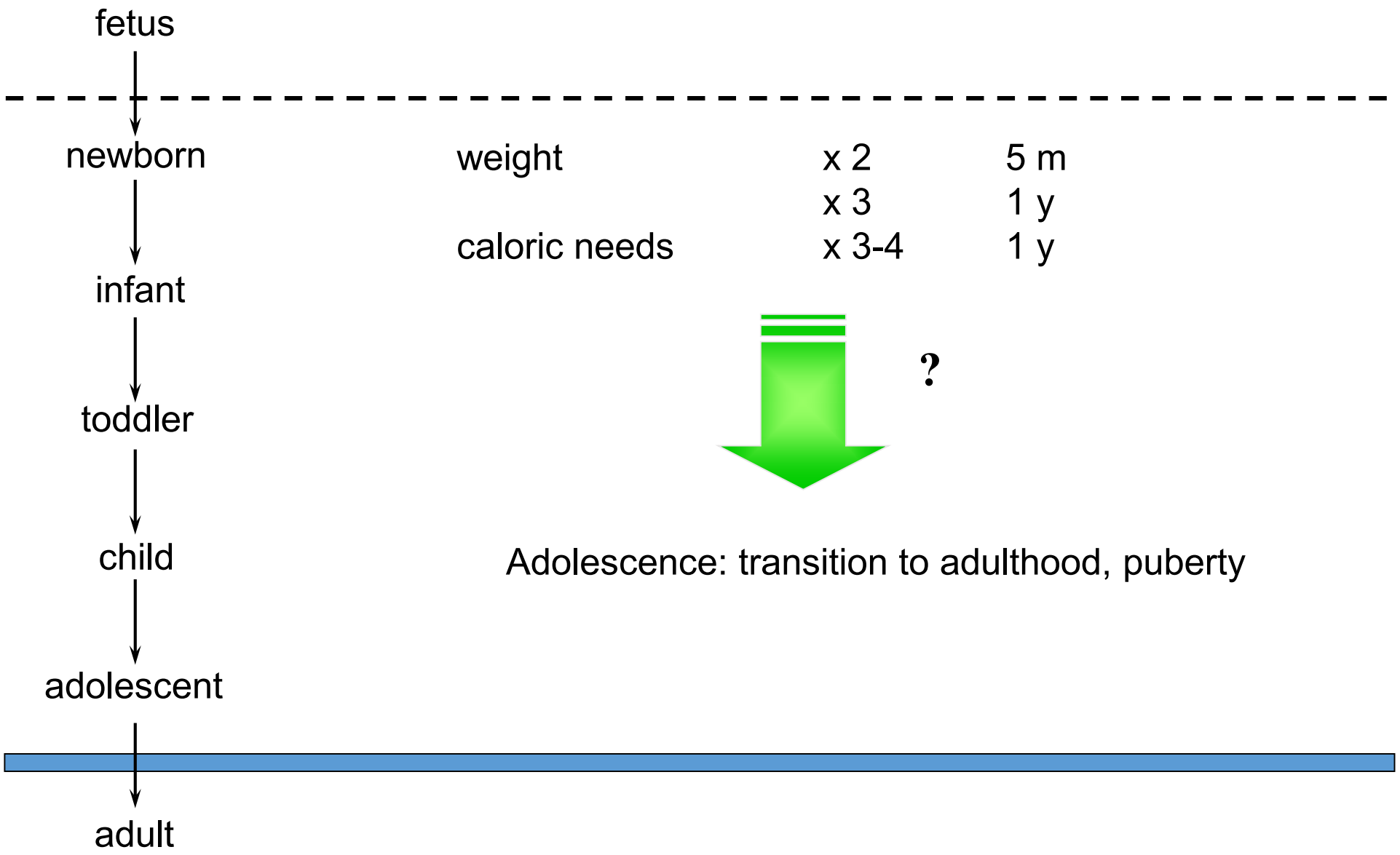
k.allegaert@erasmusmc.nl

developmental (dys)continuum





Pharmacokinetics

Absorption
Distribution
Metabolism
Elimination

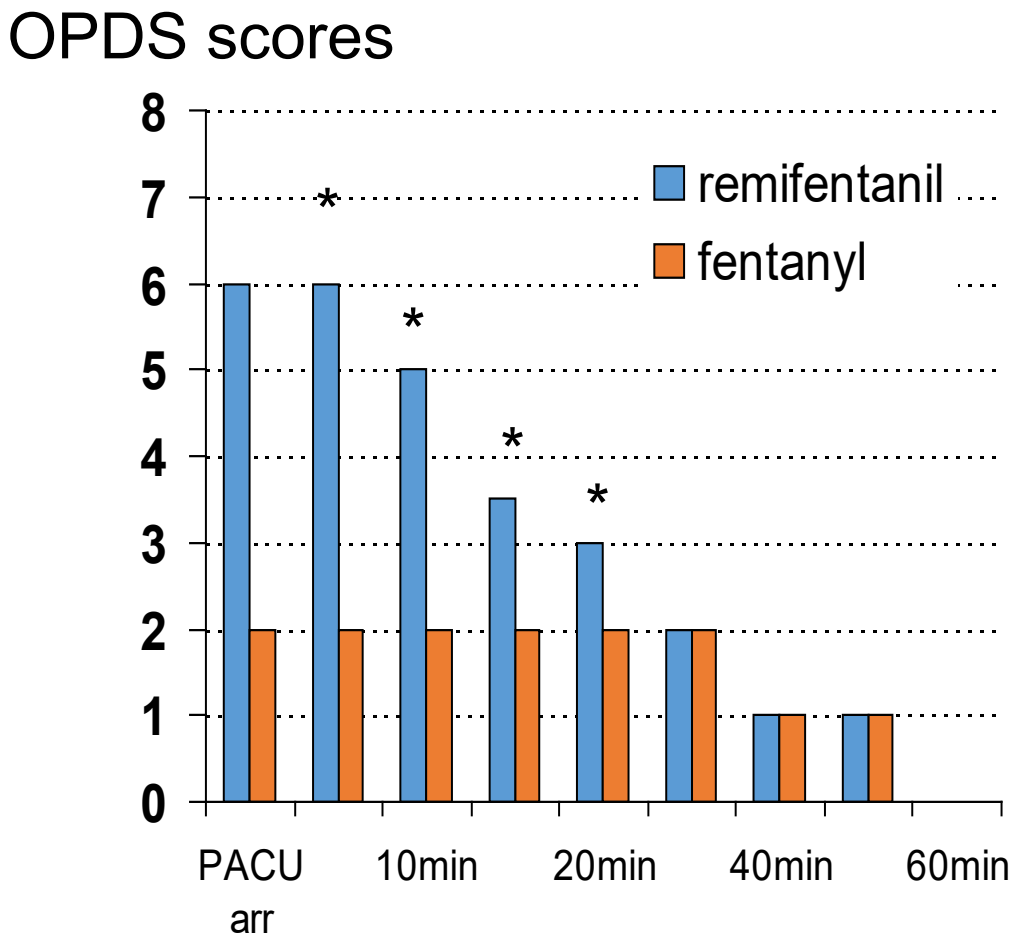
e.g.
transcutaneous absorption
higher body water content
reduced metabolic capacity
reduced elimination capacity

Pharmacodynamics

concentration-effect
maturational differences

e.g.
neurotoxicity of ethanol
hypothyroidism-related cretinism
neurotoxicity of hypoglycaemia
bilirubin toxicity (brain barrier)

