Methadone dosing strategies in preterm neonates can be simplified

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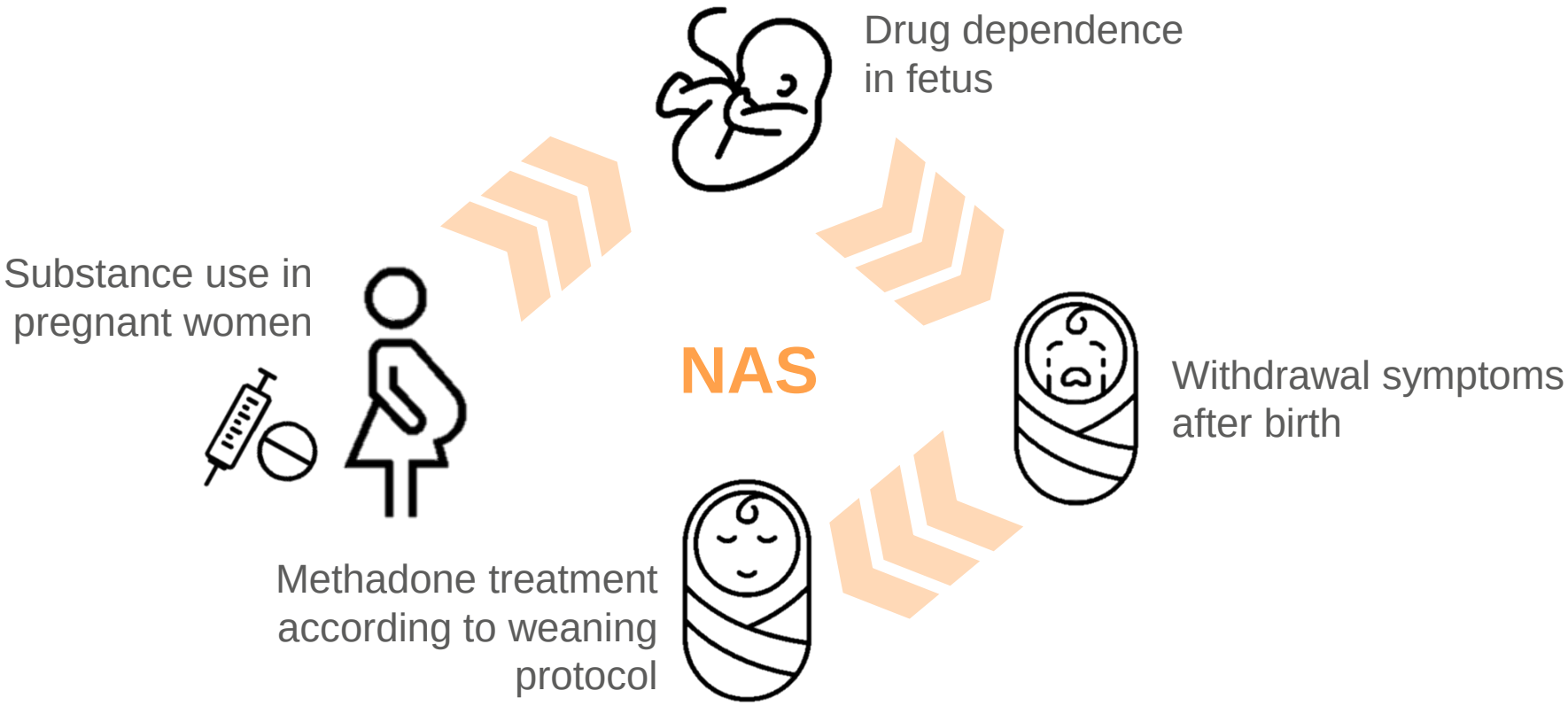
Neonatal abstinence syndrome



Current knowledge & research questions

Current knowledge

- Maternal opioid usage is increasing [1]
- Better short-term outcomes in infants who received methadone compared to morphine [2]
- Current recommendations are often quite complex and require weaning period

Research questions

- Characterize pharmacokinetics (PK) of methadone in preterm neonates?
- Influence of age & weight on PK profile of methadone in preterm neonates?
- Assess target exposure levels?
- Can dosing protocol be simplified?

