Developmental pharmacology of analgesics

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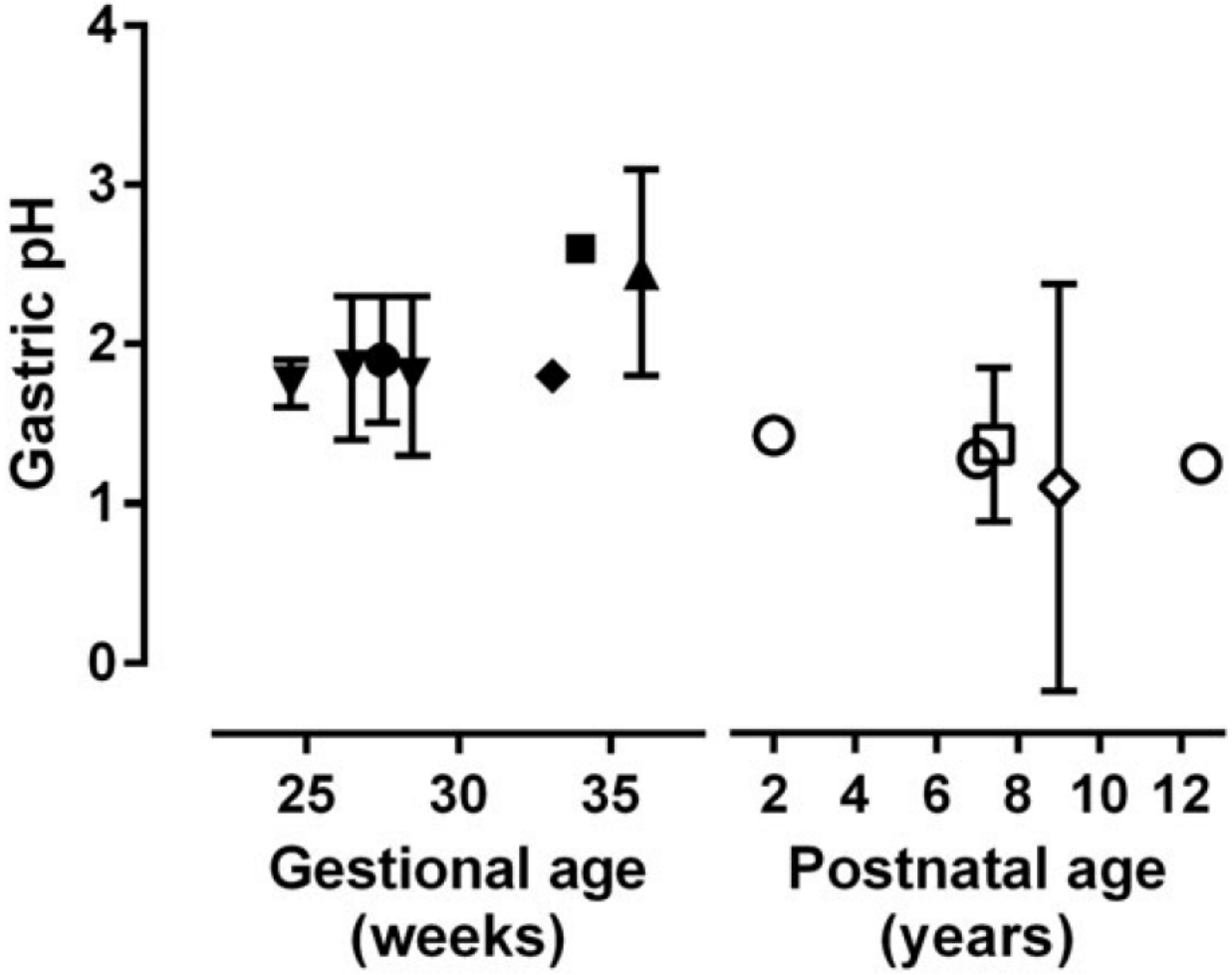
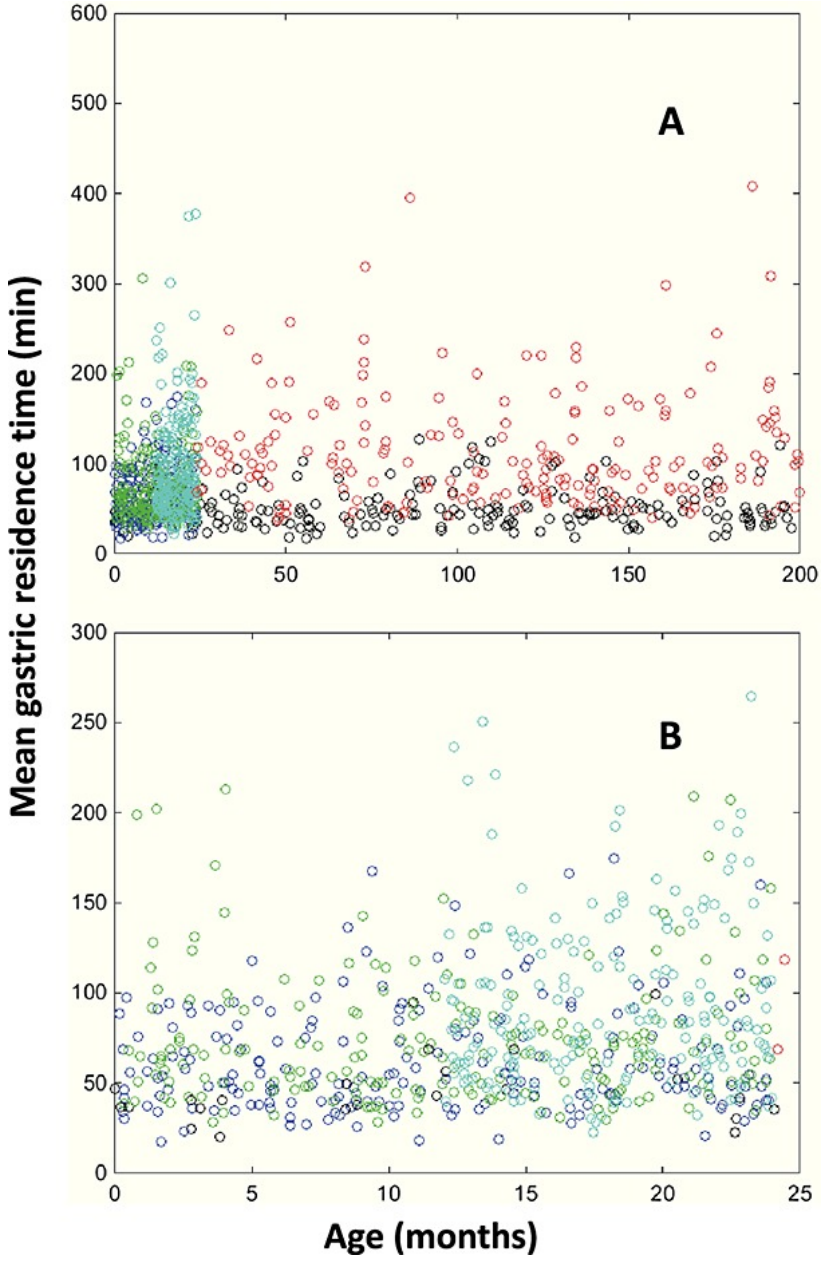
Disclosure statement

- I have no financial interests or conflicts of interest with any pharmaceutical company to disclose relating to this presentation

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

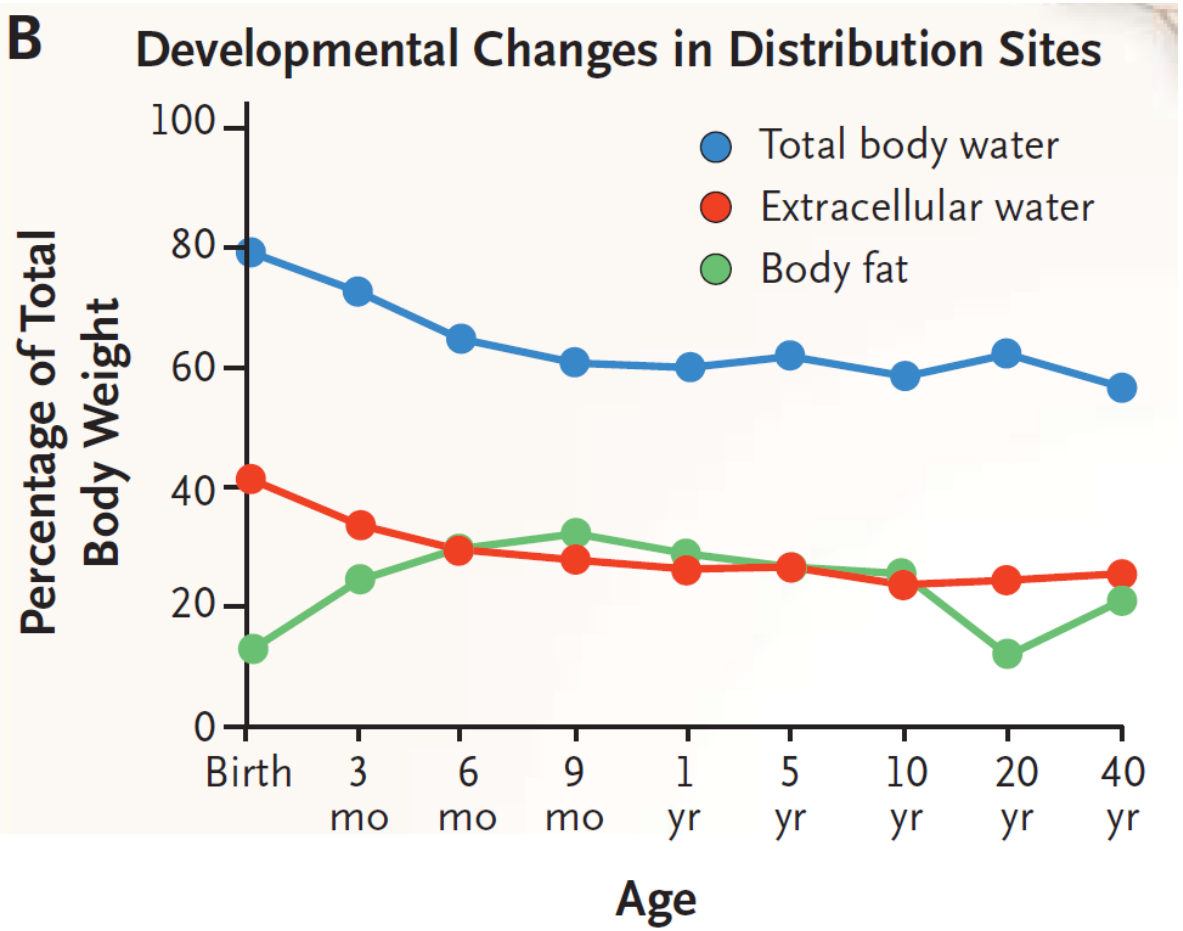
Absorption

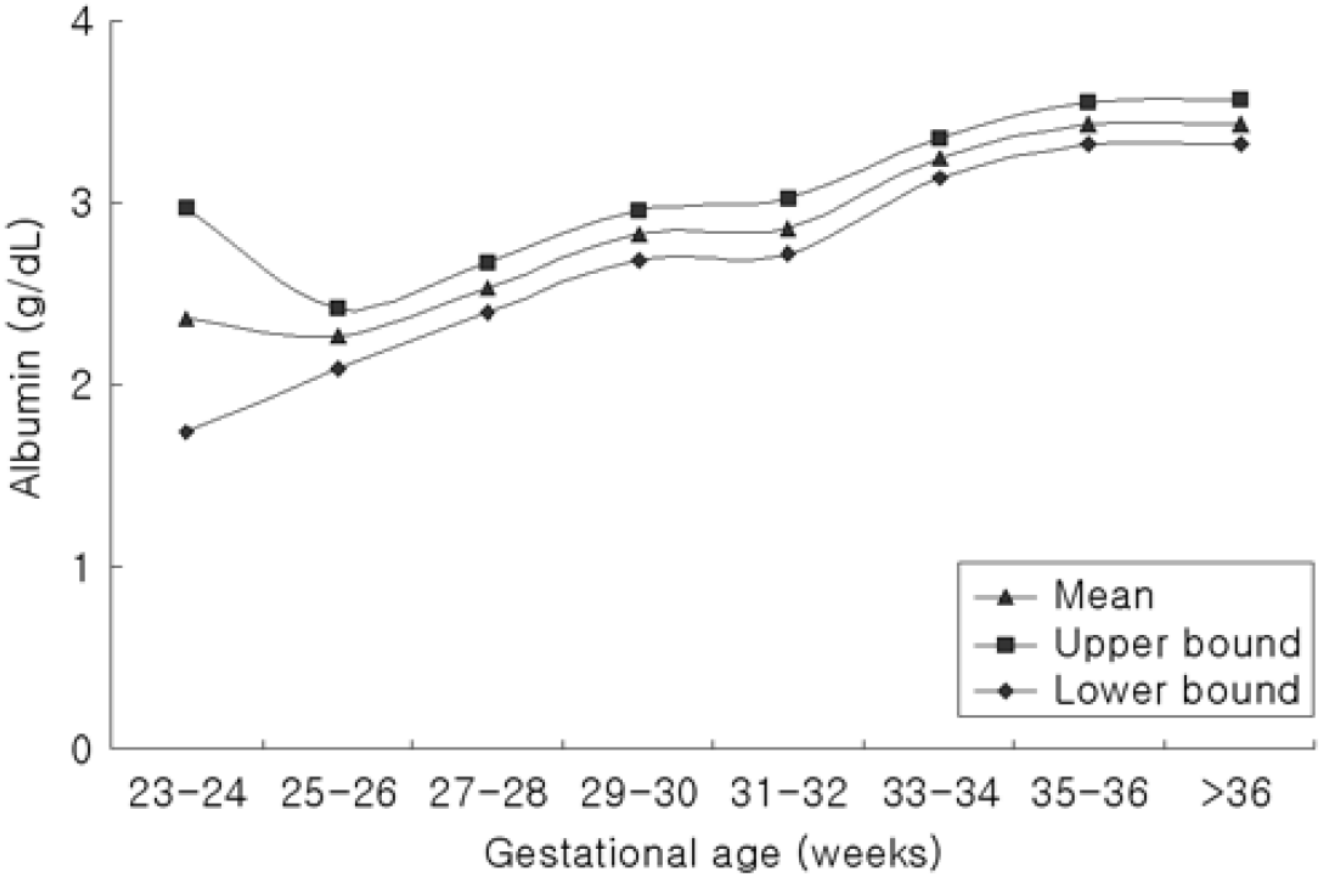




Nicolas et al. Biopharm Drug Dispos 2017; 38: 209-230.
Bonner et al. Biopharm Drug Dispos 2015; 36: 245-257.