remifentanil and postoperative pain



T&A

Evaluation=OPDS

50 µg/kg of morphine during surgery in the remifentanil group

Inadequate postoperative analgesia in the remifentanil group

Davis et al. Anesth Analg 2000

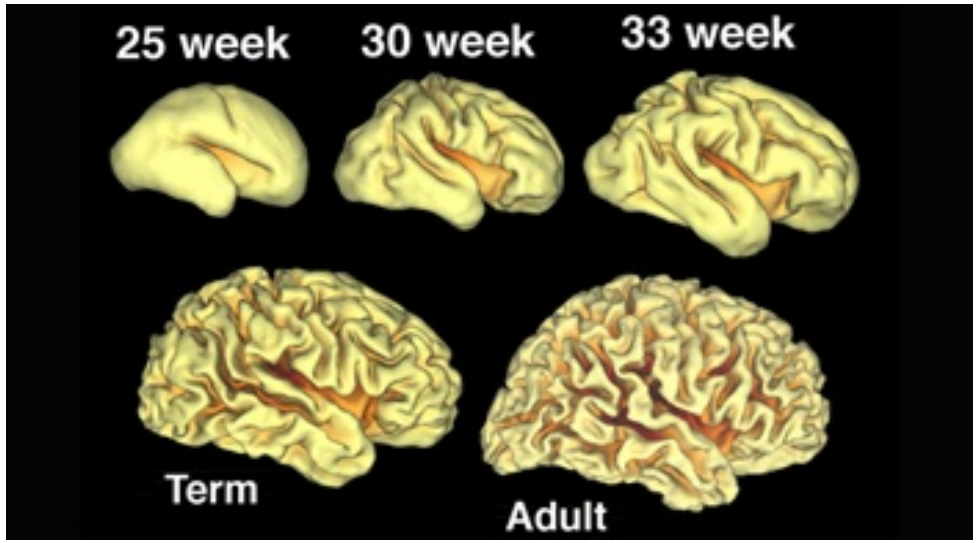
TAILORED

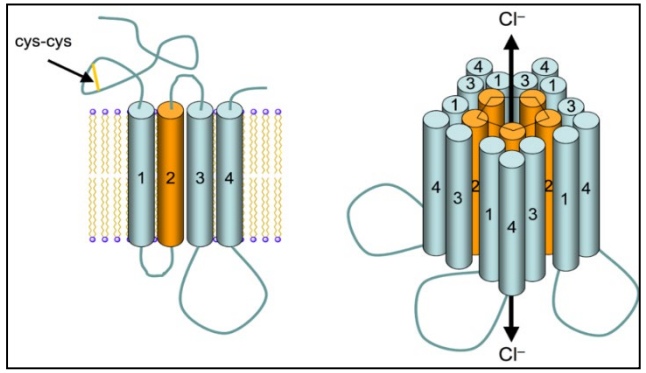


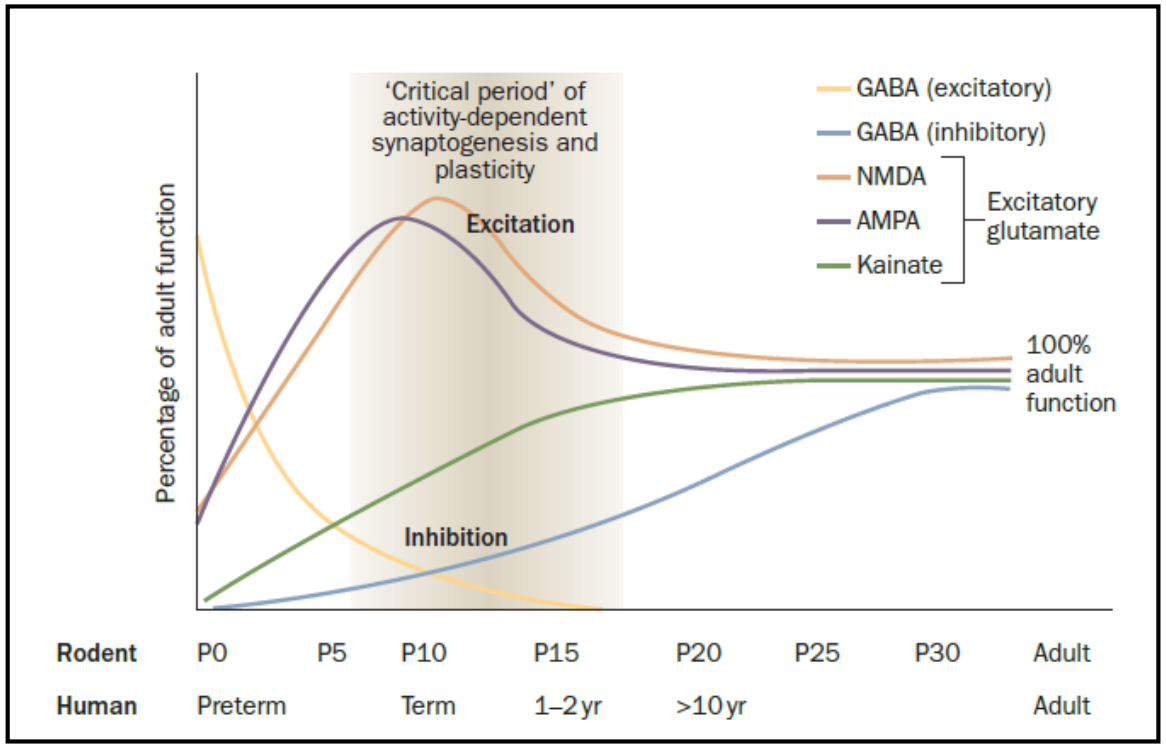
DRIVEN

Epileptogenesis in the immature brain: emerging mechanisms

Sanjay N. Rakhade and Frances E. Jensen







Rakhade et al, Nat Rev Neurol 2009

conflict of interest… clinical pharmacology

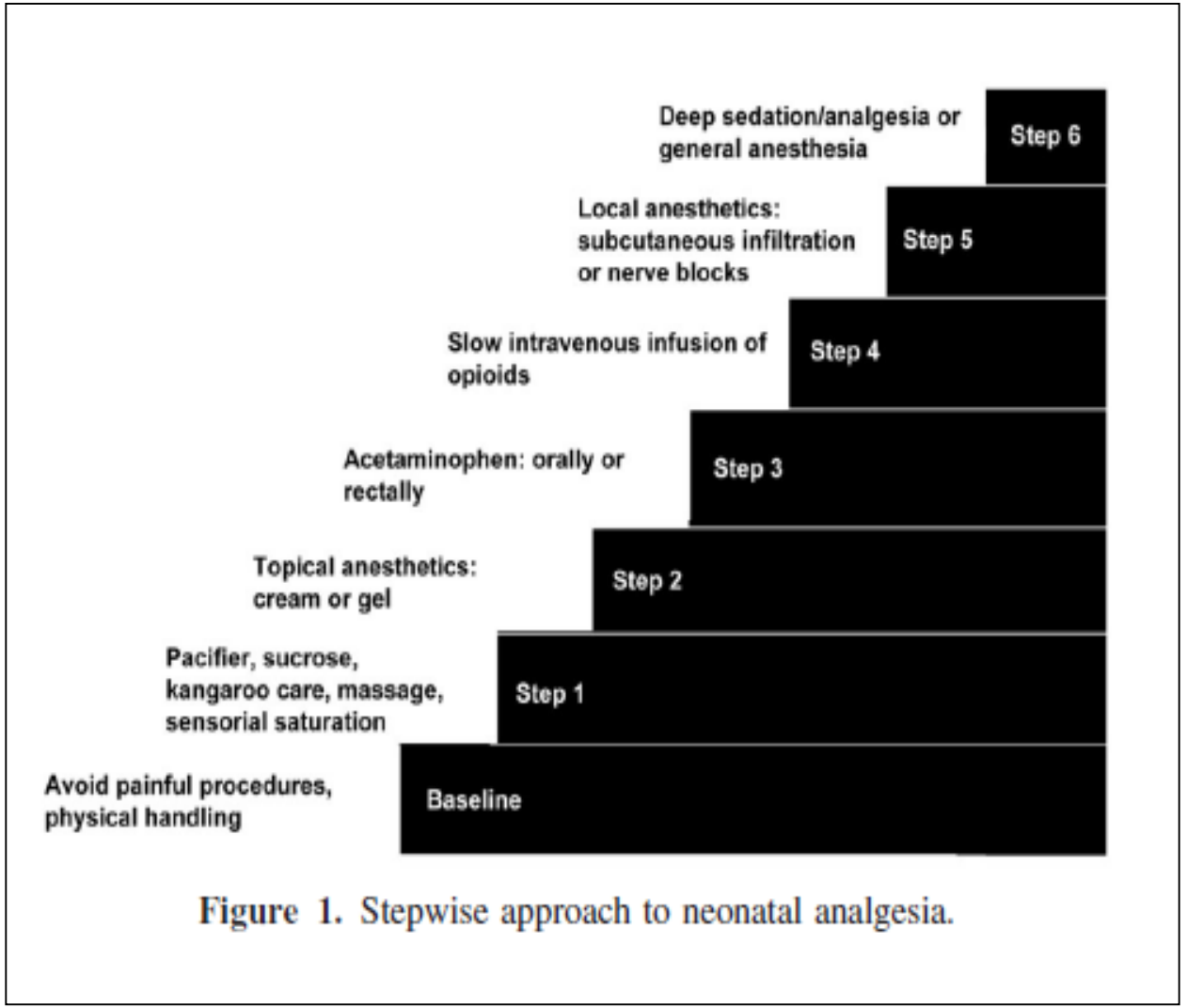
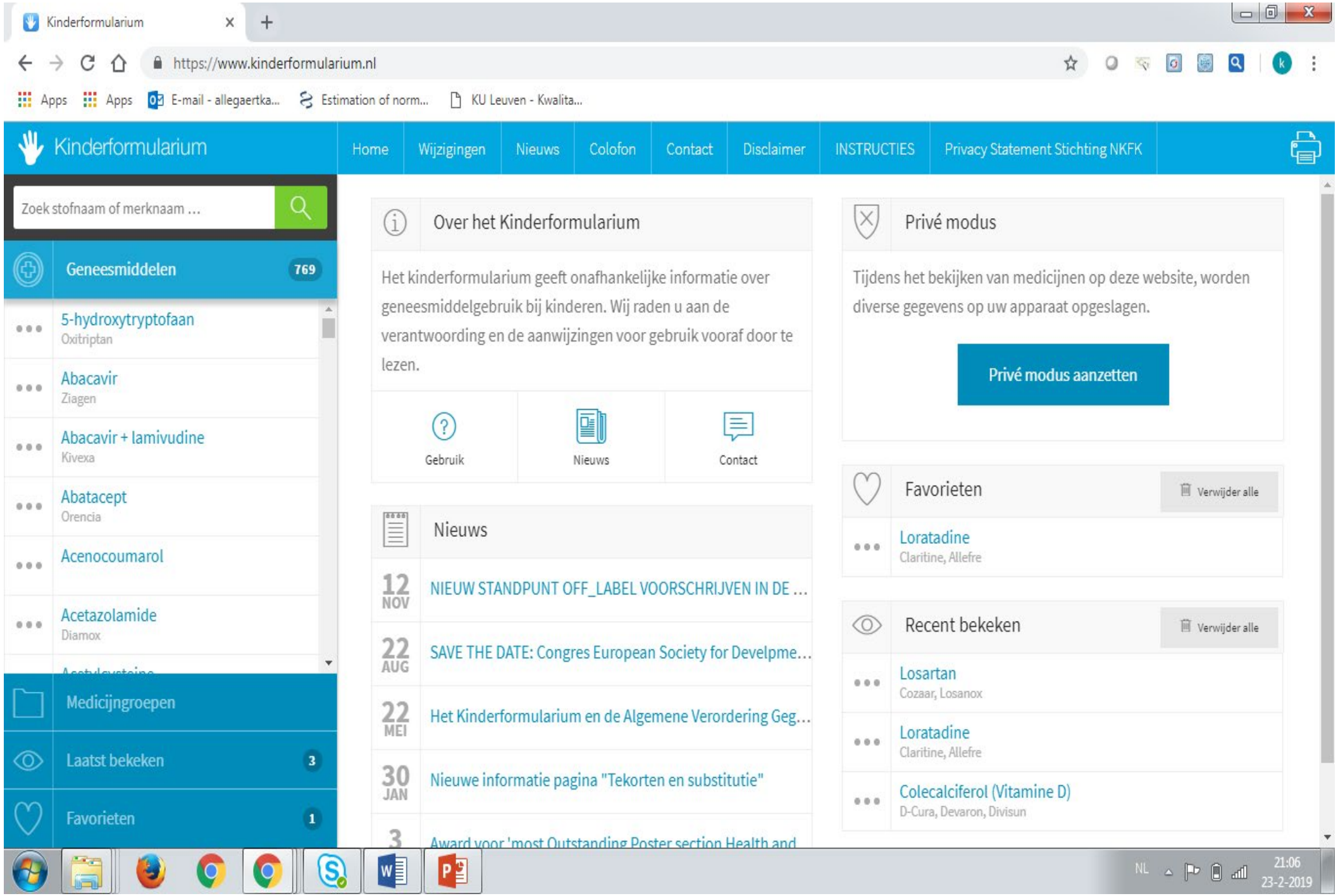


Figure 1. Stepwise approach to neonatal analgesia.