Outcome	Methadone (n = 58)	Morphine (n = 58)
LOS		
Mean (SD)	21.8 (15.0)	23.2 (8.8)
Median (IQR)	16 (14 to 22)	20 (16 to 27)[c]

LOS = Length of stay

… YES

[1] JAMA 2012;307 (18):1934-40
[2] JAMA 2018;172 (8): 741-48

How to answer these questions?

1. Characterize pharmacokinetic data
   - Single center open-label PK study in preterm neonates
   - 0.1 mg/kg po methadone

2. Develop population PK model
   - Estimate PK parameters (CL, Vd)
   - Assess influence of demographics (weight / postnatal age / …)

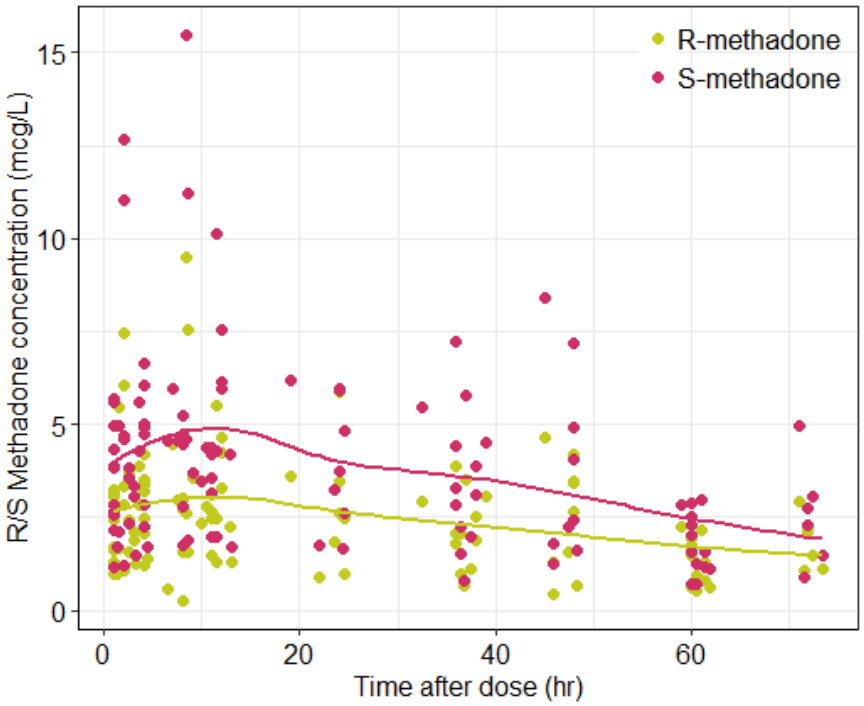
3. Evaluate methadone dosing recommendations
   - Investigate exposure levels (AUC)
   - Examine feasibiliy of current and simplified dosing recommendations

CL = Clearance
Vd = Volume of distribution
AUC = Area under the curve

Results - Pharmacokinetic data

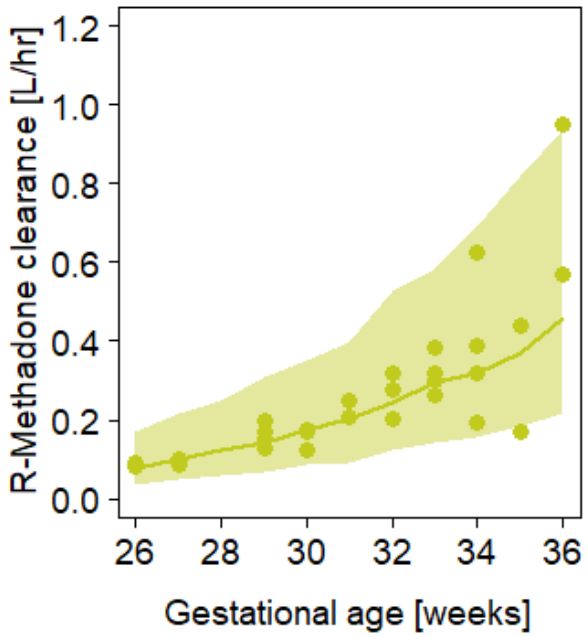
Study participants (n=31) Median (range)	
Bodyweight (kg)	1.6 (0.93 – 2.7)
Gestational age (weeks)	32 (26 – 36)
Postnatal age (days)	3 (0 – 15)
Post menstrual age (weeks)	32 (26 – 37)
Maternal age (years)	25 (17 – 34)
Sex	
Female	10 [32%]
Male	20 [65%]
Unknown	1 [3%]