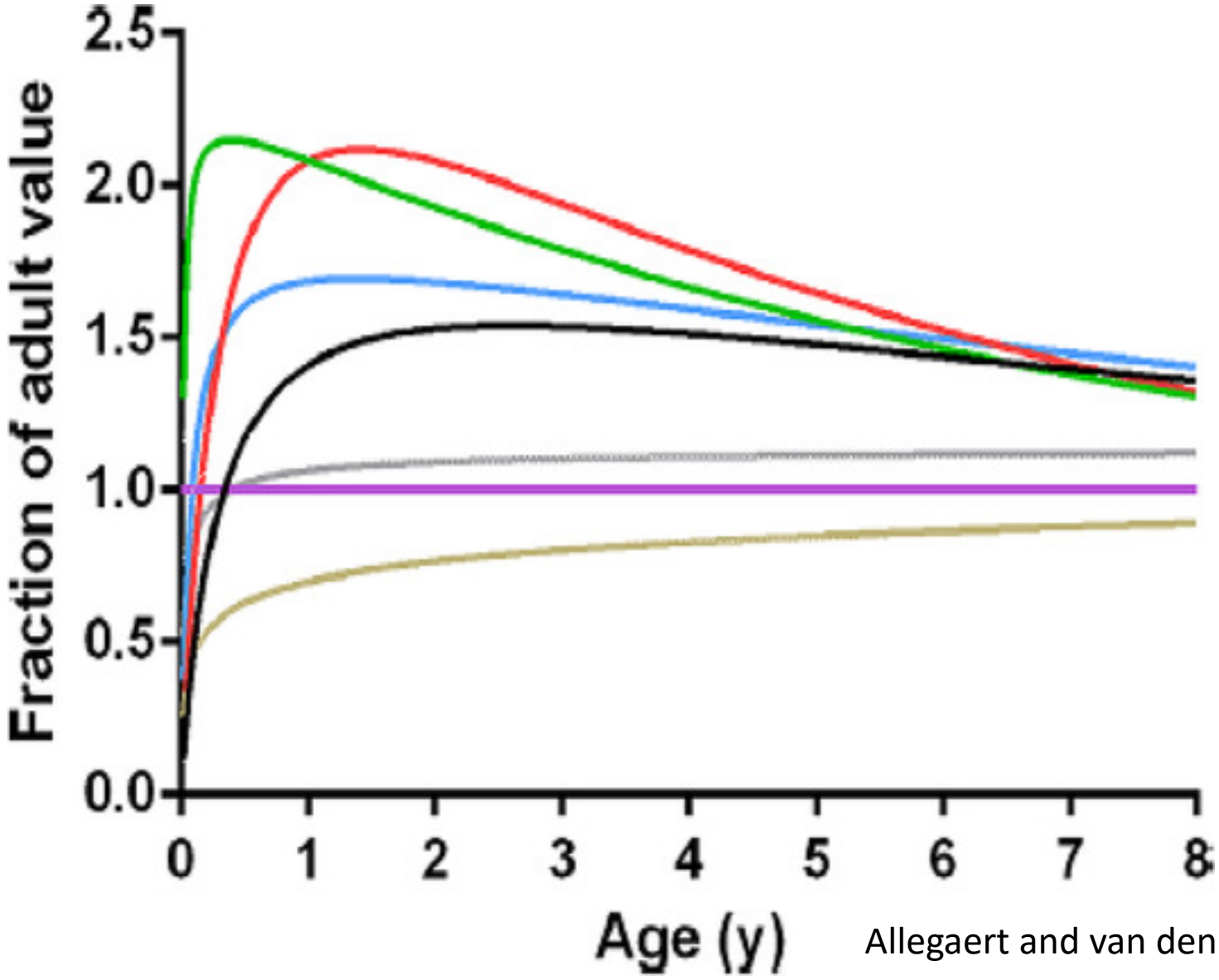
Distribution





Kearnes et al. N Engl J Med 2003; 349: 1157-1167.
Lee et al. Korean J Pediatr 2005; 48: 148-153.

Metabolism – Phase I



CYP 3A

CYP 1A2

CYP 2C19

CYP 2C9

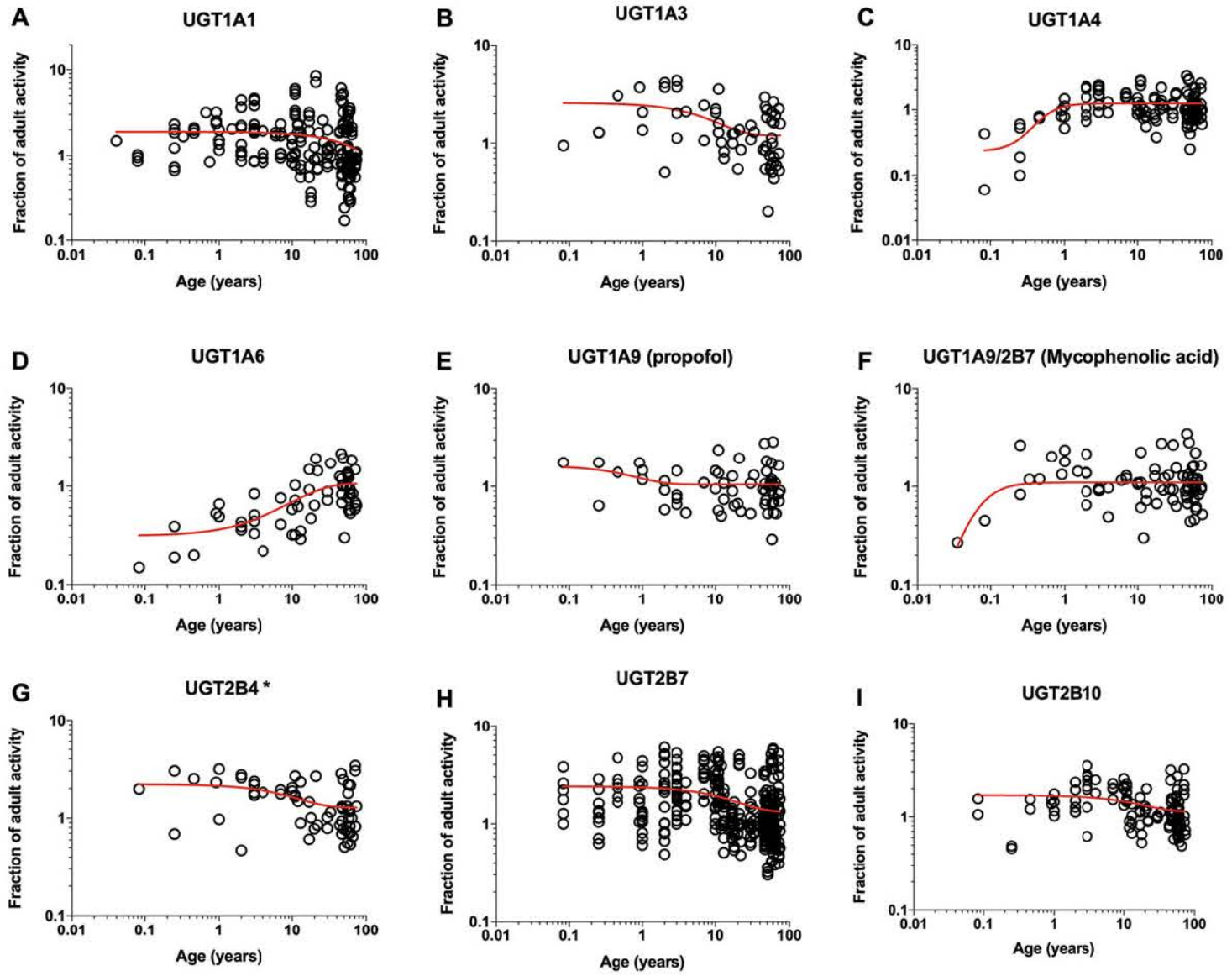
CYP 2A6

CYP 2B6 and 2D6

CYP 1E2

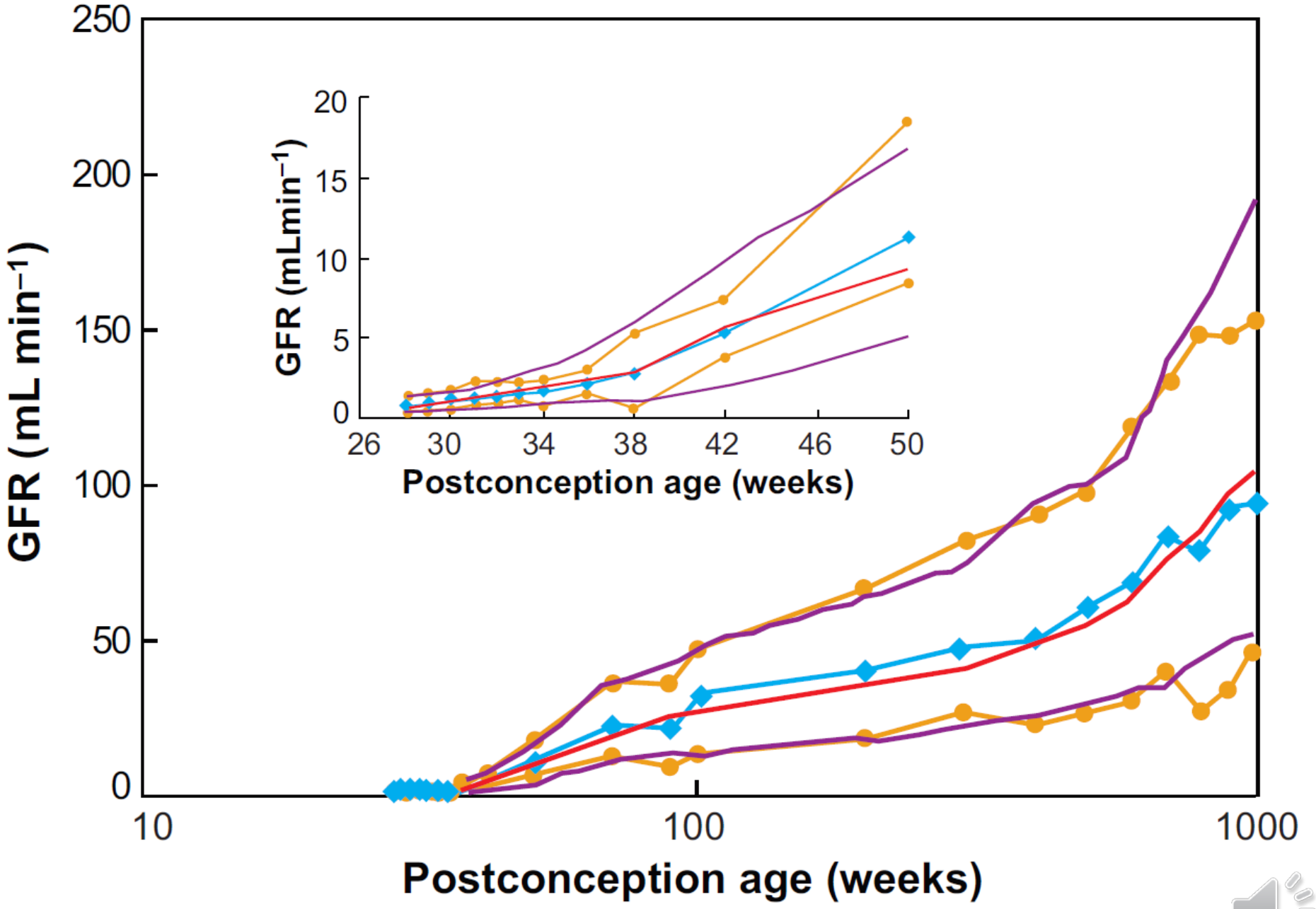
Allegaert and van den Anker. J Clin Pharmacol 2019; 59: S33-S41.

Metabolism – Phase II



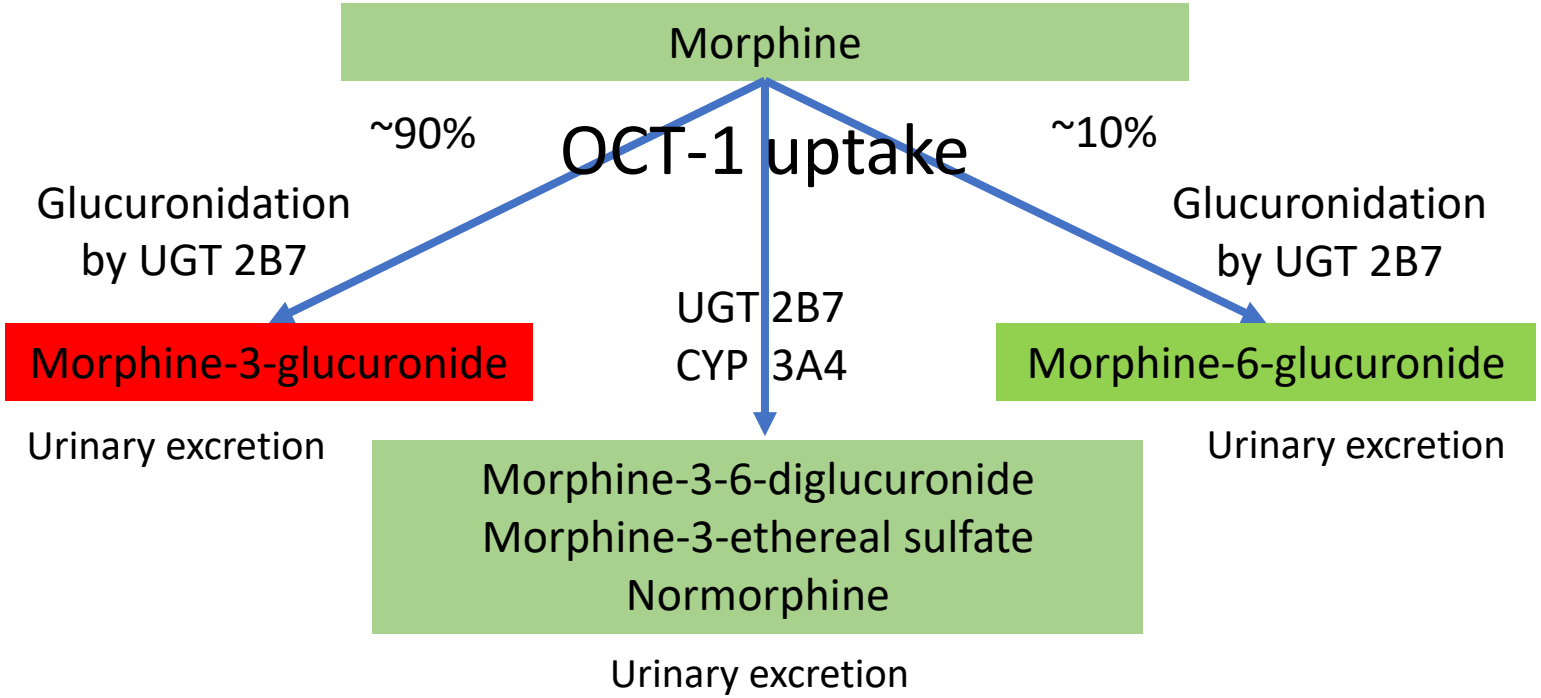
Badee et al. J Clin Pharmacol 2019; 59: S42-S55.