Kinderformularium
https://www.kinderformularium.nl
Apps
Apps
E-mail - allegaertka...
Estimation of norm...
KU Leuven - Kwalita...
Kinderformularium
Home
Wijzigingen
Nieuws
Colofon
Contact
Disclaimer
INSTRUCTIES
Privacy Statement Stichting NKFK
Zoek stofnaam of merknaam ...
Geneesmiddelen 769
5-hydroxytryptofaan
Oxitriptan
Abacavir
Ziagen
Abacavir + lamivudine
Kivexa
Abatacept
Orencia
Acenocoumarol
Acetazolamide
Diamox
Medicijngroepen
Laatst bekeken 3
Favorieten 1
Over het Kinderformularium
Het kinderformularium geeft onafhankelijke informatie over geneesmiddelgebruik bij kinderen. Wij raden u aan de verantwoording en de aanwijzingen voor gebruik vooraf door te lezen.
Gebruik
Nieuws
Contact
Nieuws
12 NOV
NIEUW STANDPUNT OFF_LABEL VOORSCHRIJVEN IN DE ...
22 AUG
SAVE THE DATE: Congres European Society for Develpme...
22 MEI
Het Kinderformularium en de Algemene Verordering Geg...
30 JAN
Nieuwe informatie pagina "Tekorten en substitutie"
3
Award voor 'most Outstanding Poster section Health and
Privé modus
Tijdens het bekijken van medicijnen op deze website, worden diverse gegevens op uw apparaat opgeslagen.
Privé modus aanzetten
Favorieten
Verwijder alle
Loratadine
Claritine, Allefre
Recent bekeken
Verwijder alle
Losartan
Cozaar, Losanox
Loratadine
Claritine, Allefre
Colecalciferol (Vitamine D)
D-Cura, Devaron, Divisun
NL
21:06
23-2-2019

absorptie gerelateerde concepten

- onverwachte/ongewenste/onvoorspelbare absorptie
- nasale route: opioiden, benzodiazepines, ketamine, dexmedetomidine
- Inhalatie: lachgas, equimolair

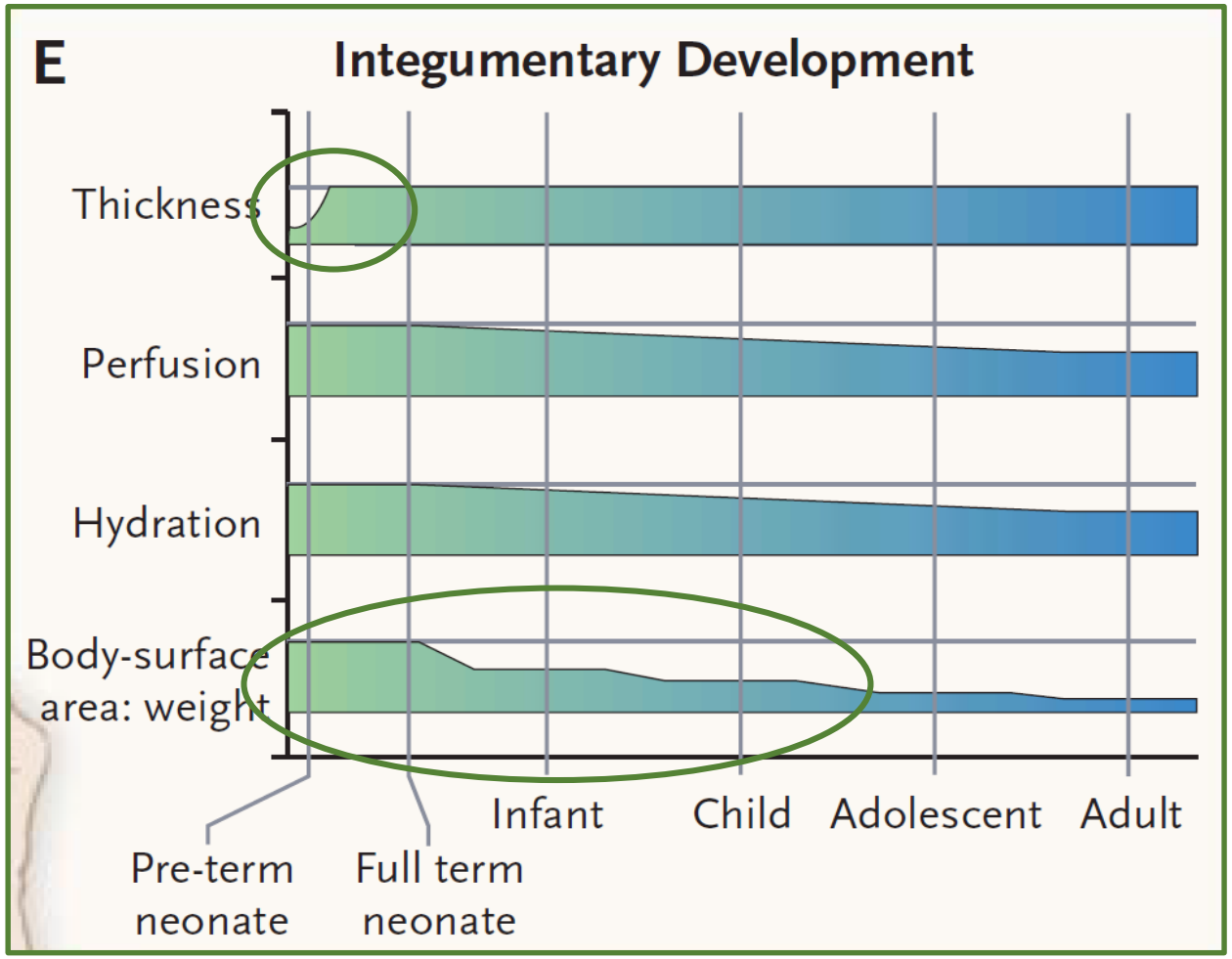
het is niet al goud dat blinkt

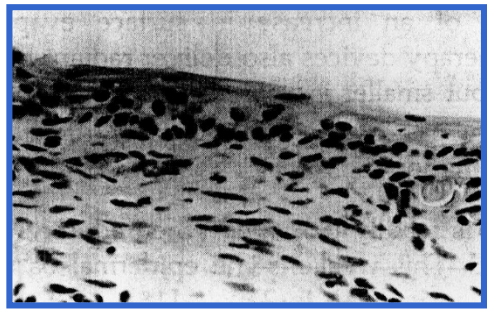
nieuwere geneesmiddelen aan de horizon ?

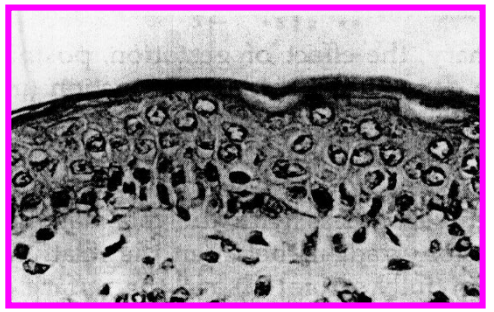
- dexmedetomide
- remi-midazolam

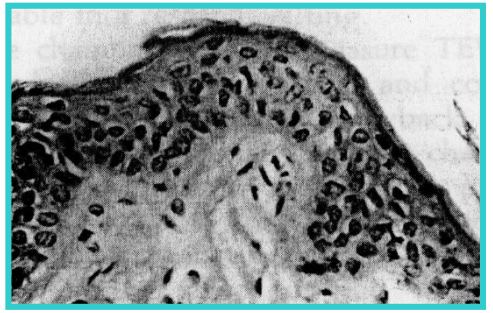
raket lancering: what goes up, must come down ?

absorption, skin: BSA > permeability









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

Kearns et al, NEJM 2003

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.