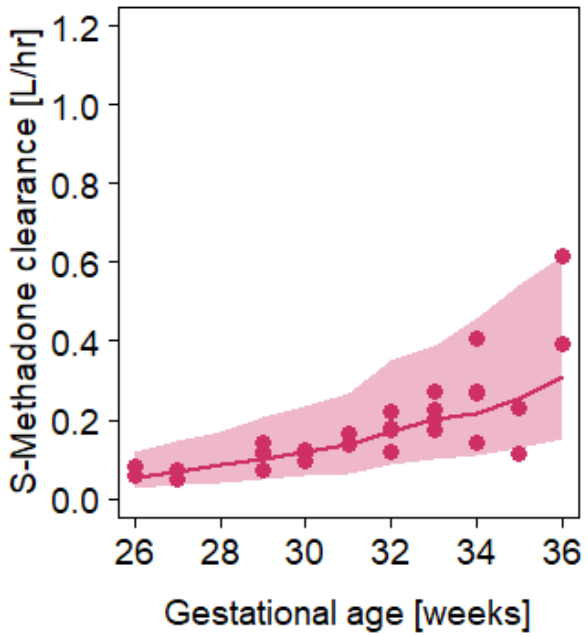
121 methadone plasma concentrations



Results - PK parameters

1. One-compartment model, first-order absorption and elimination kinetics
2. CL increases with advancing gestational age
3. CL values are higher for R-methadone (0.244 L/h) as compared to S-methadone (0.167 L/h)



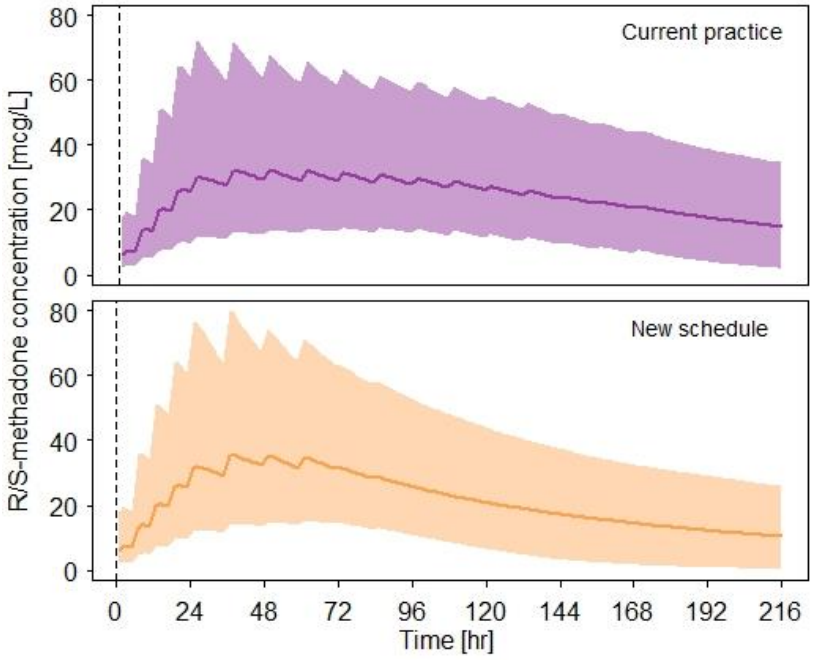


CL = Clearance

Results - Dosing strategies

Methadone exposure

	Current practice (mg/kg)	New schedule (mg/kg)	Frequency
Day 1	0.1	0.1	q6 x 4
Day 2	0.075	0.1	q12 x 2
Day 3	0.05	0.05	q12 x 2
Day 4	0.04	0.01	q12 x 2
Day 5	0.03	-	q12 x 2
Day 6	0.02	-	q12 x 2
Day 7	0.01	-	q12 x 2
Day 8	0.01	-	q24 x 1