Excretion

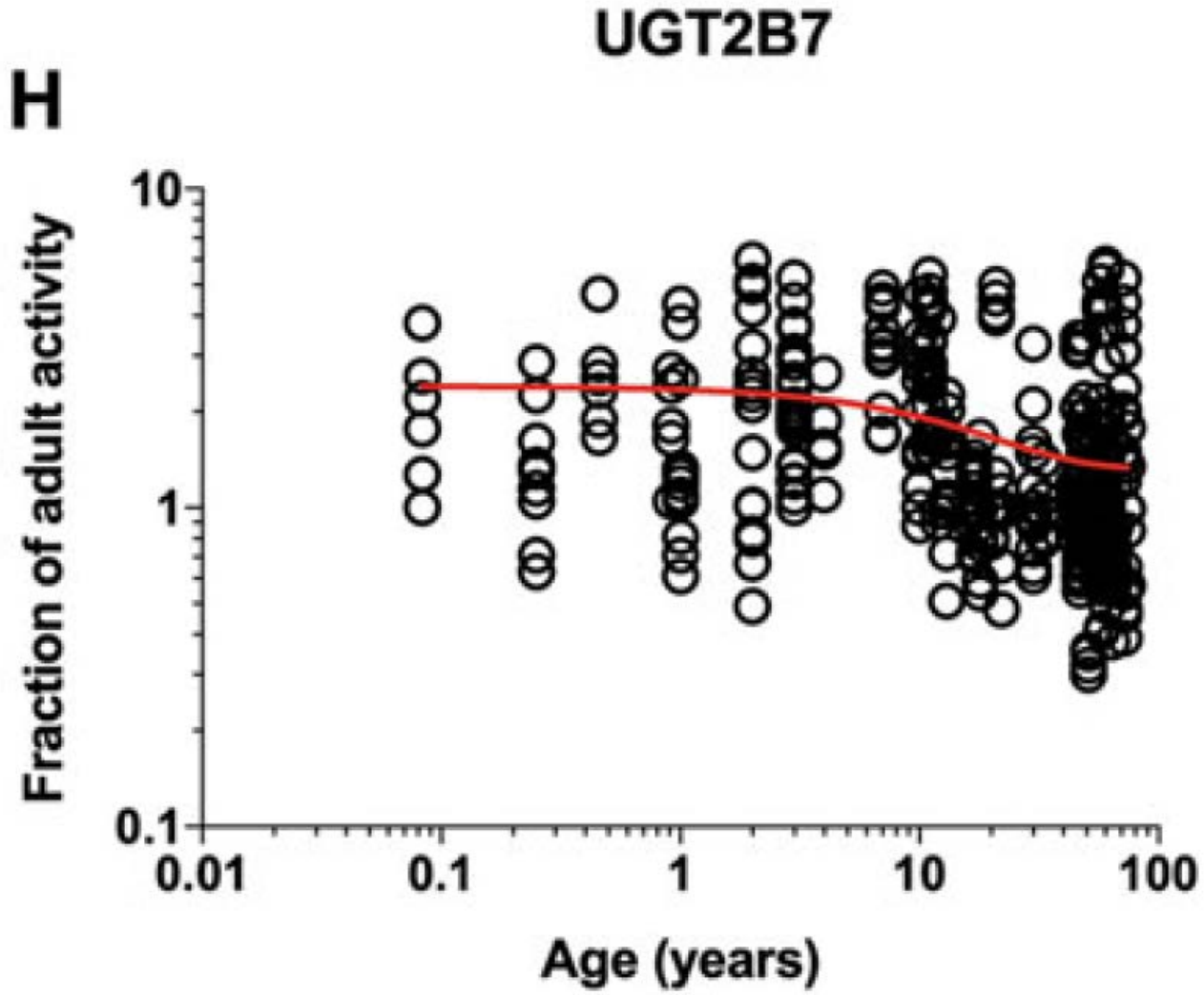


Anderson and Holford. Annu Rev Pharmacol Toxicol 2008; 48: 303-332.

Opioid metabolism

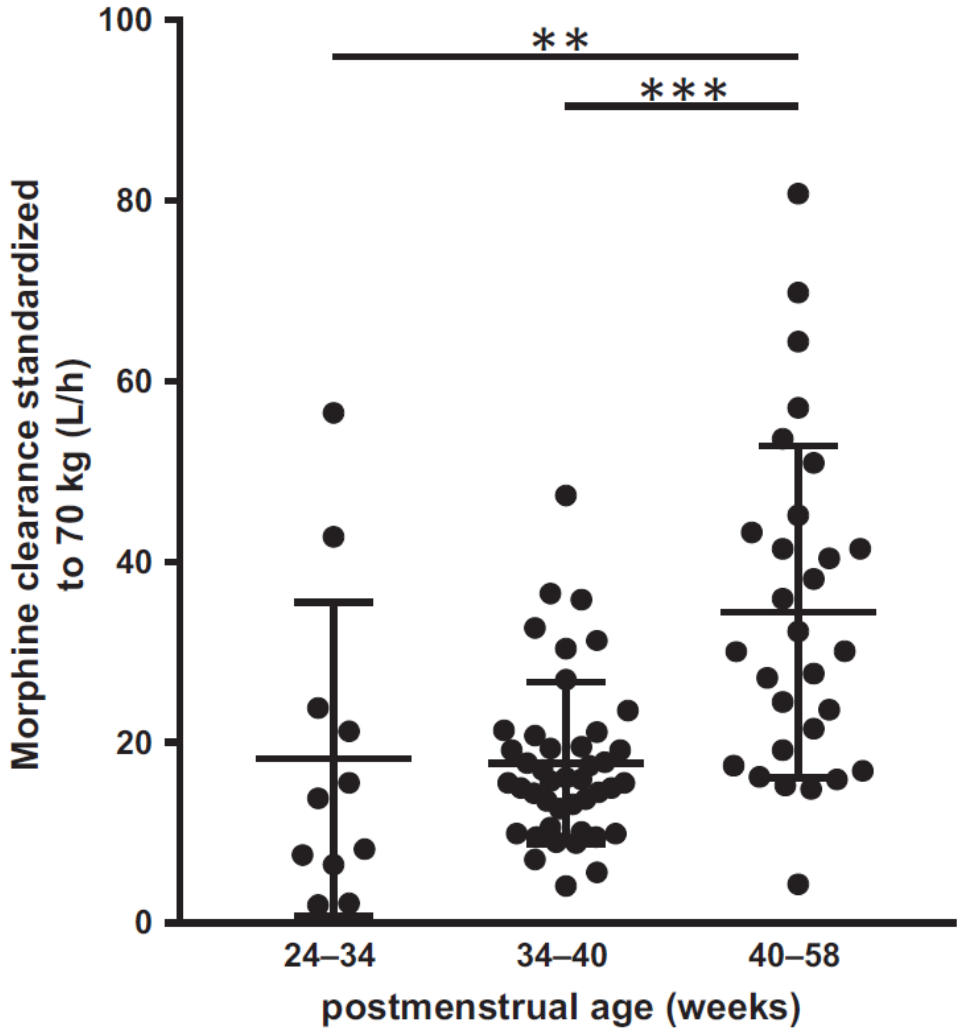


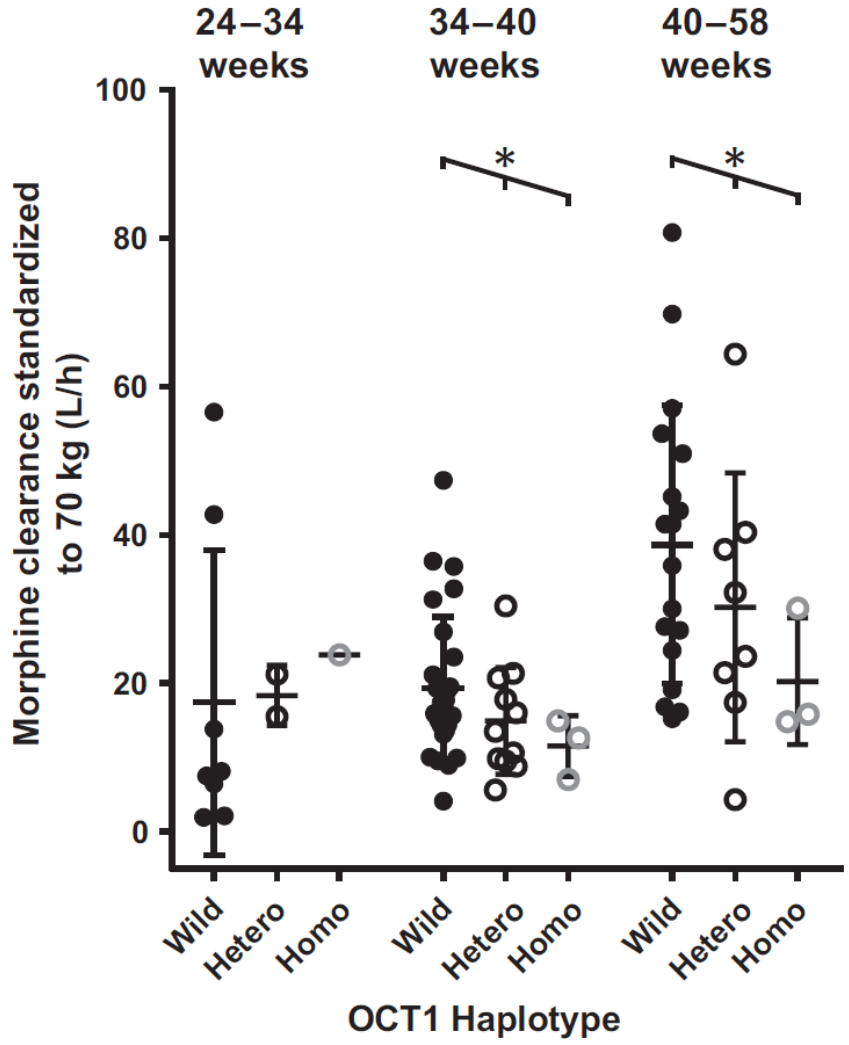
Ontogeny of morphine elimination pathways



Badee et al. J Clin Pharmacol 2019; 59: S42-S55.

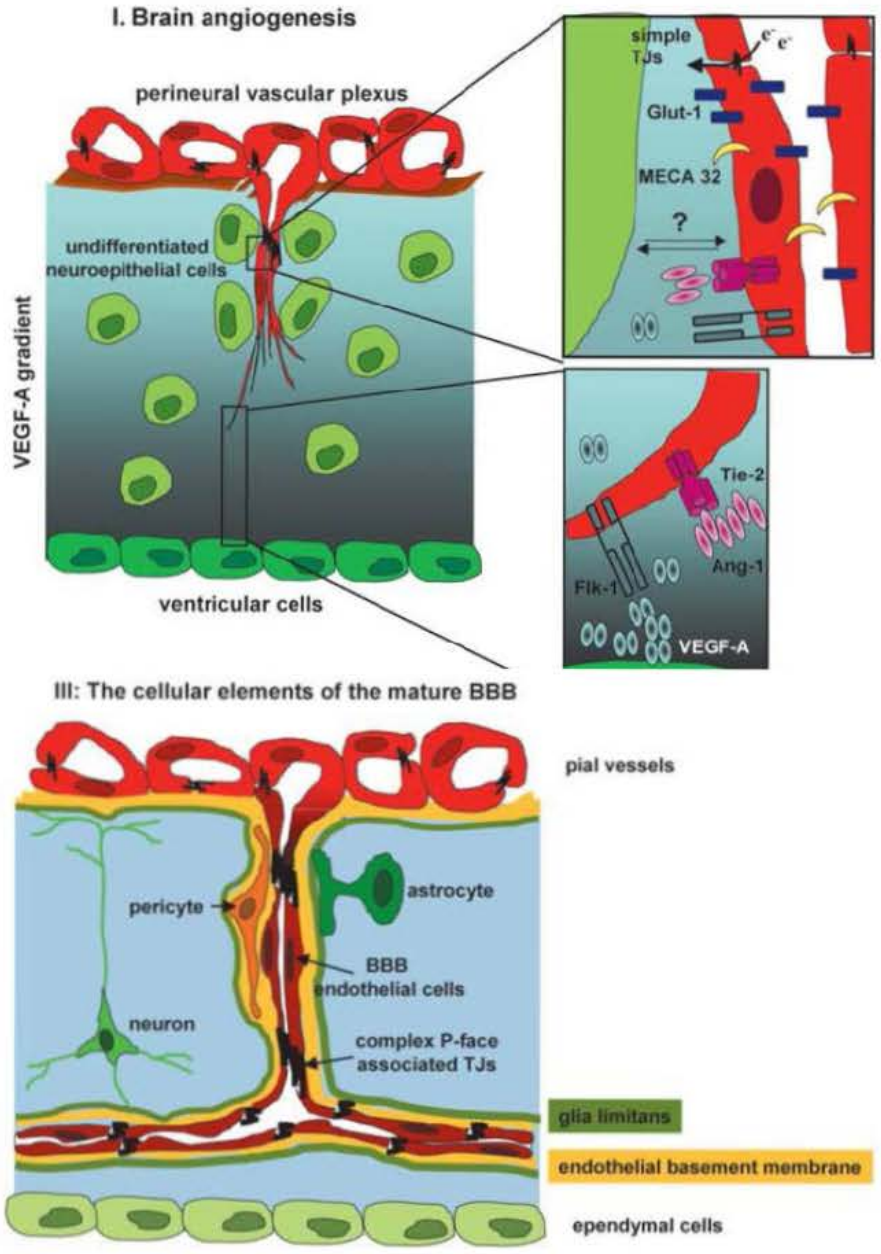
Ontogeny of morphine elimination pathways

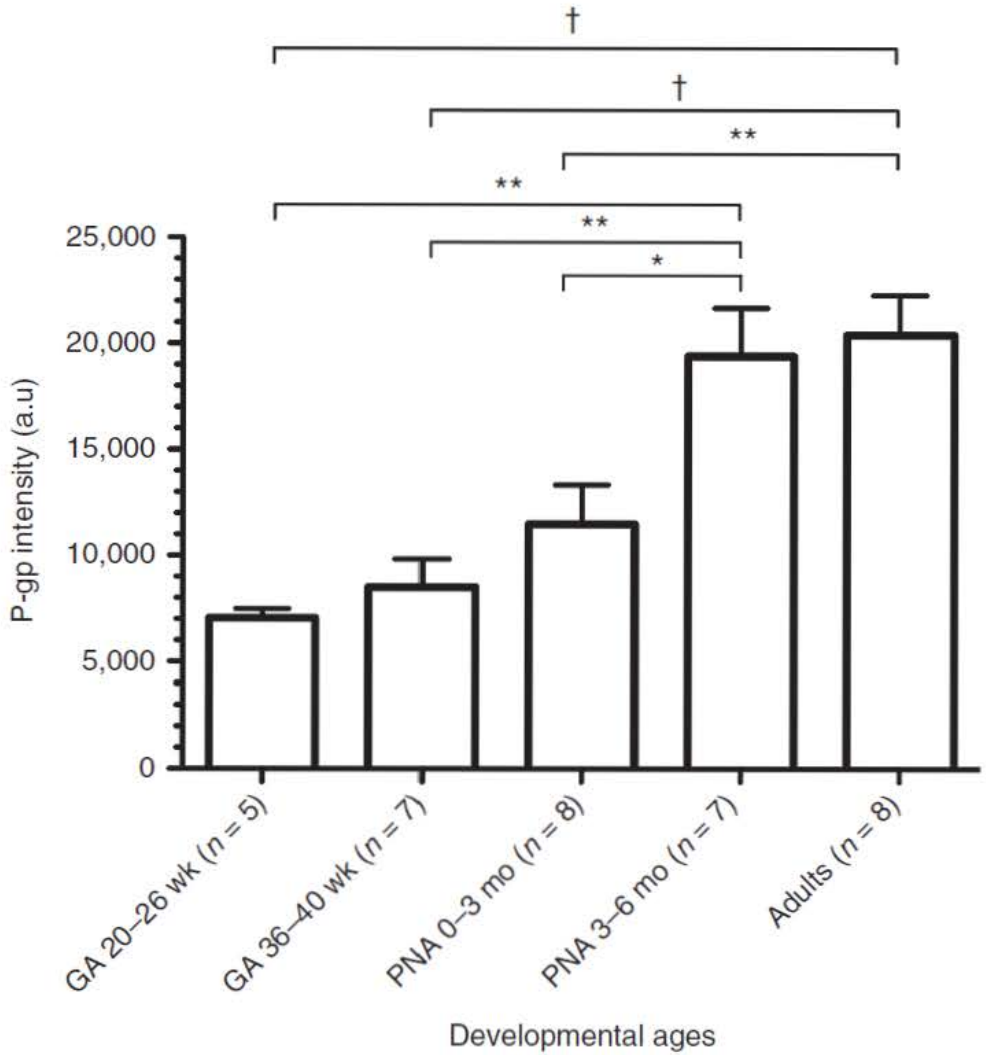




Hahn et al. Clin Pharmacol Ther 2019; 105: 761-768.