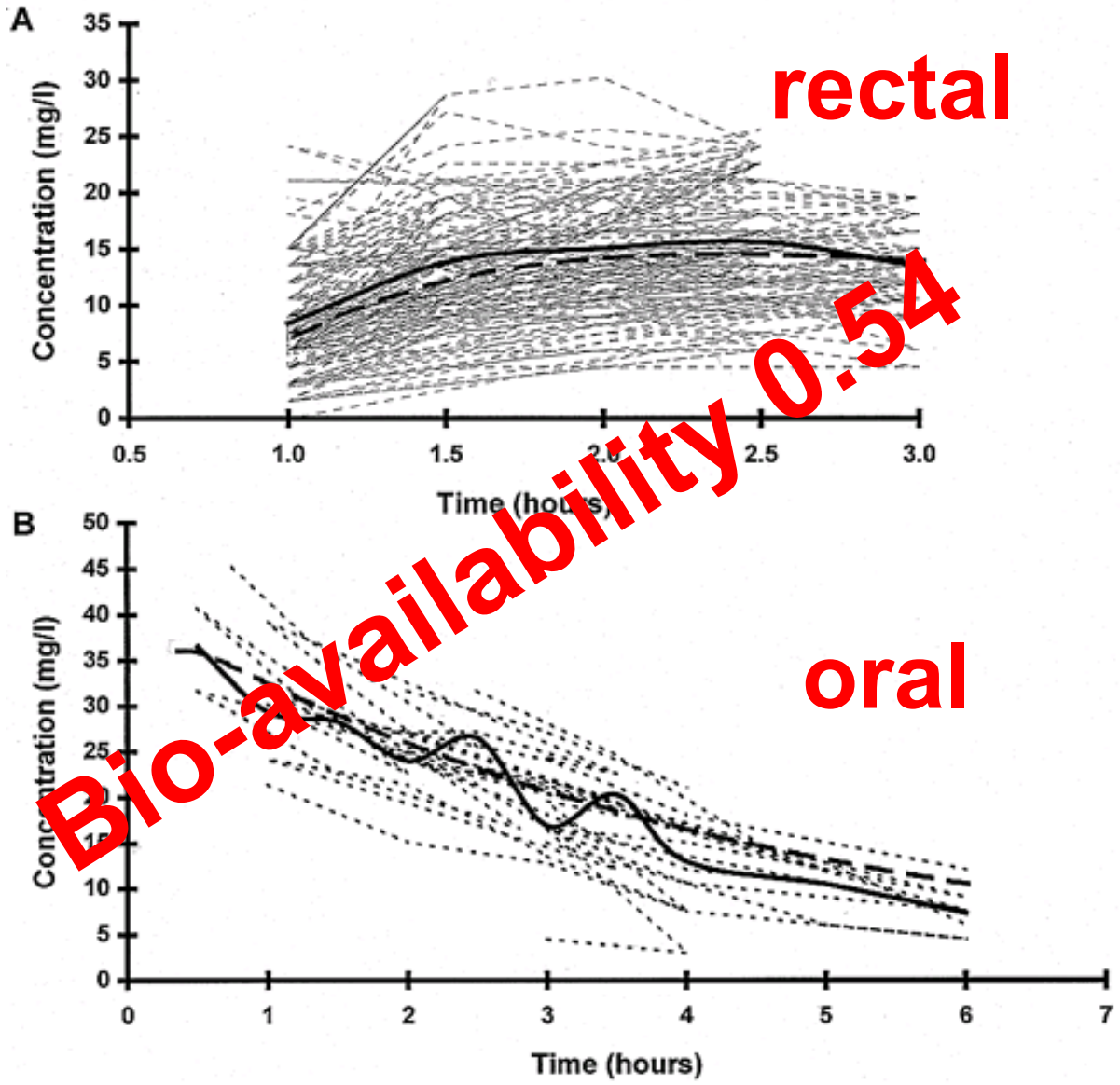




Preterm neonates are exposed to a range of painful procedures and topical anesthetics as EMLA are used routinely for pain management. Because premature neonates are low weight and consequently they are easily overdosed, routinely use of EMLA should be carefully evaluated.



developmental pharmacology, absorption



Anderson et al, Anesthesiology 1999

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)

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]

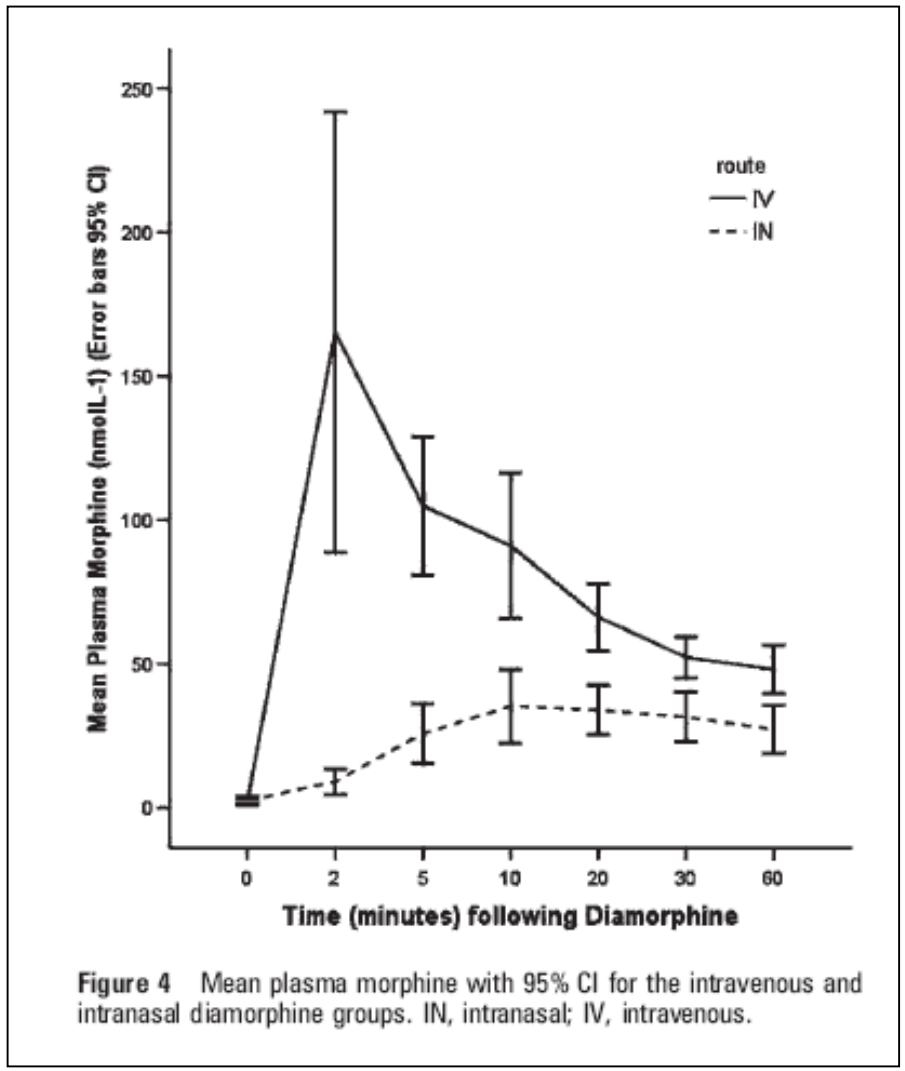


Figure 4 Mean plasma morphine with 95% CI for the intravenous and intranasal diamorphine groups. IN, intranasal; IV, intravenous.



Wat is het?

- Equimolair mengsel = 50%N2O – 50%O2
- MEOPA: Melange Equimolaire d’Oxigène et Protoxyde d’Azote
- Kalinox® - Entonox® - Medimixe® – Antasole® - Oxinox®



Werkingsmechanisme N_2O 50 %

equimolair mengsel 50% N_20 en 50% O_2
reukloos, kleurloos

Farmacologisch:

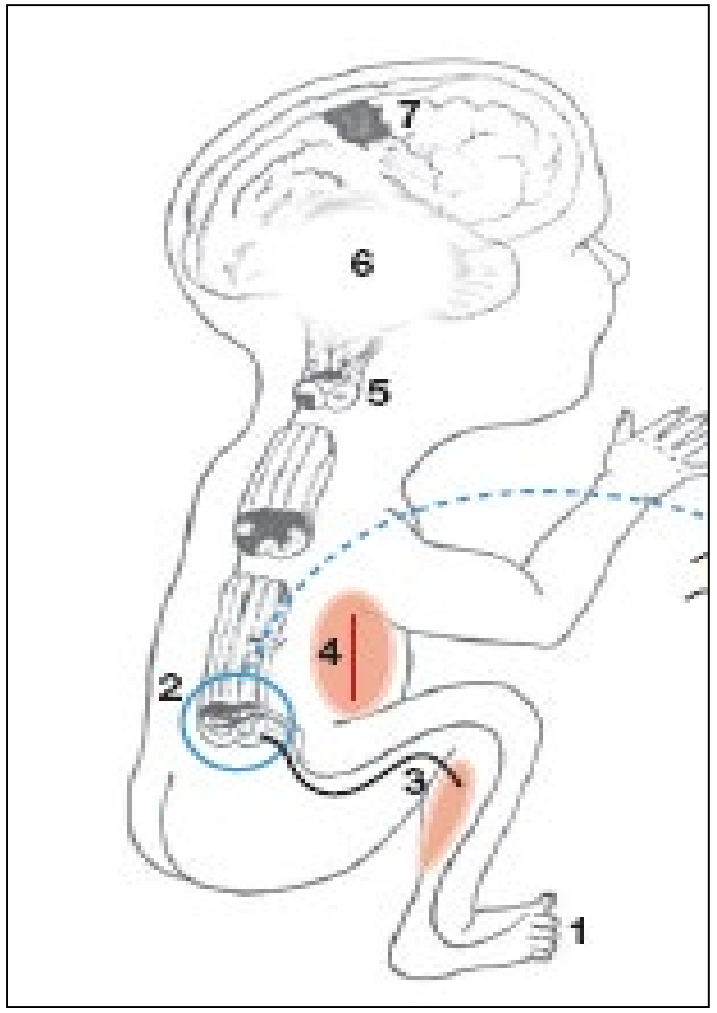
- snelle diffusie (kleine molecule)
- zwakke oplosbaarheid in bloed
  - snelle toename vrije conc
- geen metabolisatie
- klaring door diffusie
  - snelle eliminatie
- beste effect
  - opstarten bij rustige patient
  - in combinatie niet andere middelen
    - EMLA, distractie
  - eerst 3 minuten toedienen
  - rust, lawaai, …

Werkingsmechanisme N_2O 50 %

‘dissociatief anestheticum’

analgesie
sedatie
anxiolyse
variabele amnesie
bewaarde lw-reflexen
euforiserend

μ-receptor interactie (naloxone)
stimulatie descenderende banen
GABA-receptor, alpha-1/alpha-2,
Dopamine, NMDA-receptoren



Equimolar Nitrous Oxide/Oxygen Versus Placebo for Procedural Pain in Children: A Randomized Trial

WHAT'S KNOWN ON THIS SUBJECT: The most frequent cause of pain in children is diagnostic or therapeutic procedure–related pain. Inhalation of nitrous oxide in oxygen is a well-known effective analgesia, without major adverse effects and widely used in pediatric settings for minimally invasive procedures.

WHAT THIS STUDY ADDS: We determined through a randomized, placebo-controlled, double-blind clinical assay that nitrous oxide inhalation was notably more effective than placebo in decreasing pain by nearly half for minor pediatric procedures in patients aged 3 to 18 years.

Fixed 50% Nitrous Oxide Oxygen Mixture for Painful Procedures: A French Survey

Daniel Annequin, MD*; Ricardo Carbajal, MD‖; Pierre Chauvin, MD, PhD‡; Olivier Gall, MD§; Barbara Tourniaire, MD¶; and Isabelle Murat, MD, PhD§

TABLE 3. Procedural Pain Assessed by Nurses in Children Receiving 50:50 Nitrous Oxide Oxygen Mixture

	Number of Patients (n = 975)	Pain Assessment (0–10 Numerical Scale)	
		Median	Interquartile
Lumbar puncture	269	0	0–2
Bone marrow aspiration	222	2	0–4
Laceration repair	206	2	0–4
Minor procedures*	74	2	0–5
Minor surgery†	52	1.5	0–3.5
Punctures‡	46	1	0–3
Fracture	42	2	0–3
Dental care	43	0	0–2
Pulmonary endoscopy	21	2	1–4

*Surgical dressing, burn dressing, gauze removal of open wounds, venous canulation, clip removal, cast remodelling, pin removal or section, bladder catheterization, and nasal packing.
† Nail surgery, foreign body exploration and extraction, laceration exploration, and abscess drainage.
‡ Lymph nodes, renal biopsy, and hematoma.