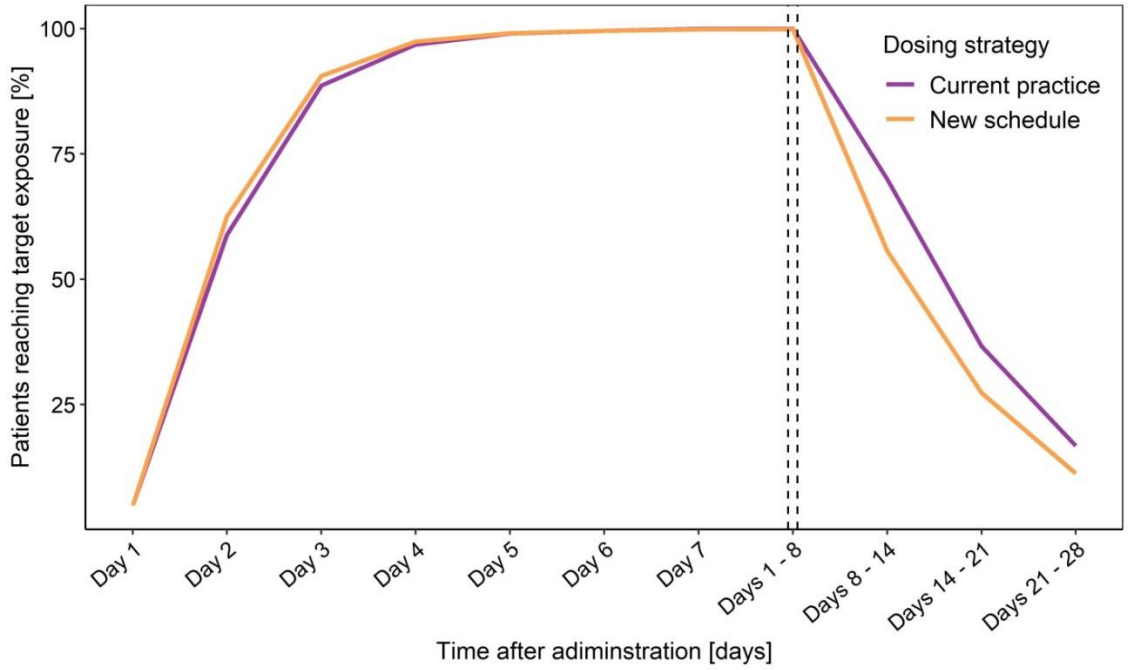
Target exposure ?
985 mcg·h/L [1]

[1] JPEDS 2015, 167: 1214-20

Results - Dosing strategies

Target methadone exposure

Dosing protocol	Percentage (%) reaching target exposure of 985 mcg·h/L											
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Days 1-8	Days 8-14	Days 14-21	Days 21-28
Current practice	5	59	89	97	99	100	100	100	100	70	37	17
New schedule	5	62	91	97	99	100	100	100	100	56	27	11



Conclusion

- Clearance of methadone ***increases*** with advancing gestational age

- Pharmacokinetic ***differences*** between the two enantiomers were observed (higher CL for R-methadone)

- Complex dosing schemes could be replaced by a ***simplified*** and ***shortened*** dosing strategy (validation study required!)

Discussion

- Unexplained variability
  - Polymorphisms of CYP2B6 enzyme
- Breastfeeding effect
  - Neonatal exposure through breastmilk is minimal
  - Decreased severity of NAS has been observed (effect due to methadone **or** calming and nursing effect of breastfeeding)
- Target exposure applied from earlier research in term neonates

- Future steps
  - Validation study of simplified methadone dosing strategies combined with assessment of genetic information

Acknowledgements

- Prof. John van den Anker
- Prof. Marc Pfister
- Dr. Samira Samiee-Zafarghandy
- Dr. Gilbert Koch

- Disclose of conflict of interest
  - The authors declare no conflicts of interest
- Grants

  - Eckenstein-Geigy Foundation, Basel, Switzerland
  - National Institute of Drug Addiction (K24DA027992)