Serum opioid concentrations may not reflect CSF concentrations

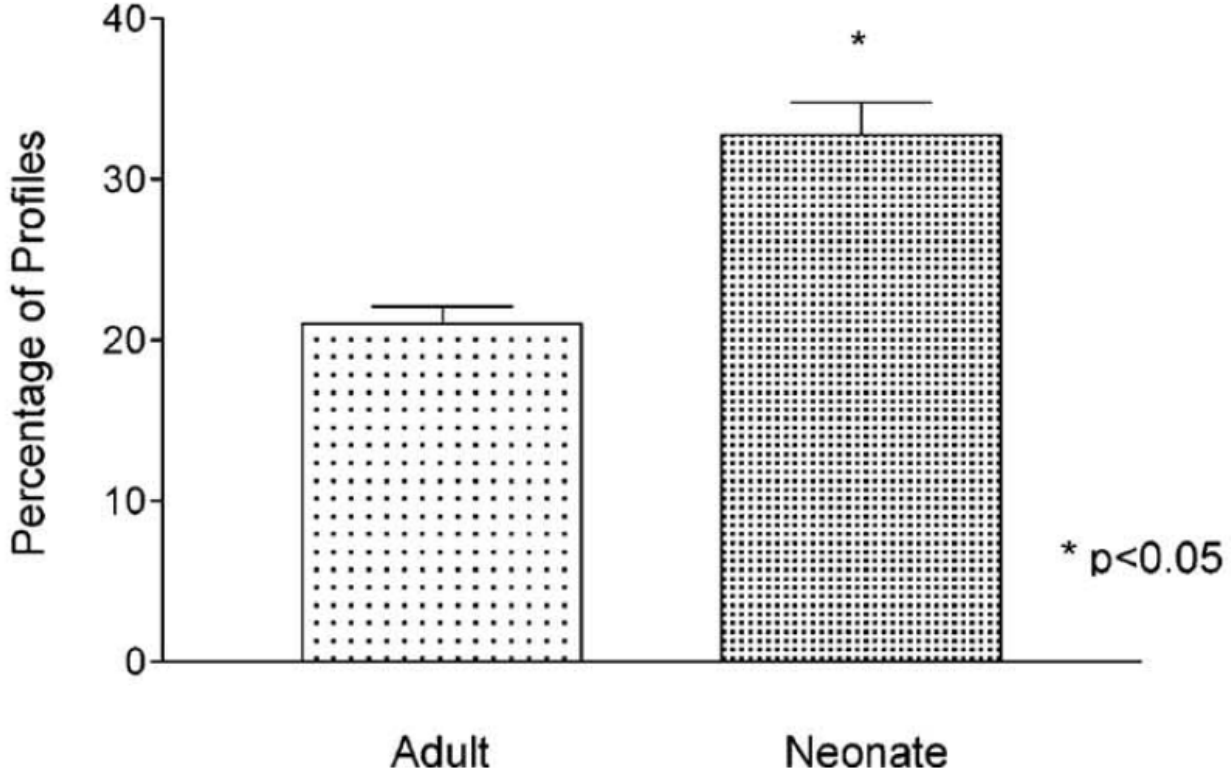




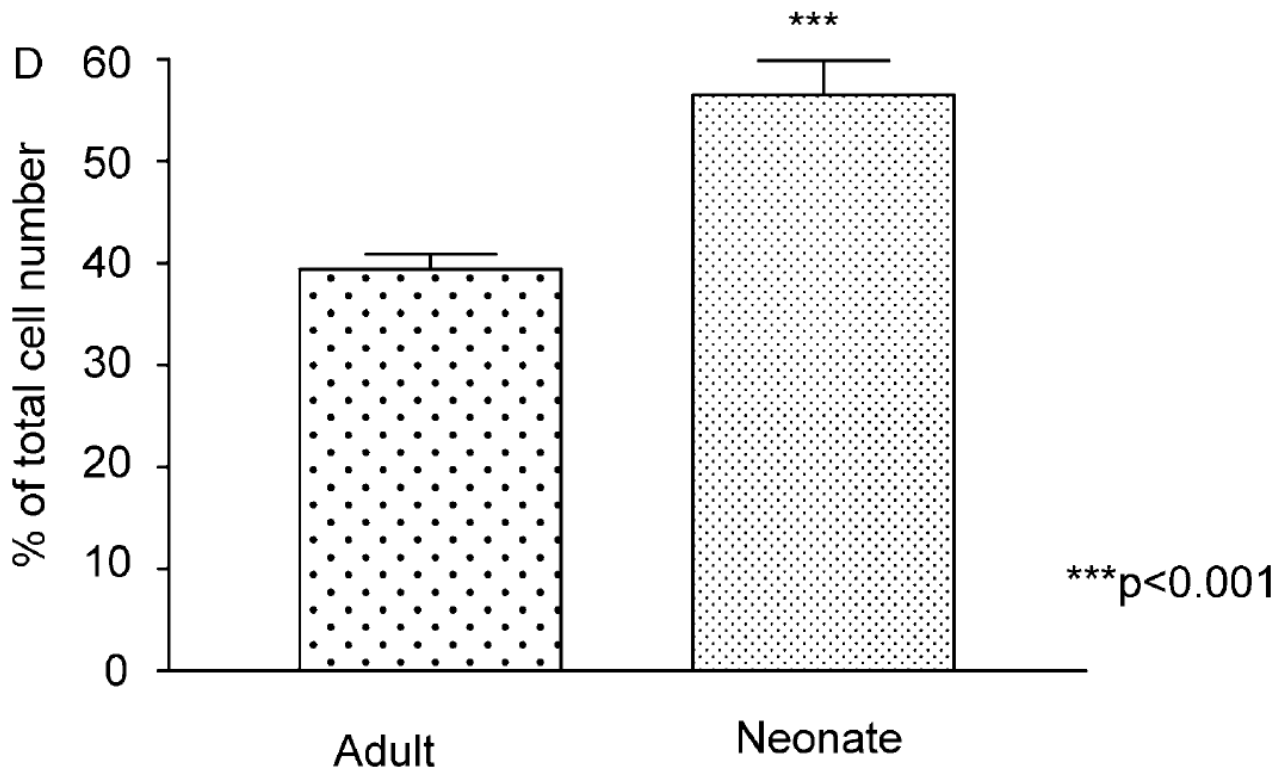
Engelhardt. Cell Tissue Research 2003; 314: 119-129.

Lam et al. Pediatr Res 2015; 78: 417-421.

Opioid receptor ontogeny



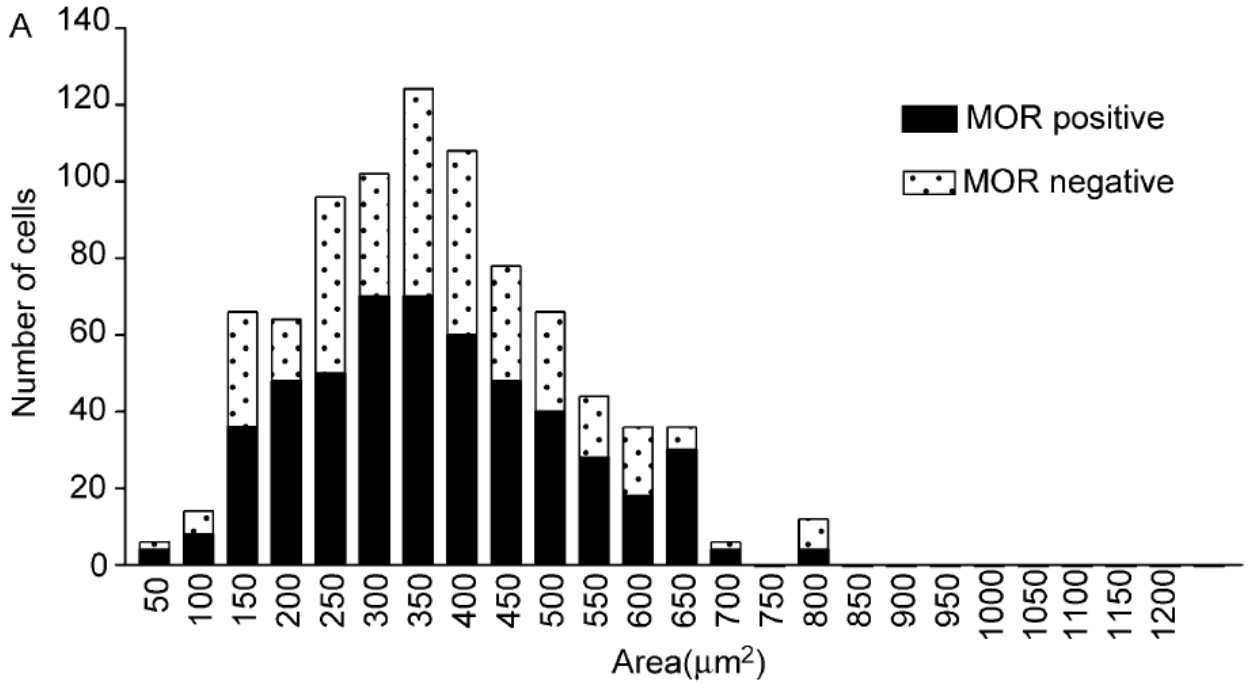
μ-opioid receptor expression in rat dorsal root ganglion



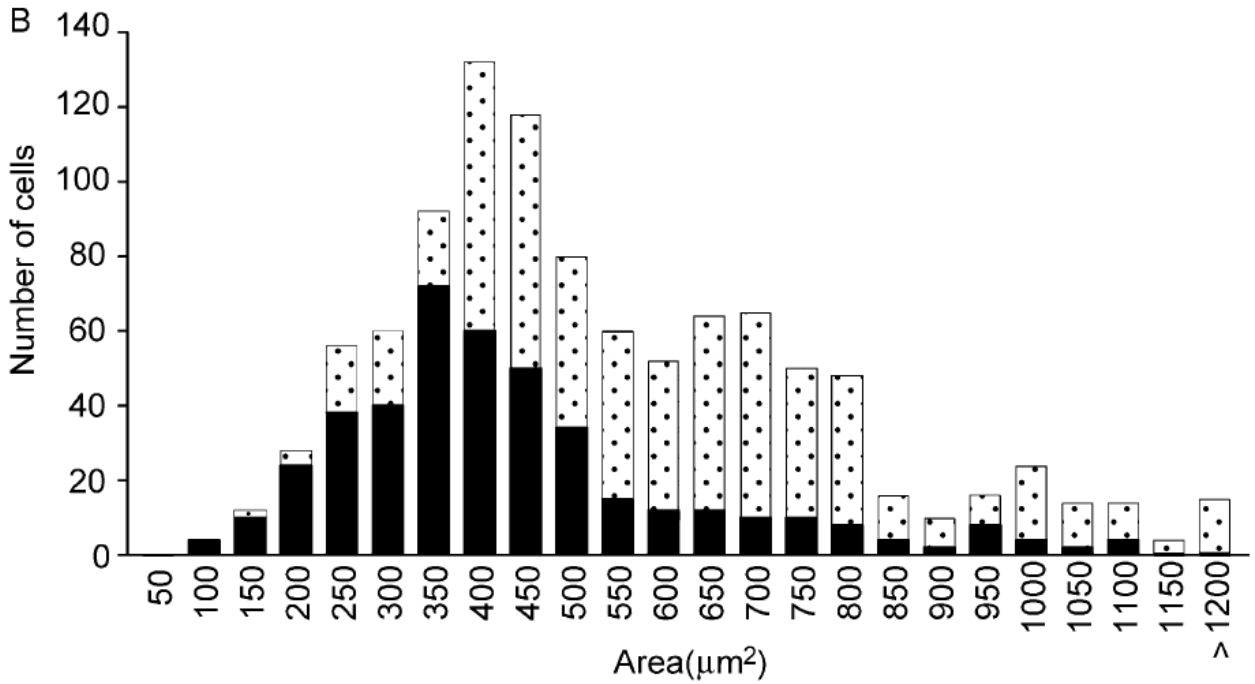
Opioid responsive cells in rat dorsal root ganglion

Nandi, et al, Fitzgerald. Pain 2004; 111: 38-50.

Opioid receptor ontogeny



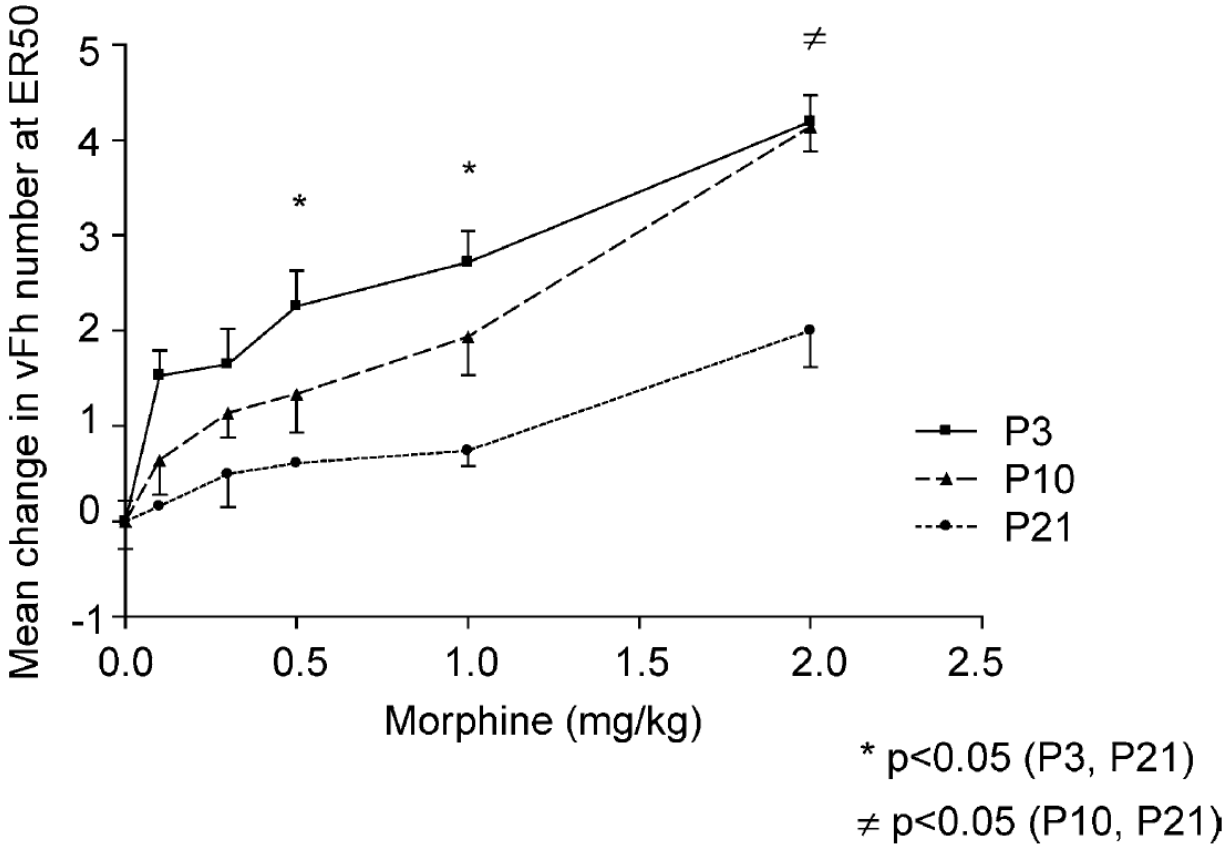
Adult rat dorsal root ganglion
(MOR positive small and medium cells)