TABLE 4. Pain Self-Assessment During Procedures in 647 Children Age Six Years or Older Receiving 50:50 Nitrous Oxide Oxygen Mixture

	Number of Patients (n = 647)	Pain Self-Assessment (0–100 VAS)	
		Median	Interquartile
Lumbar puncture	194	5	0–20
Bone marrow aspiration	158	12.5	0–40
Laceration repair	126	12	0–40
Minor procedures*	41	18	0–32
Minor surgery†	36	10	0–35
Punctures‡	25	0	0–18
Fracture	30	15	0–30
Dental care	33	20	0–40
Pulmonary endoscopy	4	15	0–30

*Surgical dressing, burn dressing, gauze removal of open wounds, venous canulation, clip removal, cast remodelling, pin removal or section, bladder catheterization, and nasal packing.
† Nail surgery, foreign body exploration and extraction, laceration exploration, and abscess drainage.
‡ Lymph nodes, renal biopsy, and hematoma.

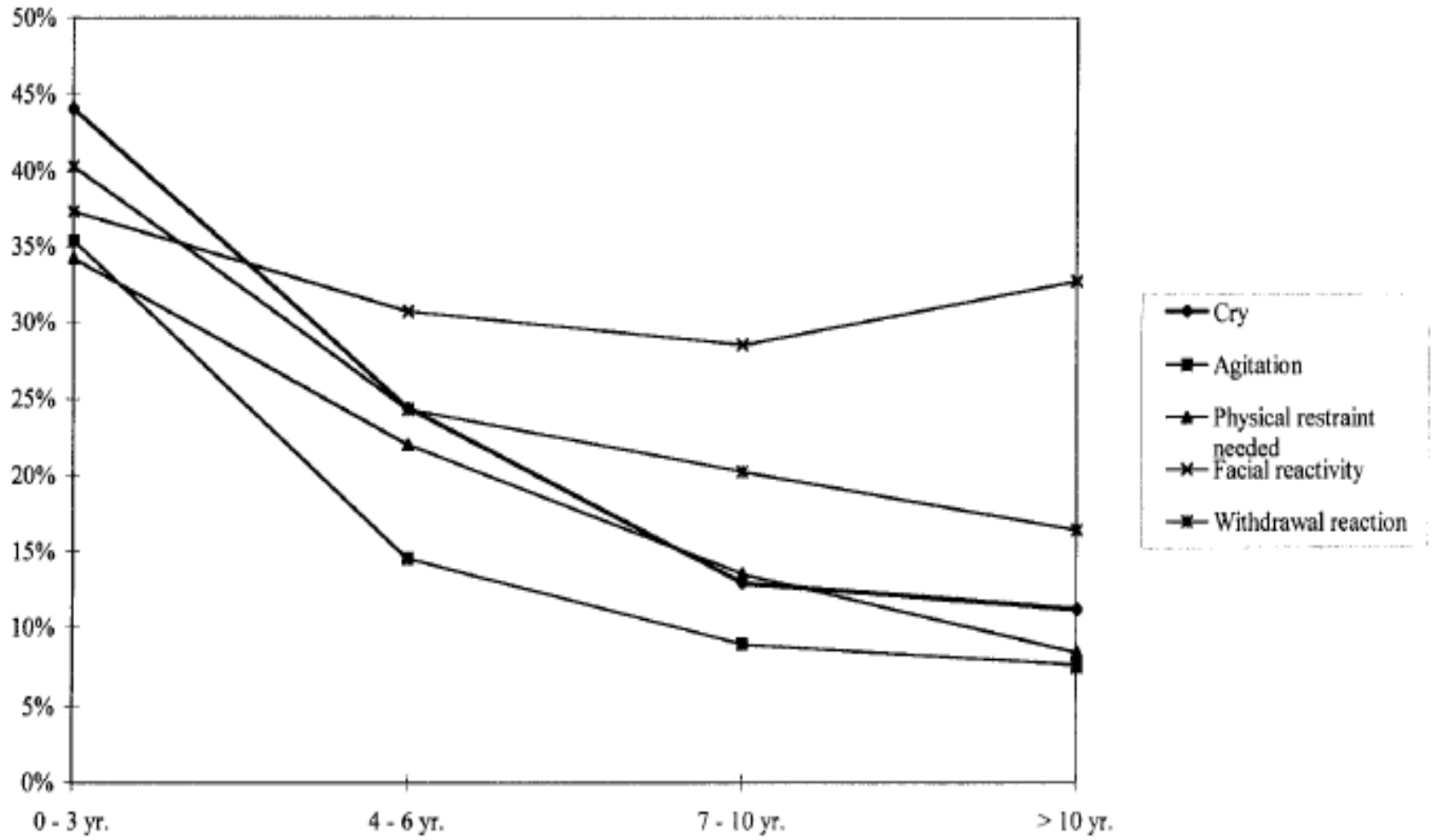


Fig 2. Child behaviors by age during EMONO analgesia for painful procedures.

Absolute contraindications for administration of nitrous oxide

Patients with:

- Intracranial hypertension
- Unconsciousness
- Pneumothorax
- Other disorders involving accumulation of gas in closed body space (eg, intestinal ileus, sinusitis)

Contraindications for administration by non-doctors

- Children younger than 4 years
- Children on psychotropic drugs
- Children with an underlying condition that might impair respiratory or brain function

absorptie gerelateerde concepten

- onverwachte/ongewenste/onvoorspelbare absorptie
- nasale route: opioiden, benzodiazepines, ketamine, dexmedetomidine
- Inhalatie: lachgas, equimolair

het is niet al goud dat blinkt

nieuwere geneesmiddelen aan de horizon ?

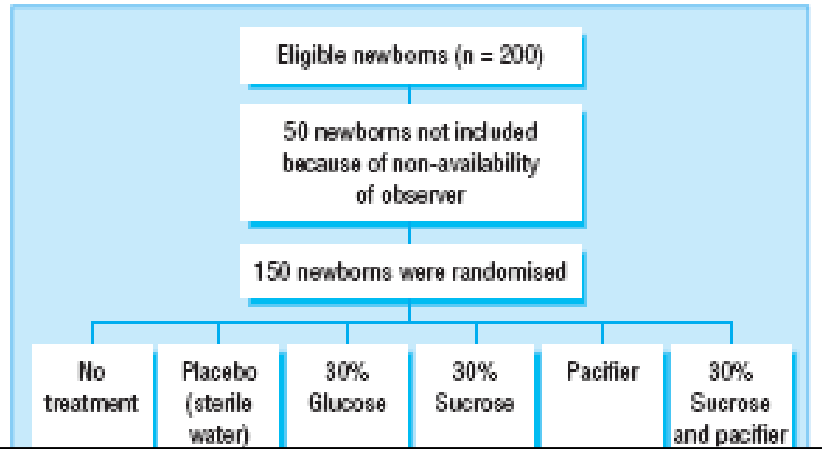
- dexmedetomide
- remi-midazolam

raket lancering: what goes up, must come down ?

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



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

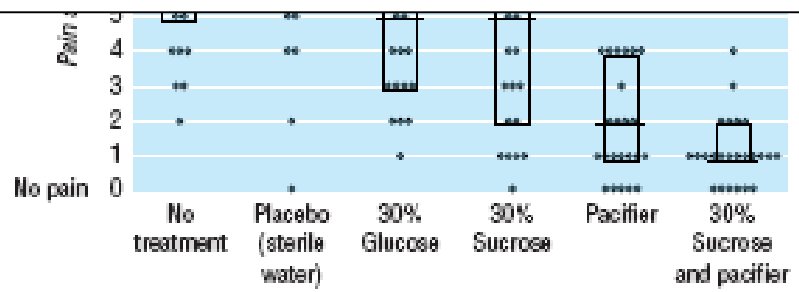
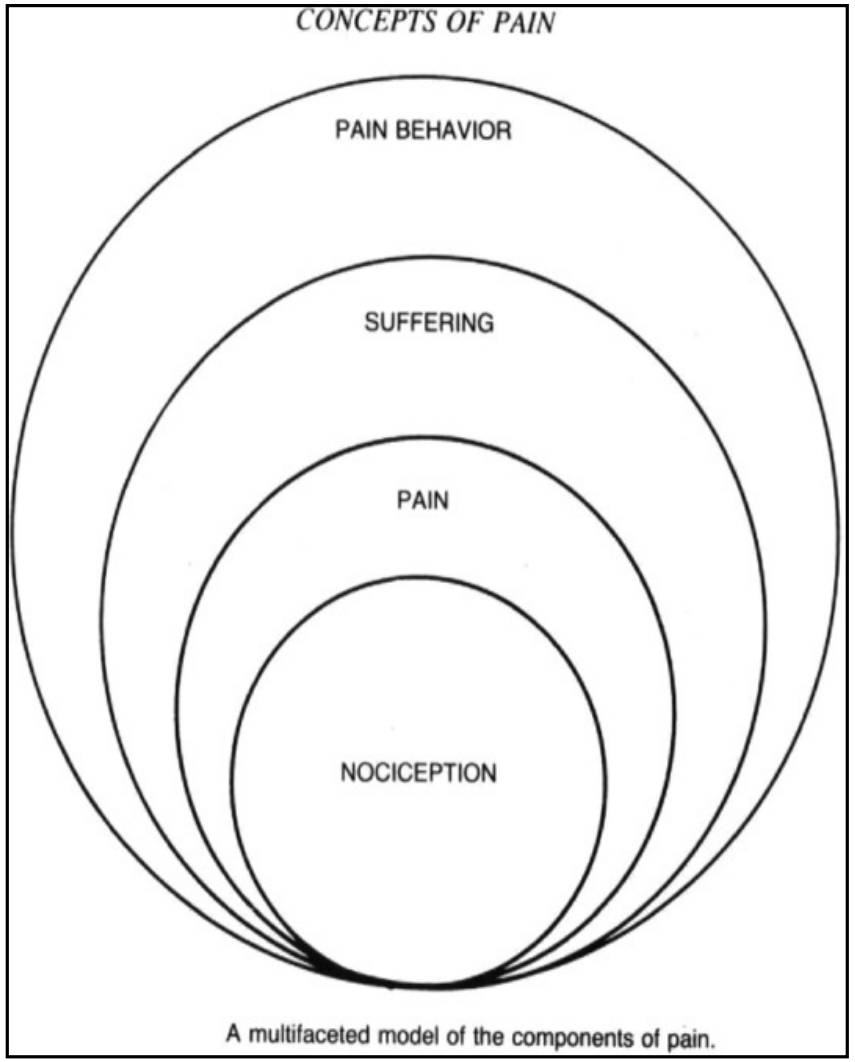


Fig 2 Pain evaluation with DAN scale (0 to 10) during venepuncture in 150 newborns randomised to six equal sized groups, with values for individual infants, median values, and interquartile ranges (for 30% sucrose and pacifier lower quartile coincides with median value)



A multifaceted model of the components of pain.