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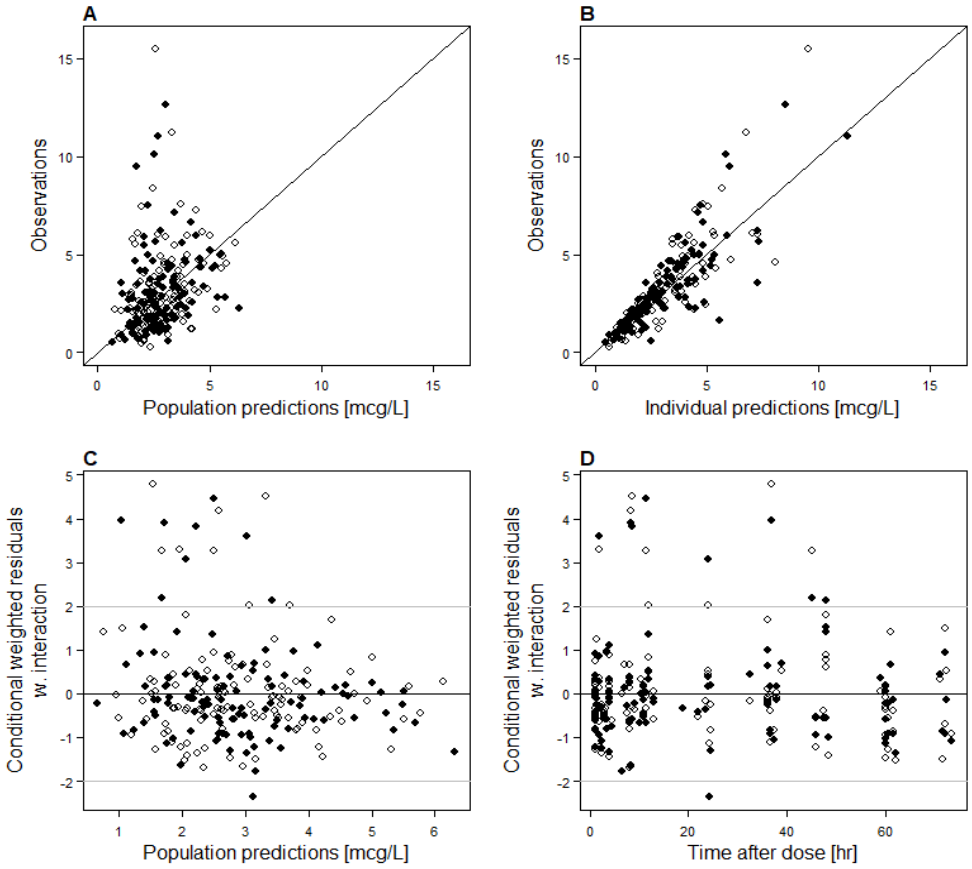
Goodness of fit

Final PK model



Parameter estimates

Final PK model

Parameter	(R)-methadone				(S)-methadone			
	Estimate	% RSE	Bootstrap analysis		Estimate	% RSE	Bootstrap analysis	
			Median	95% CI			Median	95% CI
Population parameters								
K_a (h^{-1})	1.73	0.57	1.69	1.15-2.90	2.65	0.08	1.20	0.79-1.89
V_d/F (L)	26.9	1.89	27.5	21.9-33.2	18	0.13	16.73	13.77-19.95
CL/F (L/h)	0.24	0.04	0.25	0.18-0.33	0.17	5.24	0.18	0.12-0.23
GA effect	5.29	1.75	5.86	3.14-9.07	5.16	0.46	4.99	1.94-8.74
Inter-individual variability - % CV*								
K_a (h^{-1})	0.05	-	-	-	0.05	-	-	-
V_d/F (L)	0.39	69	0.36	0.21-0.56	0.30	59	0.33	0.16-0.54
CL/F (L/h)	0.20	47	0.19	0.009-0.4	0.19	46	0.18	0.02-0.42
Residual variability								
Proportional error	0.106	-	0.101	0.07-0.13	0.115	-	0.102	0.06-0.13

$$P_i = \theta_1 * \left(\frac{GA}{GA_{median}} \right)^{\theta_2}$$