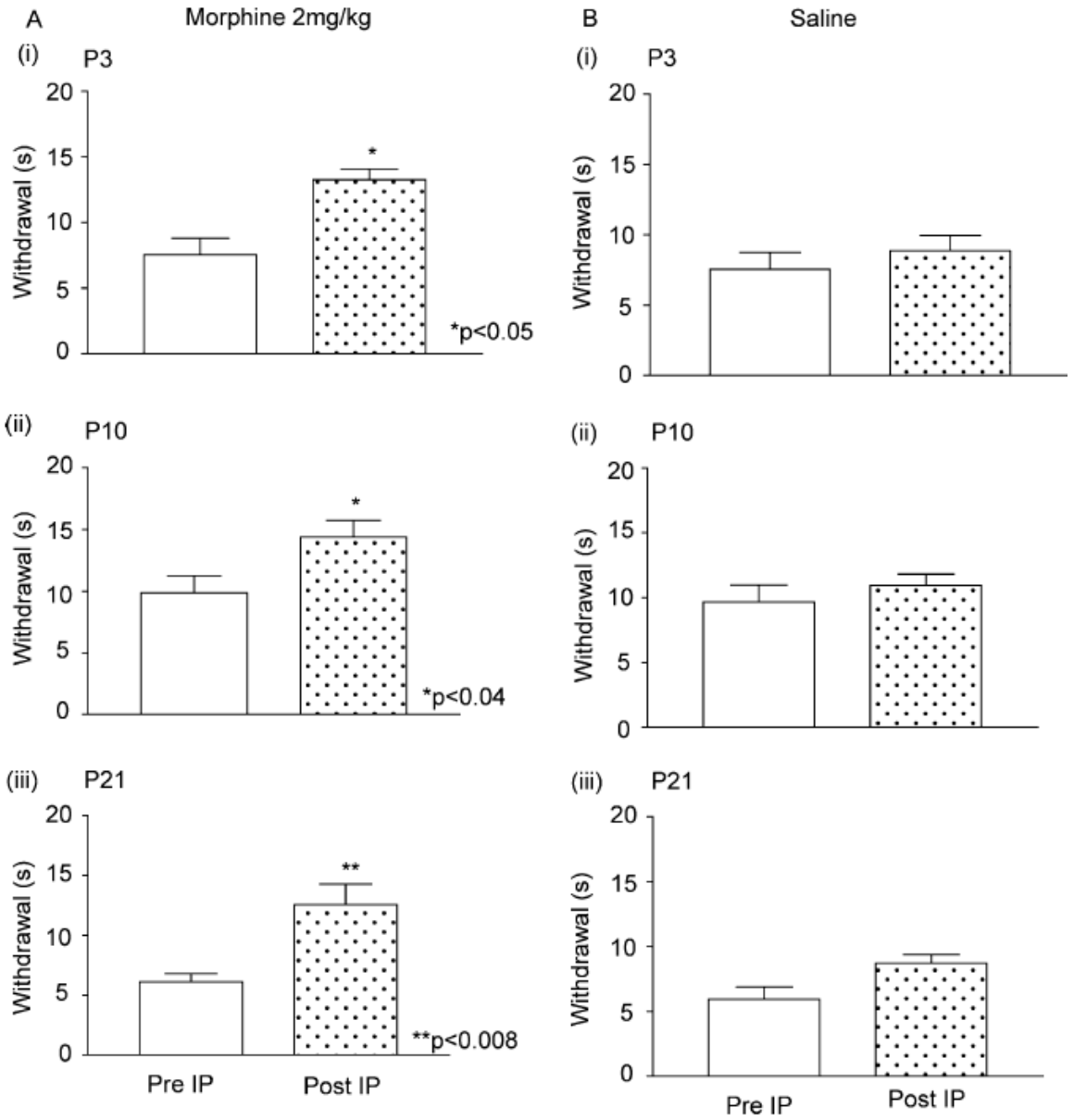
Neonatal rat dorsal root ganglion
(Diffuse distribution of MOR positive cells)

Nandi, et al, Fitzgerald. Pain 2004; 111: 38-50.

Opioid receptor ontogeny



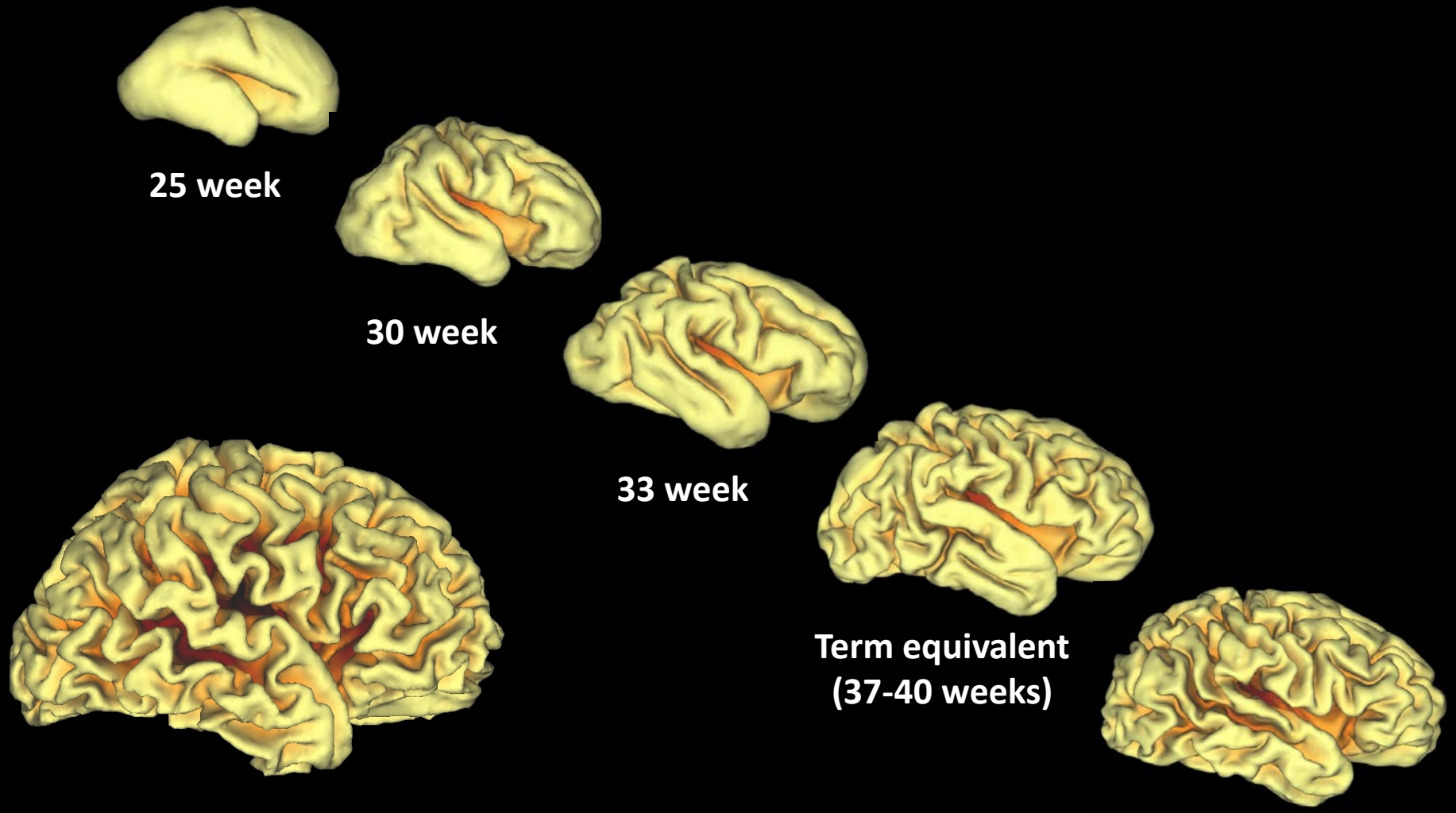
Decreased morphine sensitivity with age in the setting of mechanical stimulation



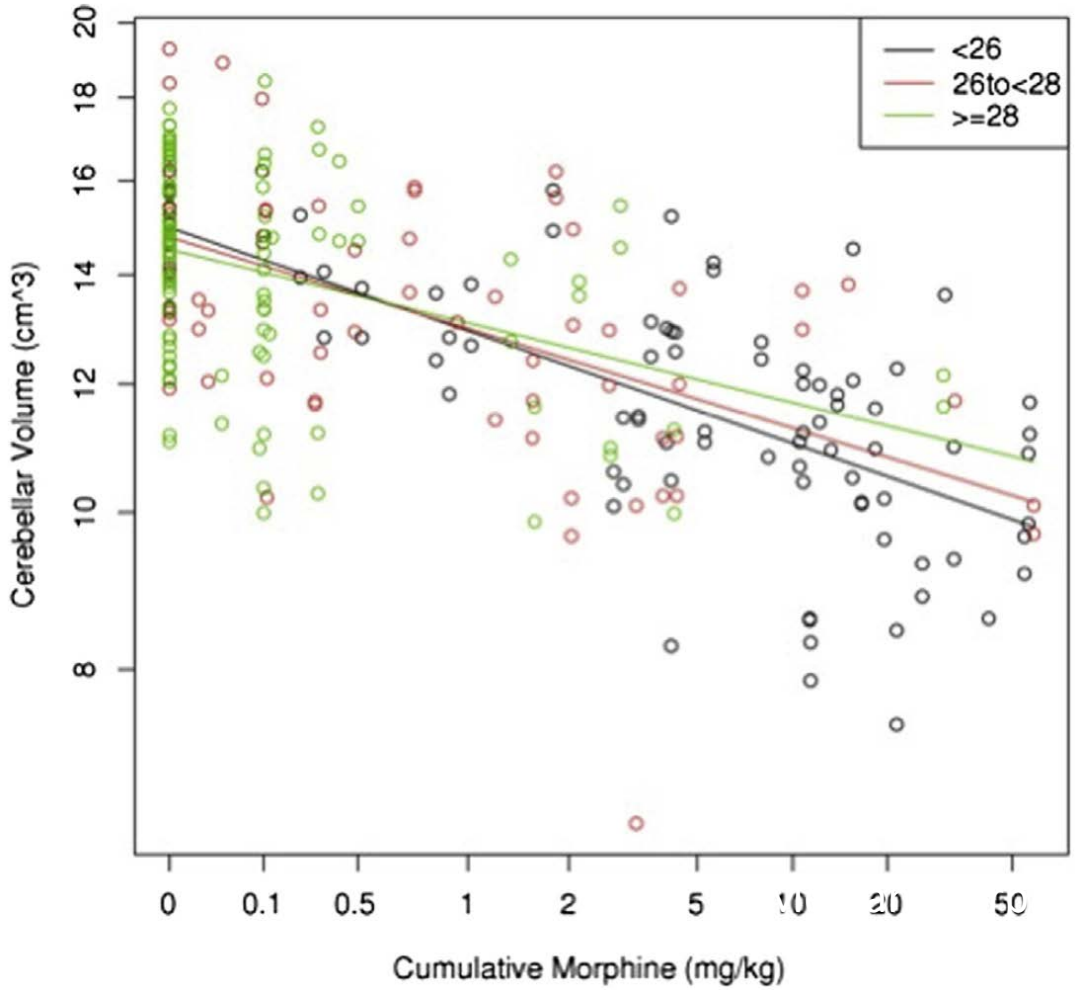
No difference in morphine sensitivity with age in the setting of thermal stimulation

Nandi, et al, Fitzgerald. Pain 2004; 111: 38-50.

Developmental impact



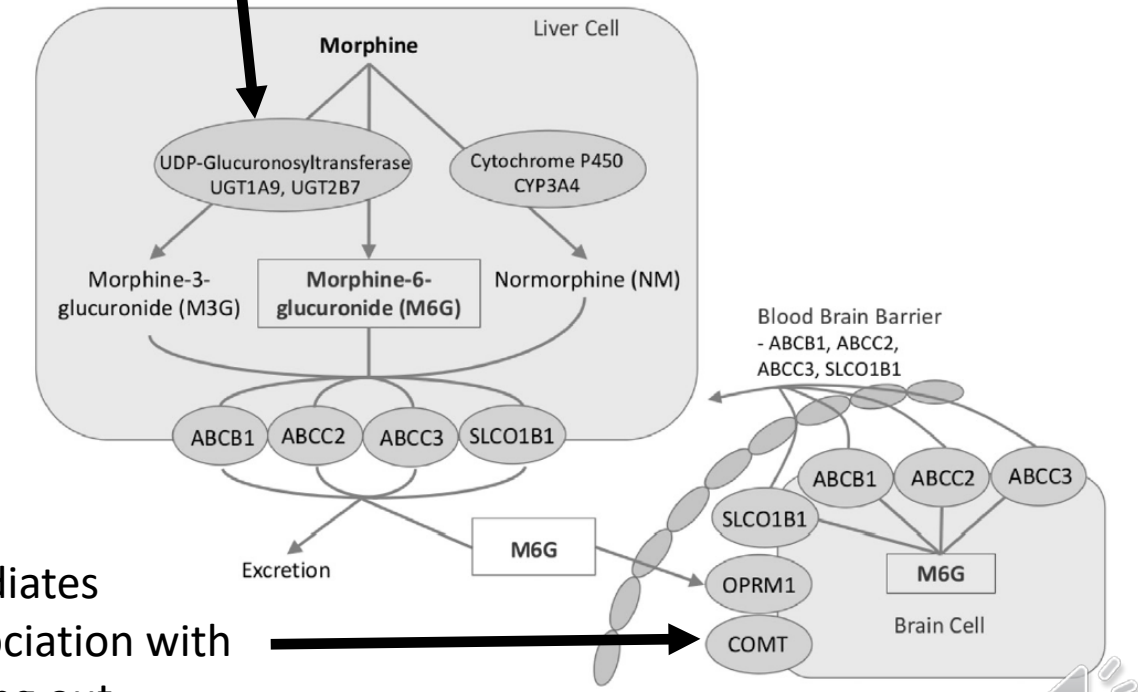
Morphine and developmental outcomes in preterm infants



Morphine exposure significantly associated with poorer motor scores (p<0.001) and cognitive outcomes (p=0.006) at 18 months CA