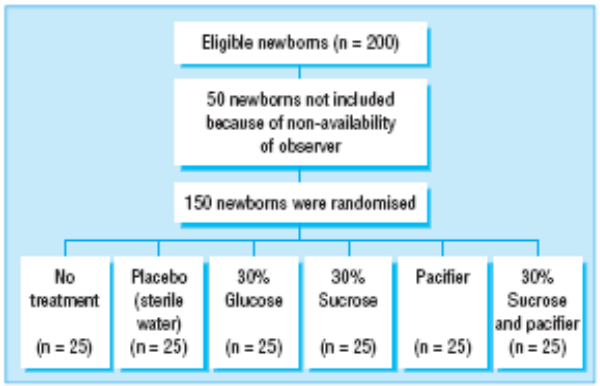


Fig 1 Trial profile and participant flow; all randomised newborns completed trial

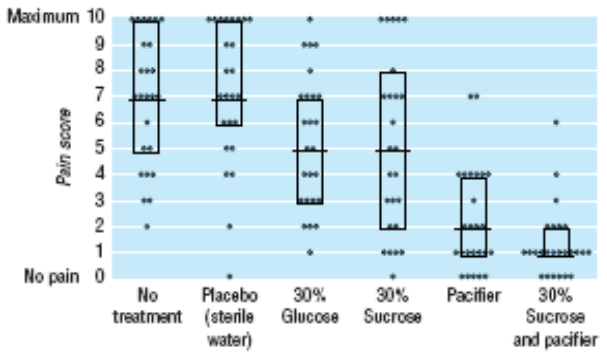


Fig 2 Pain evaluation with DAN scale (0 to 10) during venepuncture in 150 newborns randomised to six equal sized groups, with values for individual infants, median values, and interquartile ranges (for 30% sucrose and pacifier lower quartile coincides with median value)

Carbajal *et al*. BMJ 1999

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†*

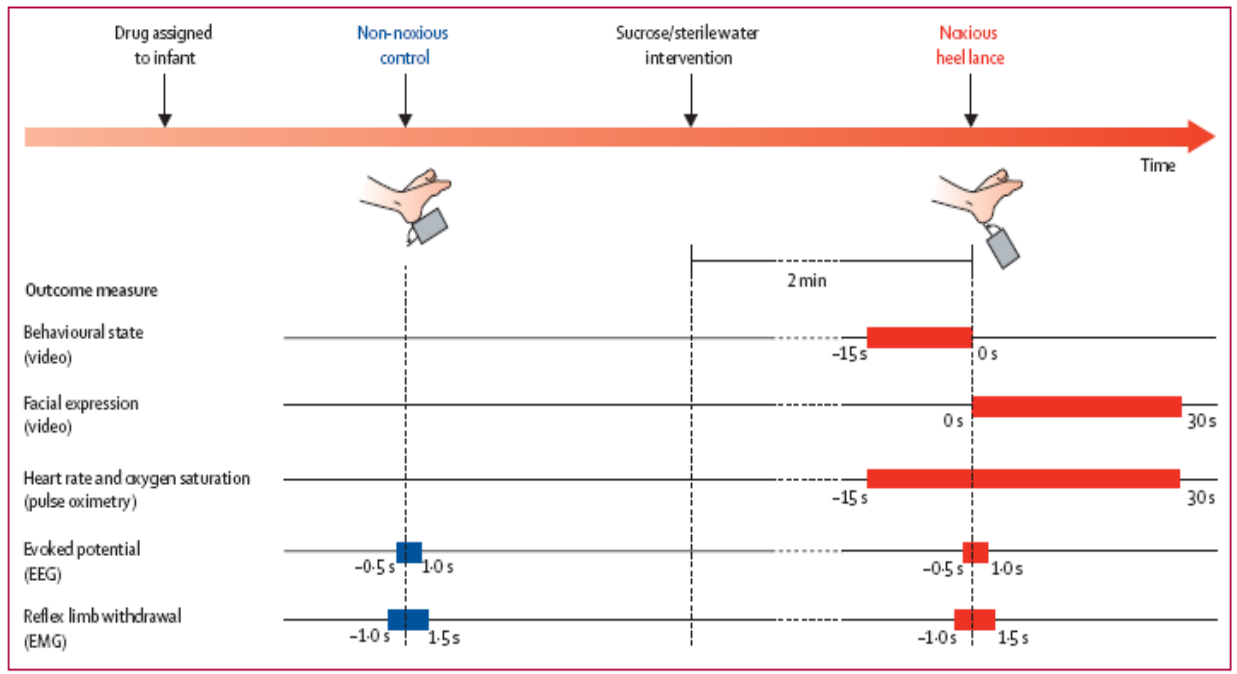


Figure 1: Experimental time line
EEG=electroencephalography. EMG=electromyography.

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

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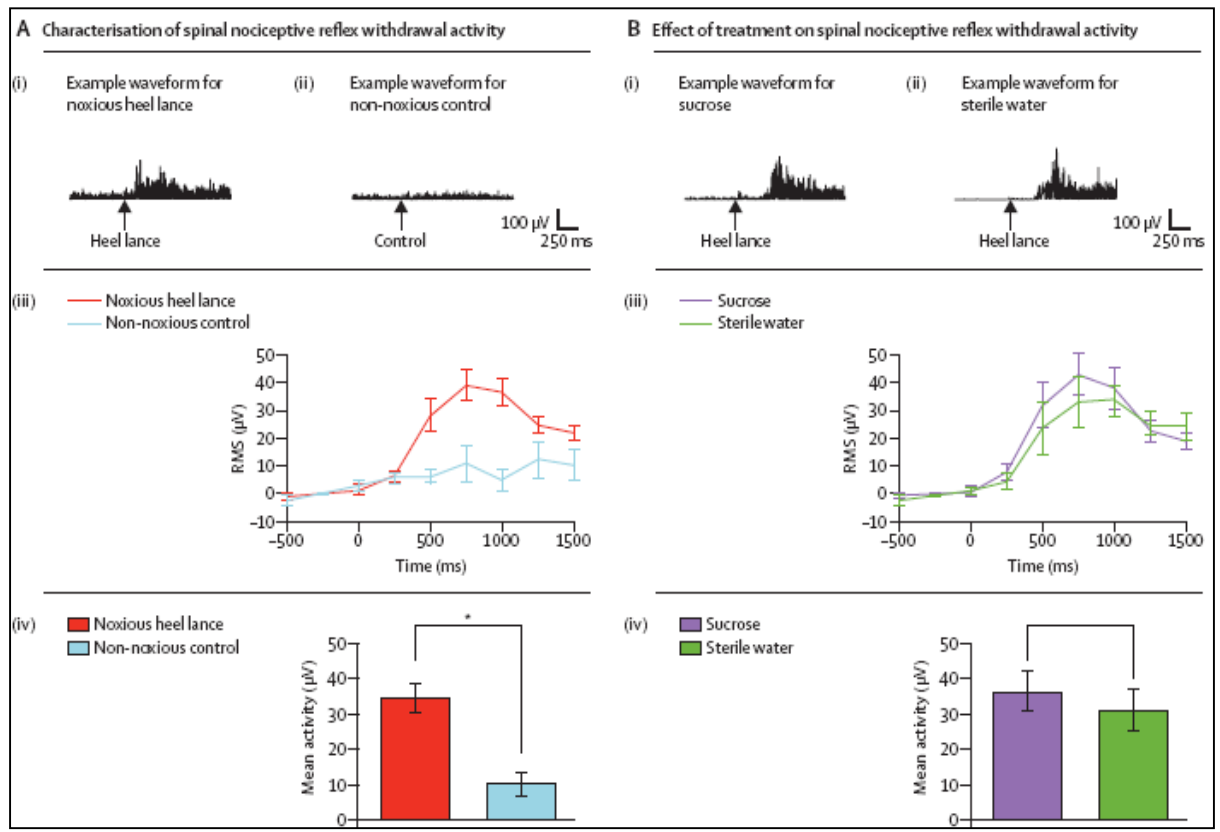