Mediates association with anxiety/depression

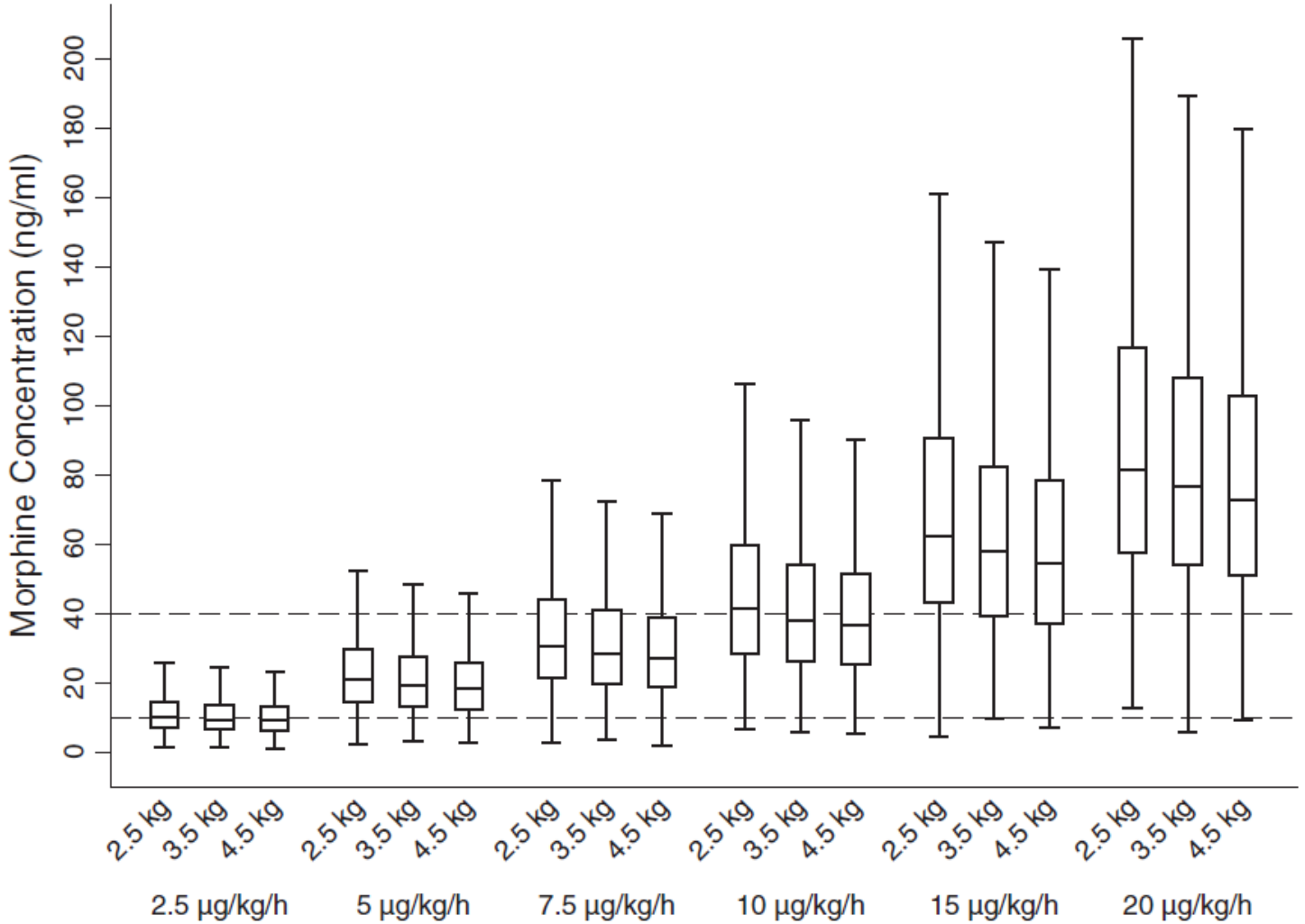
UGT 1A6?



Mediates association with acting out

Zwicker, Miller, et al. J Pediatr 2016; 172: 81-7.
Chau et al, Grunau. EBioMedicine 2019; 40: 655-62.

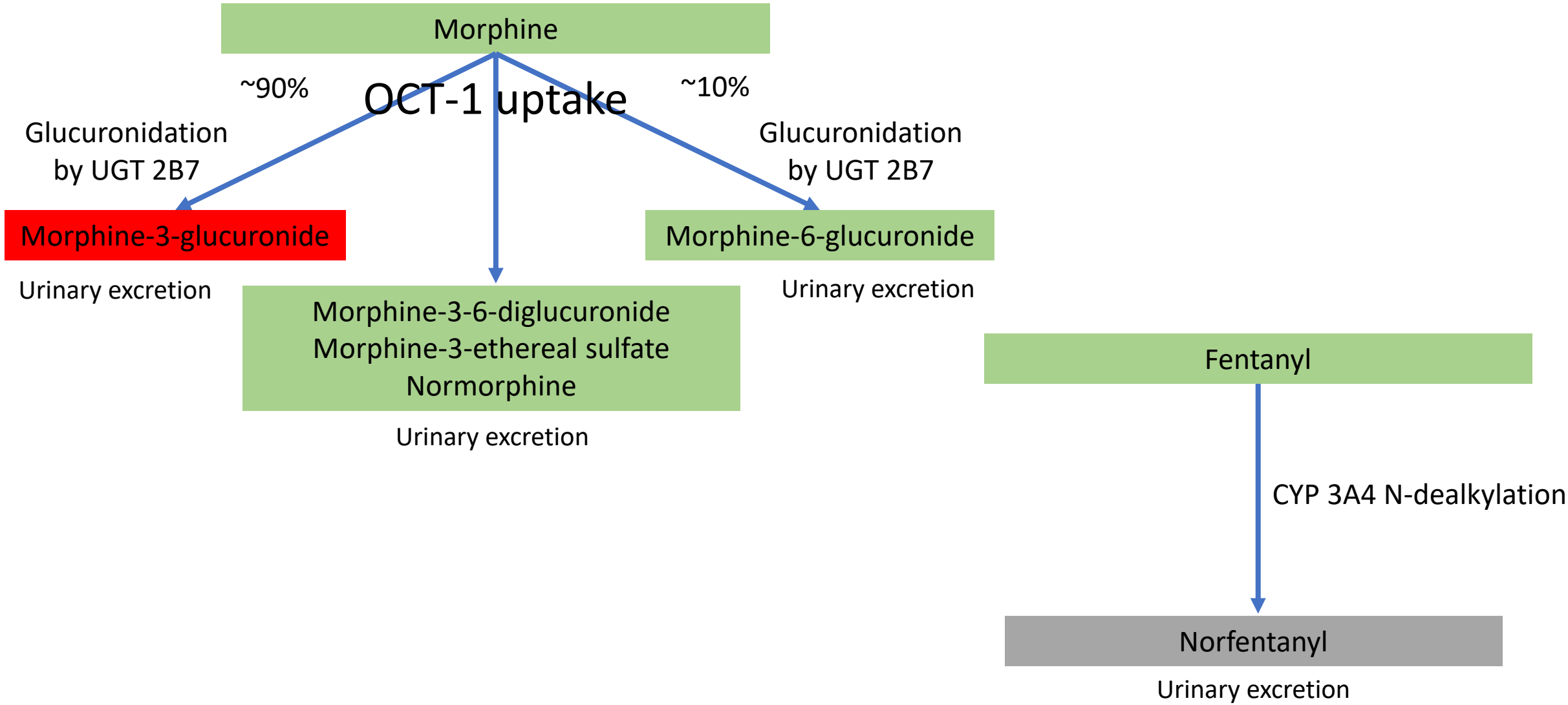
Morphine pharmacokinetics in therapeutic hypothermia



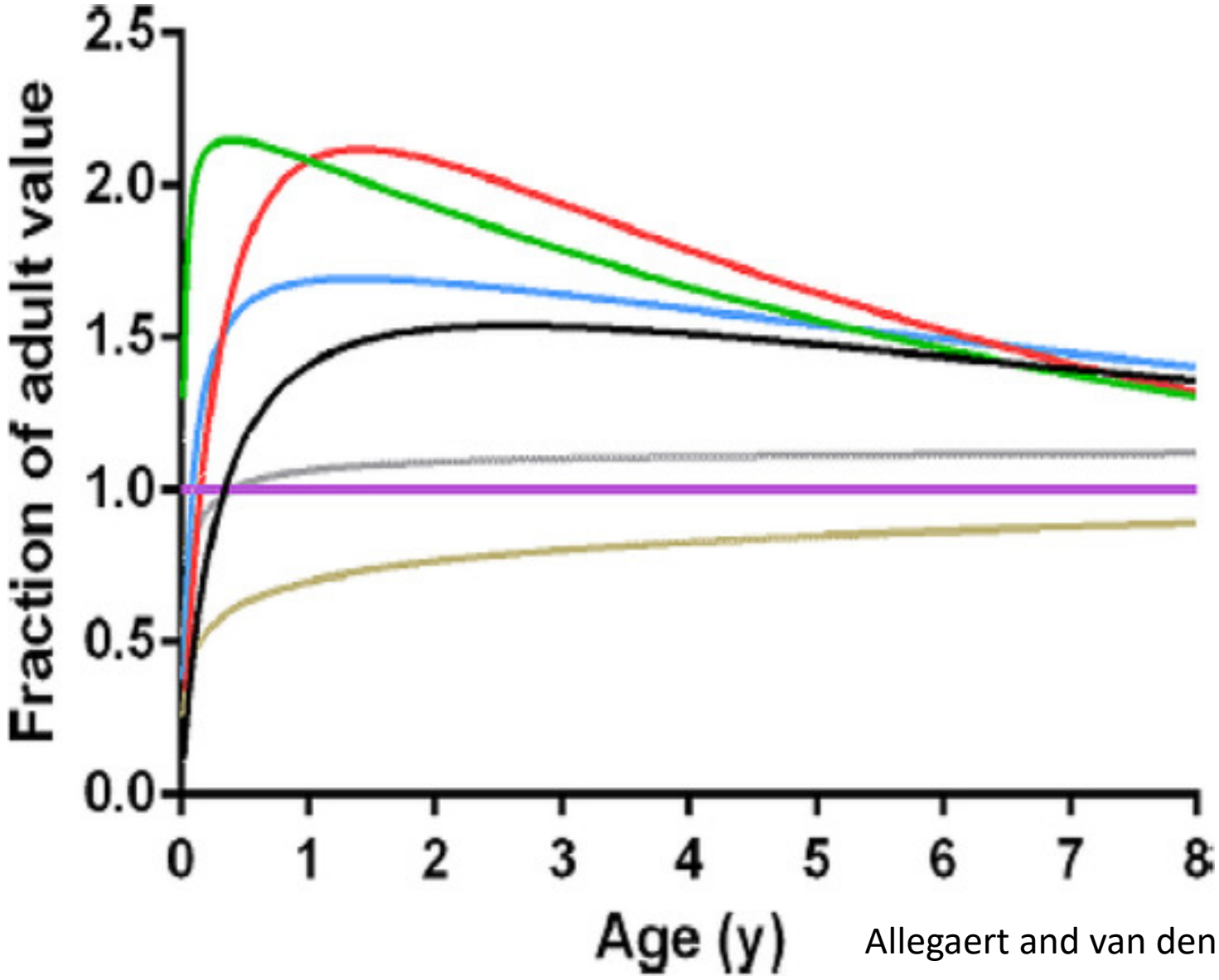
Frymoyer, Bonifacio, et al. J Clin Pharmacol 2017; 57: 64-76.

Favie, Groenendaal, the PharmaCool study group. PLoS One 2019; 14: e0211910.

Opioid metabolism



Ontogeny of major hepatic CYP enzymes



CYP 3A

CYP 1A2

CYP 2C19

CYP 2C9

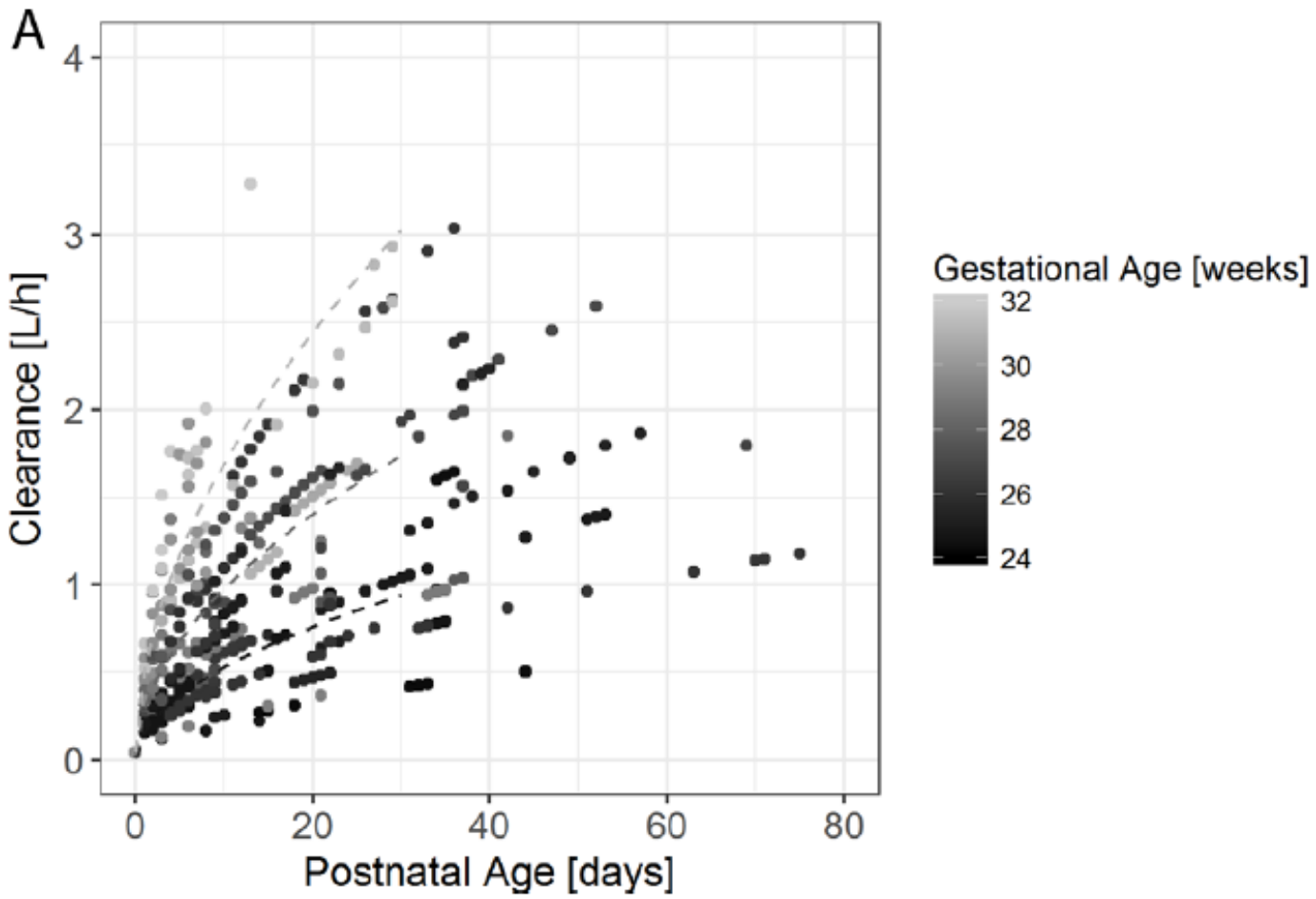
CYP 2A6

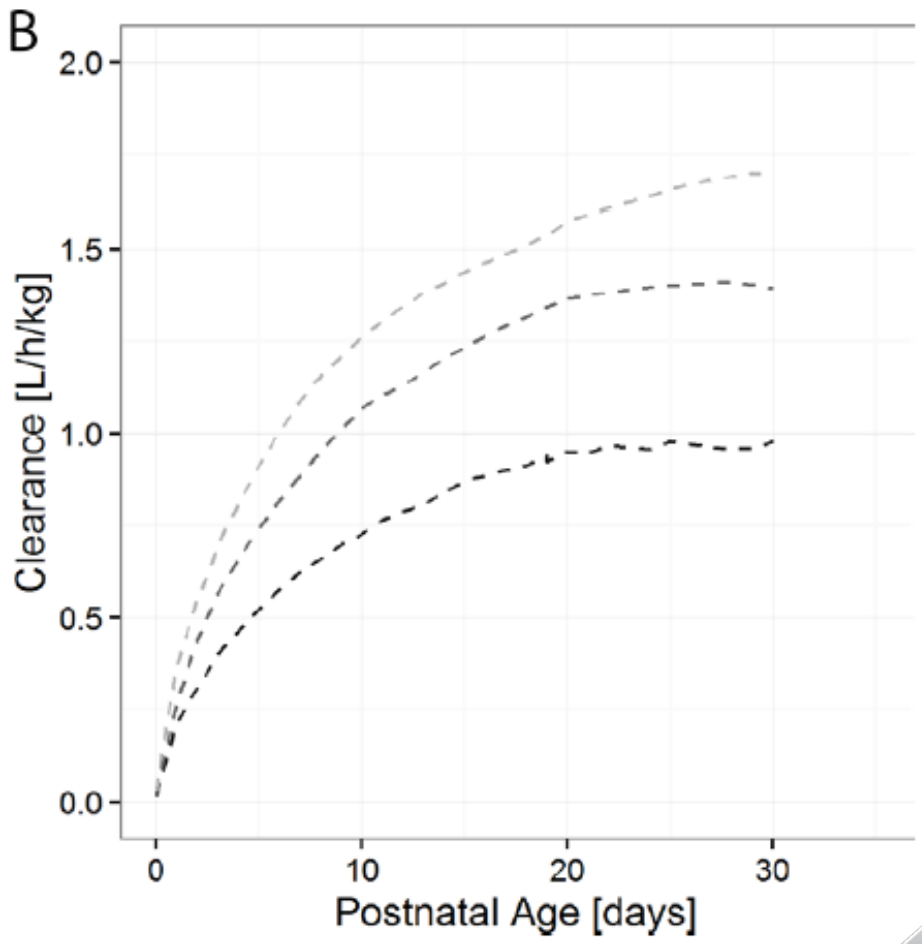
CYP 2B6 and 2D6

CYP 1E2

Allegaert and van den Anker. J Clin Pharmacol 2019; 59: S33-S41.