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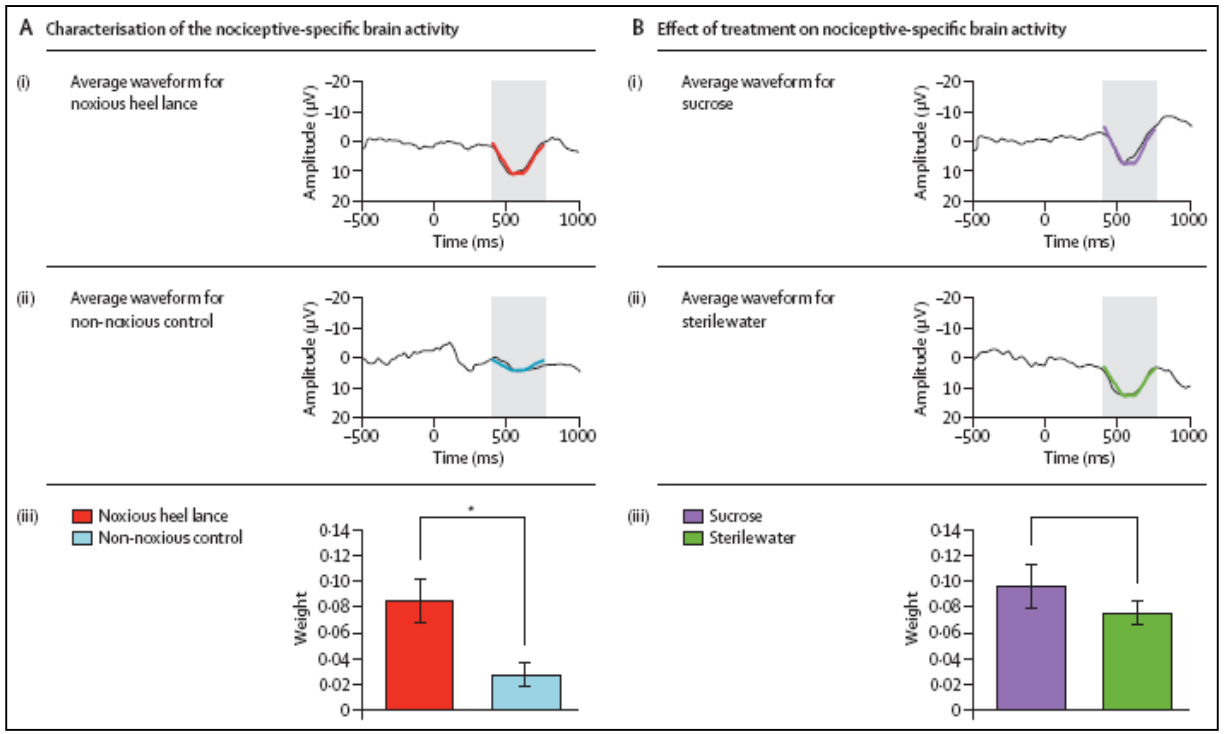
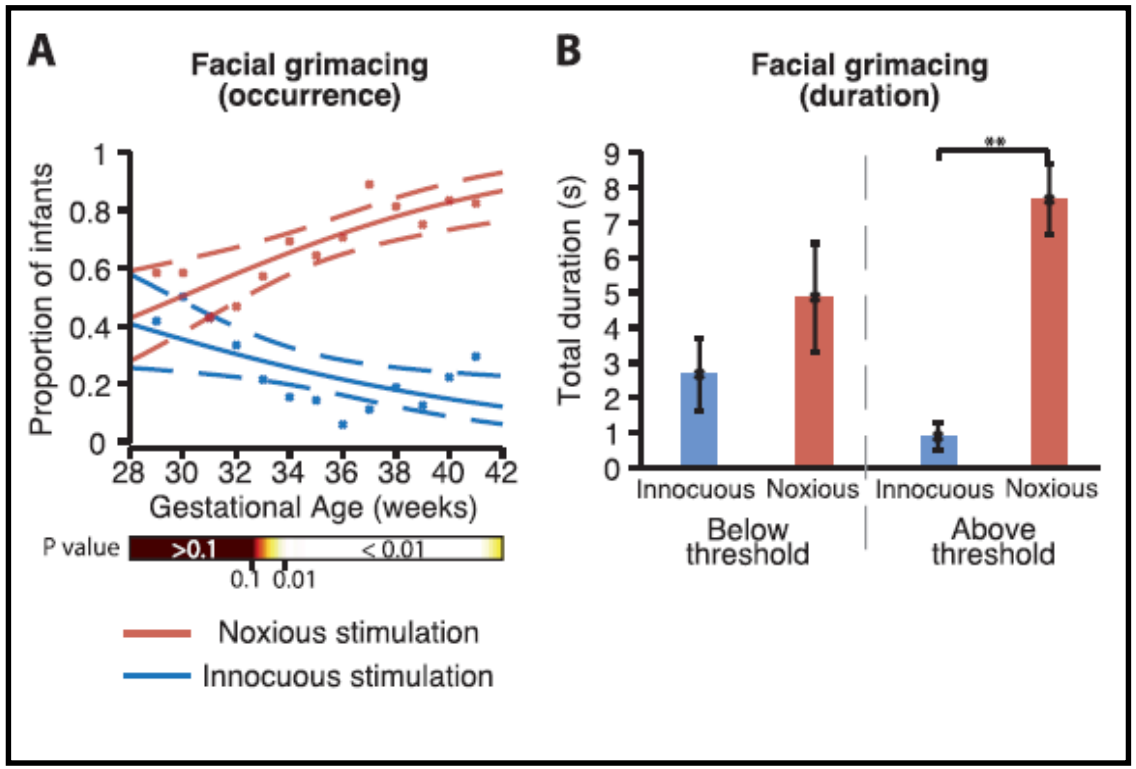
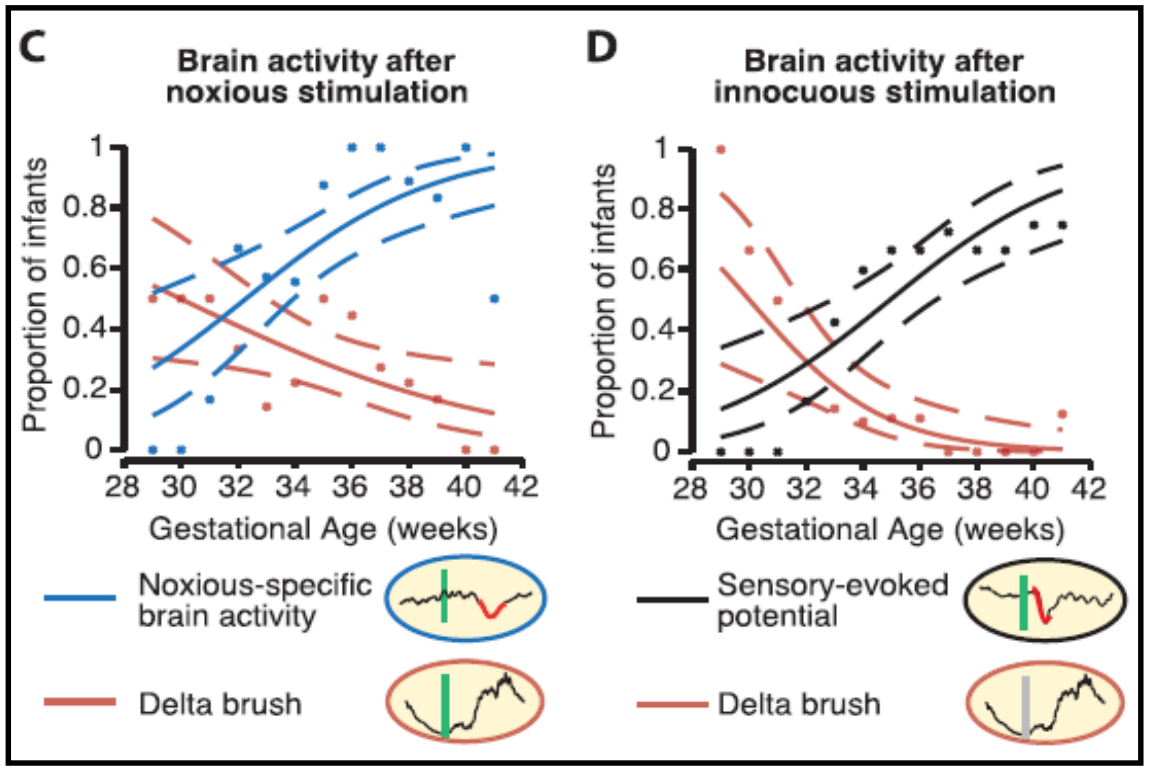
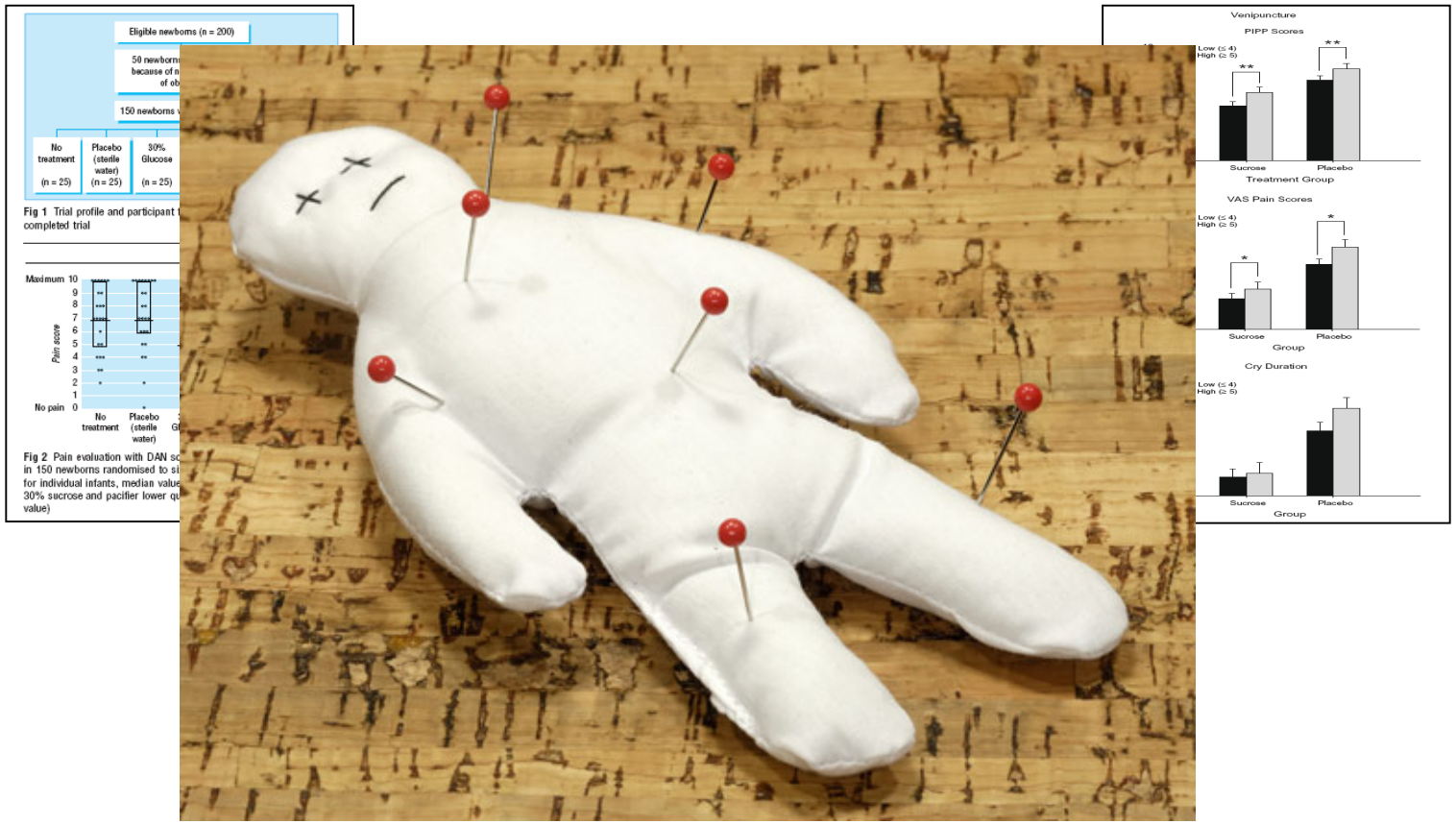






Green et al, Pain 2019


Eligible newborns (n = 200)
No treatment (n = 25)
Placebo (sterile water) (n = 25)
30% Glucose (n = 25)
Maximum 10
No pain 0
Pain score
No treatment
Placebo (sterile water)
Venipuncture
PIPP Scores
Low (≤ 4)
High (≥ 5)
Sucrose
Placebo
Treatment Group
VAS Pain Scores
Group
Cry Duration

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.