Fentanyl pharmacokinetics in preterm neonates





Voller, Flint, DINO study group. Arch Dis Child Fetal Neaontal Ed 2019; 104: F598-F603.

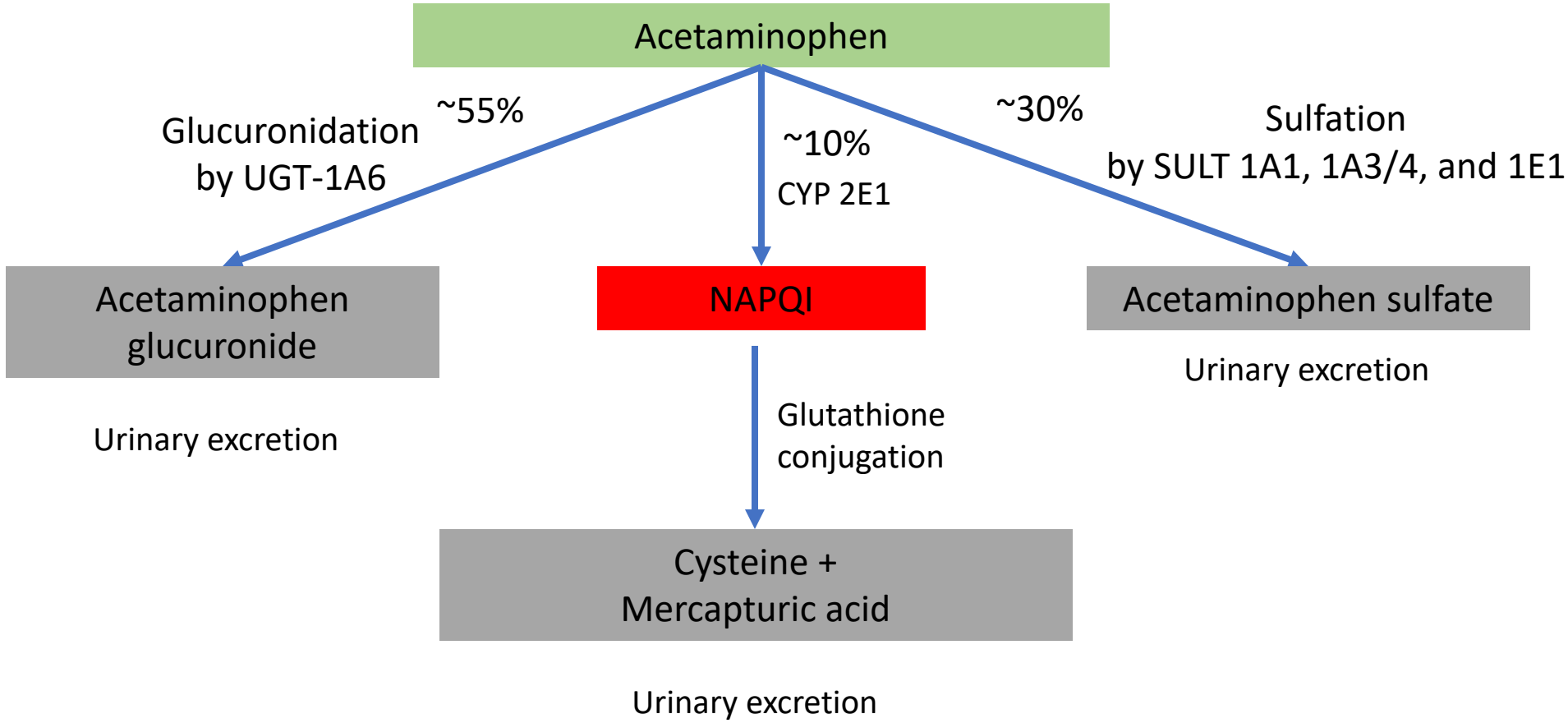
Developmental formulations

- 1 mcg/kg x 1 kg ÷ 50 mcg/mL = 0.02 mL

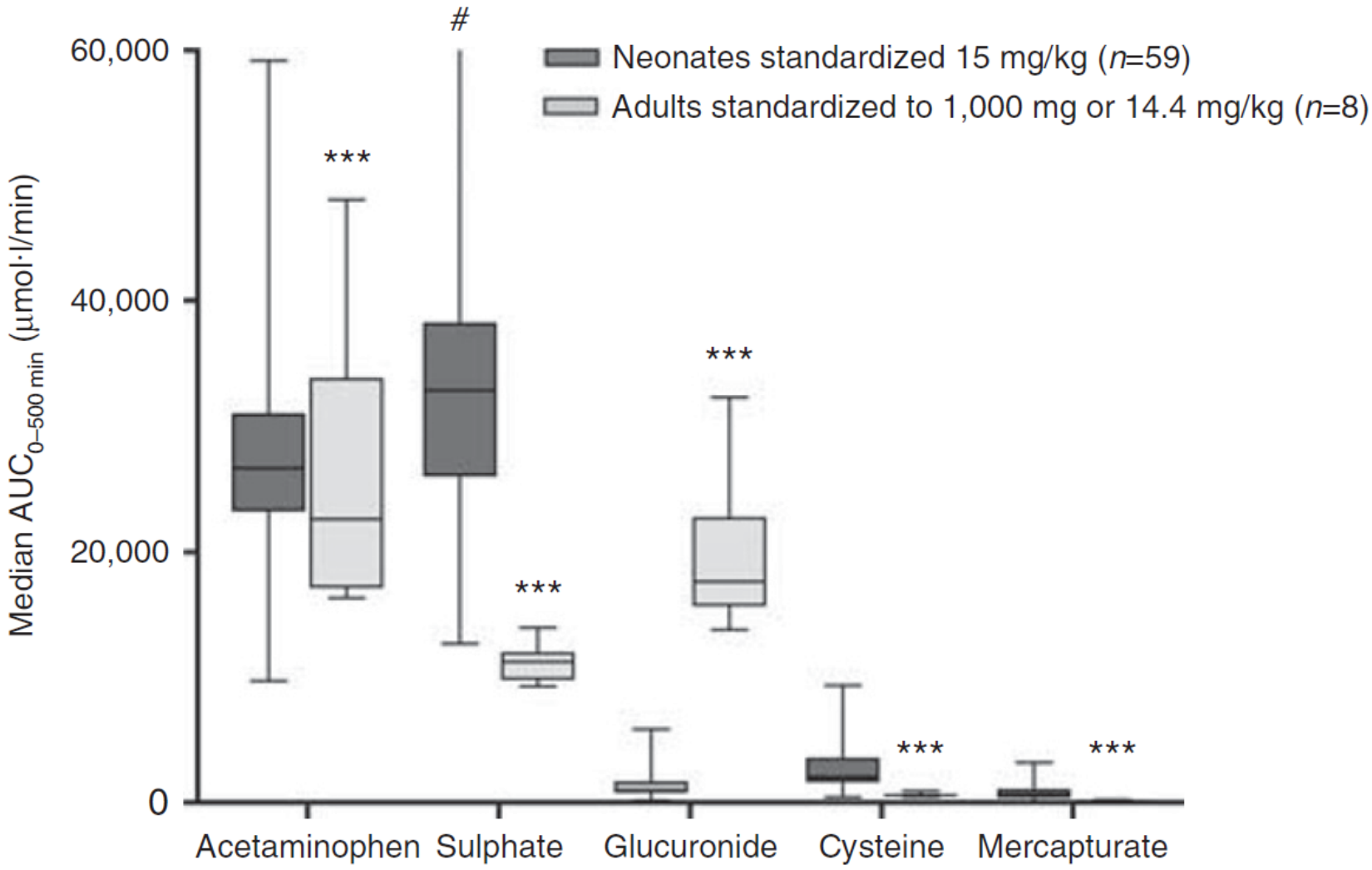
- 1 mcg/kg x 1 kg ÷ 5 mcg/mL = 0.2 mL

McCluskey et al. Am J Health Syst Pharm 2009; 66: 860-863.

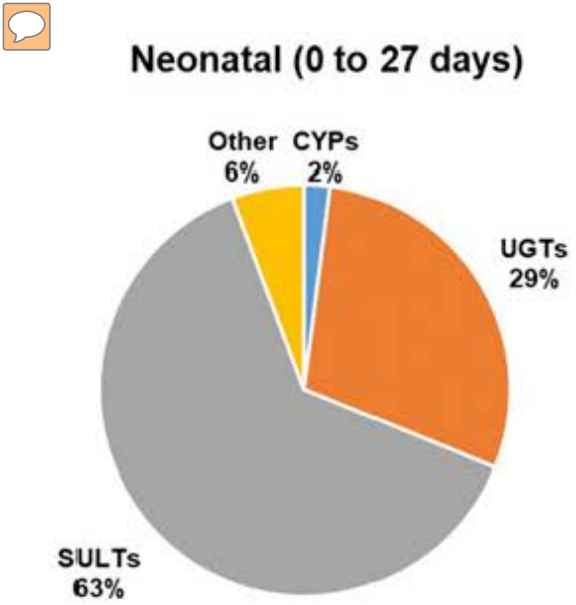
Acetaminophen metabolism

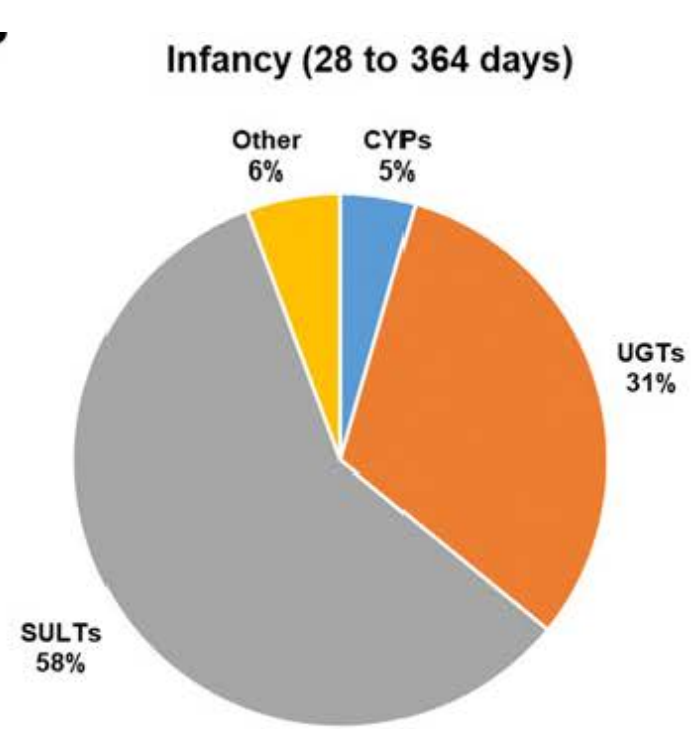


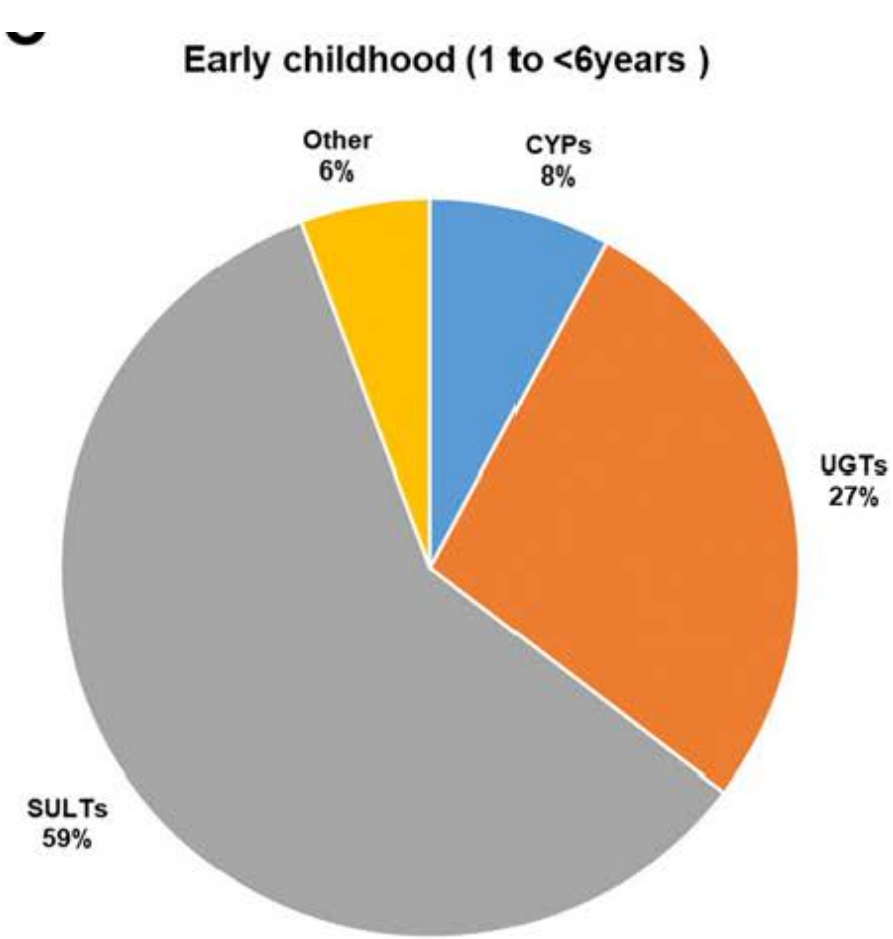
Ontogeny of acetaminophen elimination pathways in VPT neonates

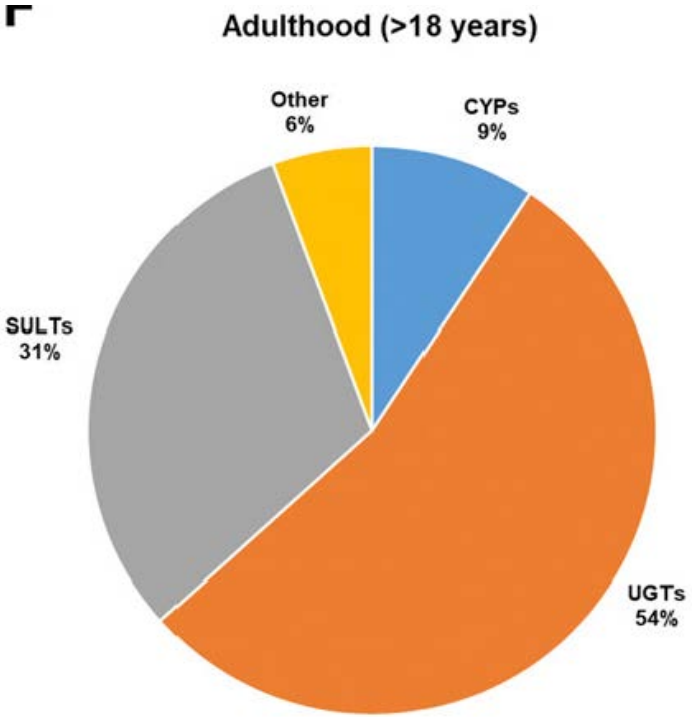


Flint et al, Simons. Pediatr Res 2017; 82: 678-84.





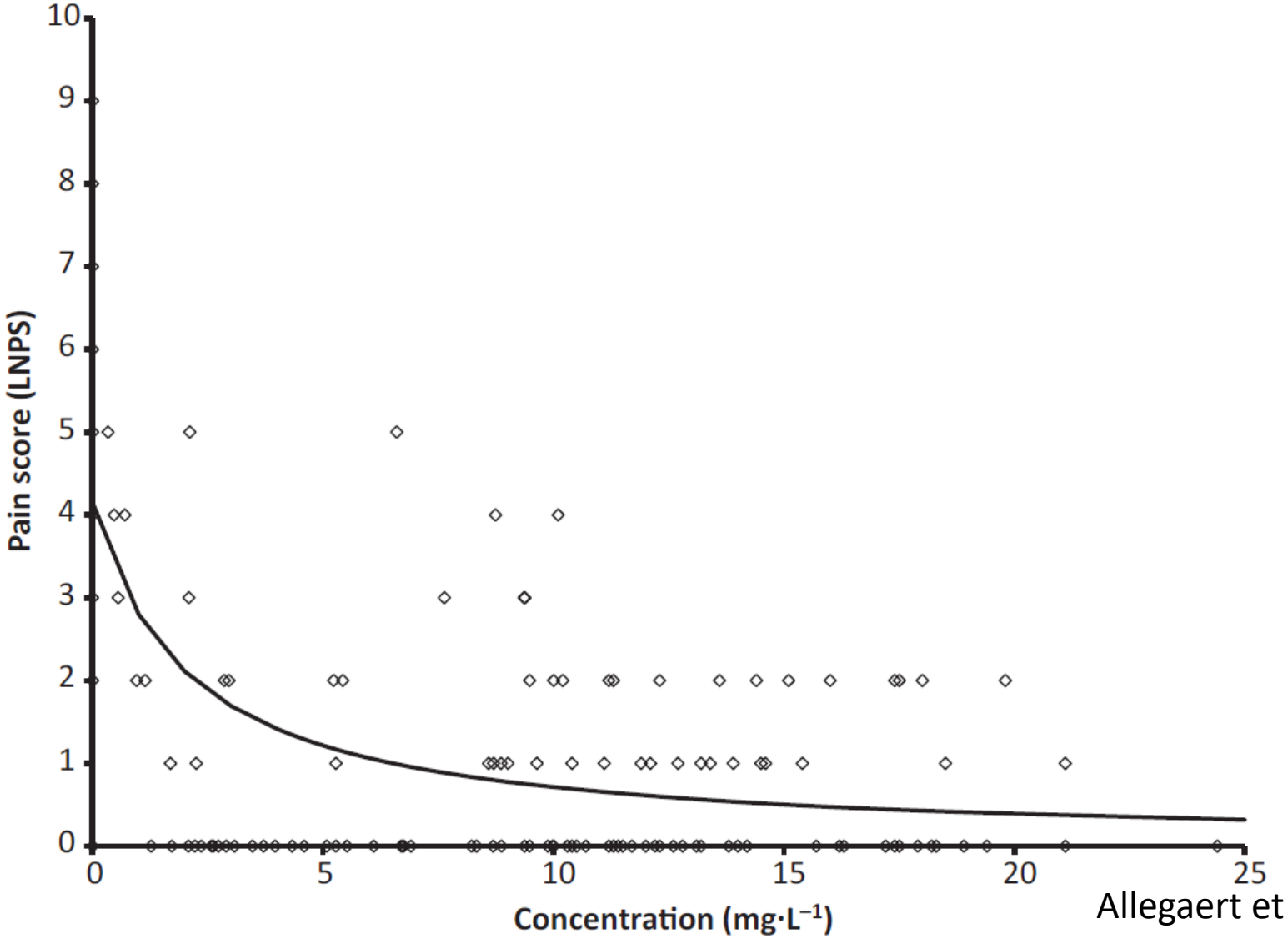




Ontogeny of acetaminophen elimination pathways

Ladumor et al. Drug Metab Dispos 2019; 47: 818-831.

Acetaminophen PD



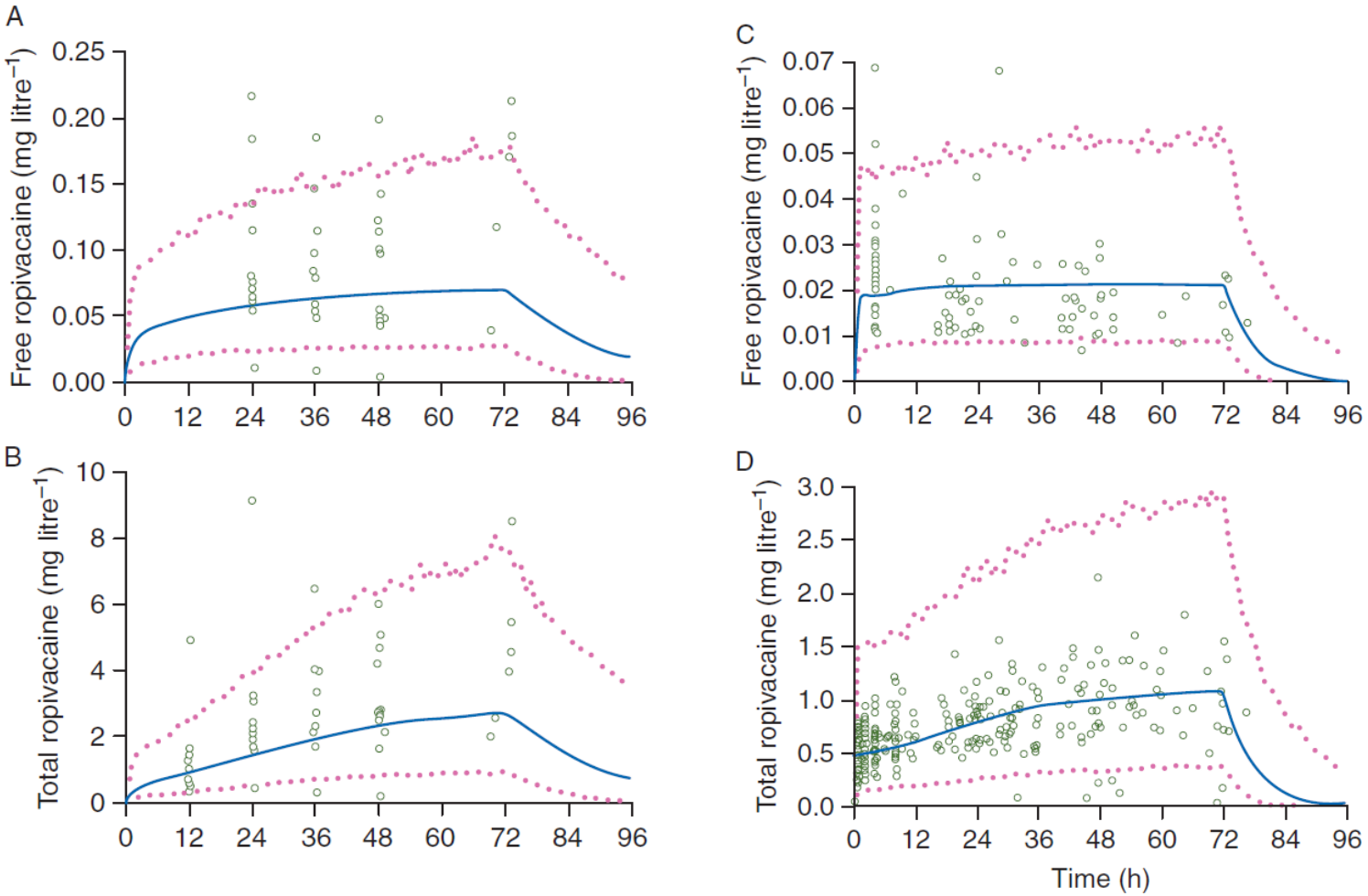
Allegaert et al. Paediatr Anaesth 2013; 23: 45-50.

Local anesthetics in brief

- Metabolism mediated by CYP enzymes, highly protein bound

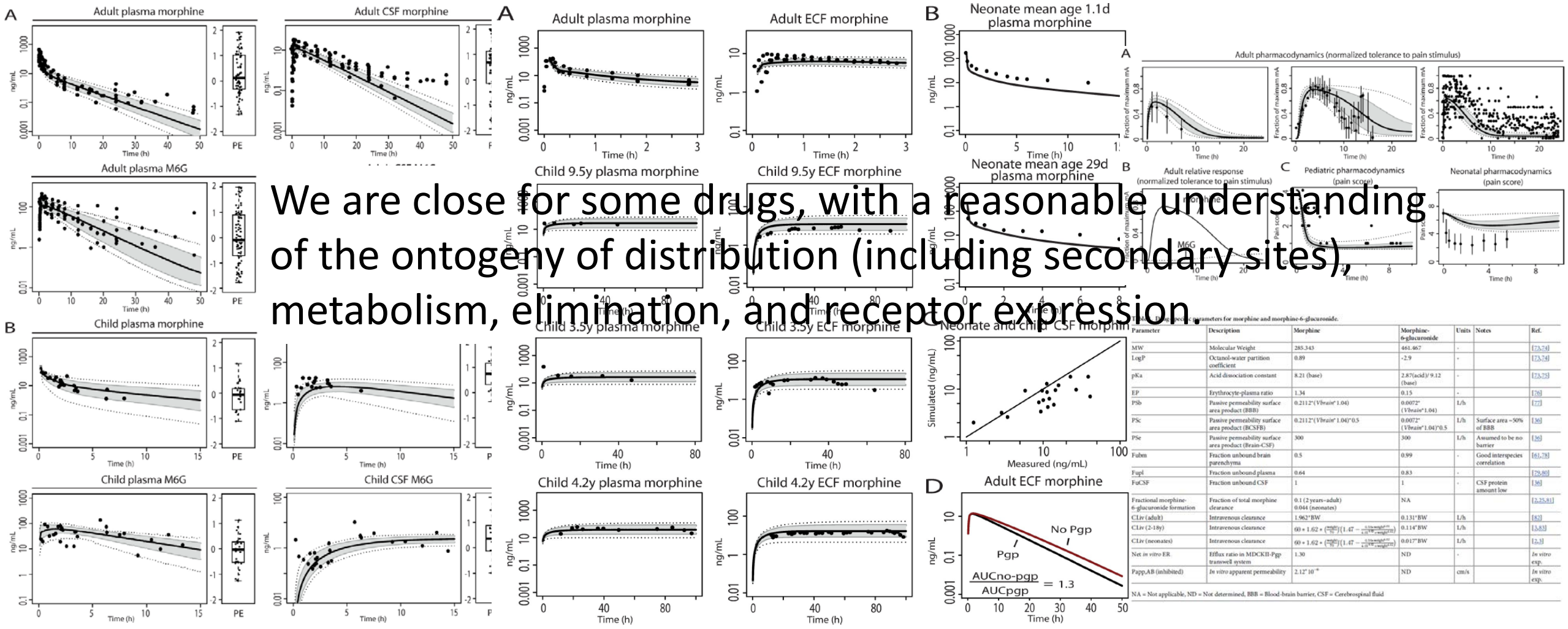
0-1 month receiving 0.2 mg/kg/hr

1-12 years receiving 0.4 mg/kg/hr



Aarons et al. Br J Anaesth 2011; 107: 409-424.

Are we there yet?



We are close for some drugs, with a reasonable understanding of the ontogeny of distribution (including secondary sites), metabolism, elimination, and receptor expression

Parameter	Description	Morphine	Morphine-6-glucuronide	Units	Notes	Ref.
MW	Molecular Weight	285.343	461.467	-		[73,74]
LogP	Octanol-water partition coefficient	0.89	-2.9	-		[73,74]
pKa	Acid dissociation constant	8.21 (base)	2.87(acid)/ 9.12 (base)	-		[73,75]
EP	Erythrocyte-plasma ratio	1.34	0.15	-		[76]
PSb	Passive permeability surface area product (BBB)	0.2112*(*Vbrain** 1.04)	0.0072* (*Vbrain**1.04)	L/h		[77]
PSc	Passive permeability surface area product (BCSFB)	0.2112*(*Vbrain** 1.04)*0.5	0.0072* (*Vbrain**1.04)*0.5	L/h	Surface area ~50% of BBB	[36]
PSe	Passive permeability surface area product (Brain-CSF)	300	300	L/h	Assumed to be no barrier	[36]
Fubm	Fraction unbound brain parenchyma	0.5	0.99	-	Good interspecies correlation	[61,78]
Fupl	Fraction unbound plasma	0.64	0.83	-		[79,80]
FuCSF	Fraction unbound CSF	1	1	-	CSF protein amount low	[36]
Fractional morphine-6-glucuronide formation	Fraction of total morphine clearance	0.1 (2 years–adult) 0.044 (neonates)	NA			[2,25,81]
CLiv (adult)	Intravenous clearance	1.962*BW	0.131*BW	L/h		[82]
CLiv (2-18y)	Intravenous clearance	$60 * 1.62 * \left(\frac{weight}{70}\right)^{0.75} \left(1.47 - \frac{0.15 * weight^{0.75}}{4.15^{0.75} + weight^{0.75}}\right)$	0.114*BW	L/h		[3,83]
CLiv (neonates)	Intravenous clearance	$60 * 1.62 * \left(\frac{weight}{70}\right)^{0.75} \left(1.47 - \frac{0.15 * weight^{0.75}}{4.15^{0.75} + weight^{0.75}}\right)$	0.017*BW	L/h		[2,3]
Net *in vitro* ER	Efflux ratio in MDCKII-Pgp transwell system	1.30	ND	-		*In vitro* exp.
Papp,AB (inhibited)	*In vitro* apparent permeability	$2.12 * 10^{-6}$	ND	cm/s		*In vitro* exp.

NA = Not applicable, ND = Not determined, BBB = Blood-brain barrier, CSF = Cerebrospinal fluid

Verscheijden et al. PLoS Comput Biol 2021; 17: e1008786
Eerdekens et al, van den Anker. J Pain Res 2019; 12: 1649-1664.

My tentative conclusions

- We have made tremendous progress to understand the ontogeny of various systems impacting drug pharmacokinetics
  - Pharmacokinetic extrapolation across age groups is hindered by the importance of all aspects of developmental pharmacokinetics
- Larger gaps exist in our knowledge of effective site concentrations and receptor ontogeny.
- Different classes of drugs have different pitfalls.
- Both short-term and long-term safety studies are vital.
  - Formulation may influence short-term safety.