These are scientifically proven ways of reducing pain in babies during vaccine injections.
Think about what worked and plan ahead to make the next vaccination less painful.

HELP inKidS SickKids aboutkidshealth

"Clinical Practice Guideline: Reducing the pain of childhood vaccination: an evidence-based clinical practice guideline" – Adapted from, *CMAJ December 14, 2010 182:E843-E855* by permission of the publisher.
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absorptie gerelateerde concepten

- onverwachte/ongewenste/onvoorspelbare absorptie
- nasale route: opioiden, benzodiazepines, ketamine, dexmedetomidine
- Inhalatie: lachgas, equimolair

het is niet al goud dat blinkt

nieuwere geneesmiddelen aan de horizon ?

- dexmedetomide
- remi-midazolam

raket lancering: what goes up, must come down ?



new tools or new toys ?



Treatment room



Wake up room

PAION





Benzodiazepine	Acting Profile	Elimination half-life h	Premedicant	Induction	General Anesthesia Maintenance[θ]	Sedative Maintenance[°]
Midazolam	Short	1-5	Oral 0.25- 0.5 mg/kg i.v. 50 µg/kg	0.2–0.35 mg/kg	0.05 mg/kg/h	0.05 mg/kg/h
Lorazepam	Long	10-18	Oral 1-2 mg i.v. 2- 4 mg	2 - 4 mg or	0.05-0.1 mg	0.05 mg/kg
Diazepam	Intermediate	20-100	Oral 5-20 mg i.v. 5-10 mg	0.2 – 0.5 mg/kg	0.1-0.2 mg/kg	0.25 mg/kg
Flunitrazepam	Long	18-26	Oral 1-2 mg i.v. 0.015- 0.03 mg/kg	0.01 mg/kg	1.2 mgh-1	0.009- 0.01 mg/ kg
Remimazolam	Ultra short	0.75	No reports	0.1- 0.3 mg/kg	0.72-3 mg/kg/h	0.72-3 mg/kg/h?

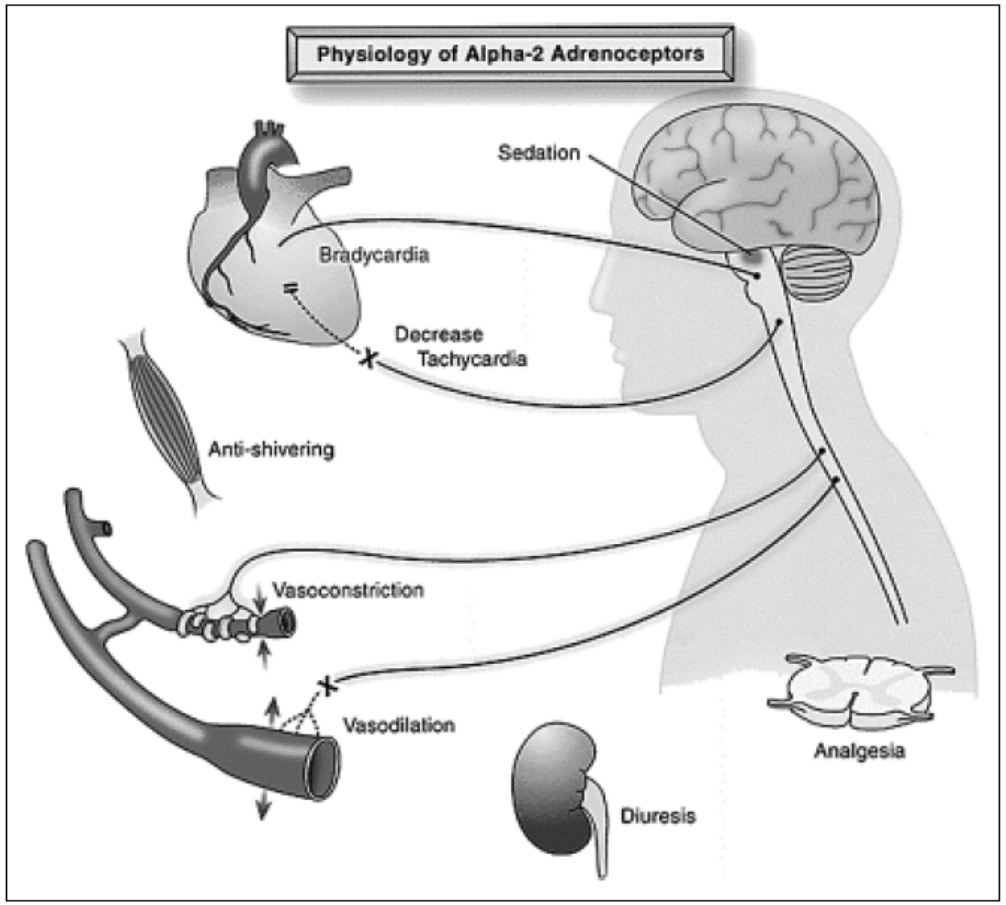
*Doses for adults. Dosage can vary.

[θ]Mixed with opioids, ketamine, or halogenated anesthetics.

[°]Procedures done under sedation plus local anesthesia.



dexmedetomide (Precedex, Dexdor) (*clonidine*)



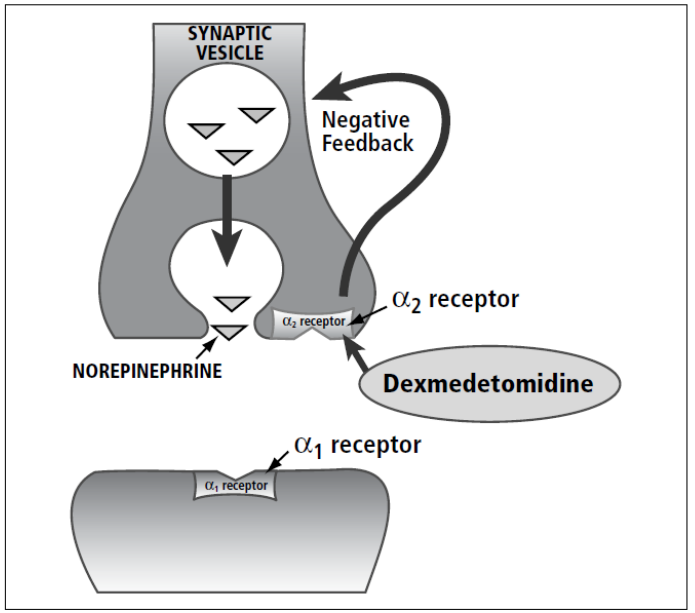


Figure 1. Physiology of the α_2-adrenoceptor agonists receptor. Reprinted from dexmedetomidine.com with permission of DocMD.com.



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American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures

Charles J. Coté, MD, FAAP, Stephen Wilson, DMD, MA, PhD, AMERICAN ACADEMY OF PEDIATRICS, AMERICAN ACADEMY OF PEDIATRIC DENTISTRY

https://pediatrics.aappublications.org/content/143/6/e20191000

TABLE 1 Appropriate Intake of Food and Liquids Before Elective Sedation

Ingested Material	Minimum Fasting Period, h
Clear liquids: water, fruit juices without pulp, carbonated beverages, clear tea, black coffee	2
Human milk	4
Infant formula	6
Nonhuman milk: because nonhuman milk is similar to solids in gastric emptying time, the amount ingested must be considered when determining an appropriate fasting period.	6
Light meal: a light meal typically consists of toast and clear liquids. Meals that include fried or fatty foods or meat may prolong gastric emptying time. Both the amount and type of foods ingested must be considered when determining an appropriate fasting period.	6

Source: American Society of Anesthesiologists. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures. An updated report by the American Society of Anesthesiologists Committee on Standards and Practice Parameters. Available at: https://www.asahq.org/For-Members/Practice-Management/Practice-Parameters.aspx. For emergent sedation, the practitioner must balance the depth of sedation versus the risk of possible aspiration; see also Mace et al[272] and Green et al.[273]

Table 1. PACU recovery and discharge scorings (modified Aldrete score).*

Parameters	Description of the patient	Score
Activity level	Moves all extremities voluntarily/on command	2
	Moves 2 extremities	1
	Cannot move extremities	0
Respiration	Breathes deeply and coughs freely	2
	Is dyspneic, with shallow, limited breathing	1
	Is apneic	0
Circulation (blood pressure)	Is 20 mmHg > preanesthetic level	2
	Is 20 to 50 mmHg > preanesthetic level	1
	Is 50 mmHg > preanesthetic level	0
Consciousness	Is fully awake	2
	Is arousable on calling	1
	Is not responding	0
Oxygen saturation as determined by pulse oximetry	Has level > 90% when breathing room air	2
	Requires supplemental oxygen to maintain level > 90%	1
	Has level < 90% with oxygen supplementation	0

*Maximum total score is 10; a score of ≥9 is required for discharge.


THINK
POSITIVE

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