

Modelling withdrawal symptoms in critically ill children

Bas Goulooze, Erwin Ista, Monique van Dijk, Dick Tibboel, Elke Krekels, Catherijne Knibbe



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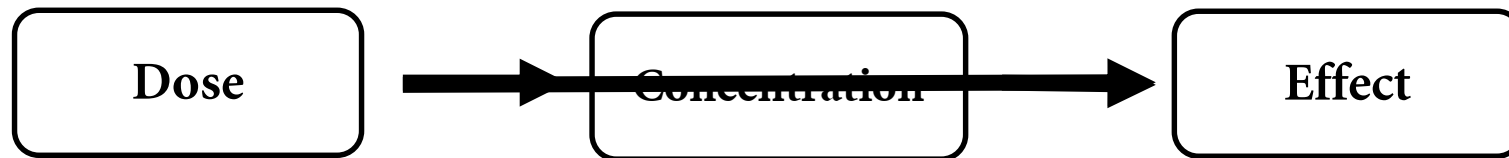
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Introduction

- Iatrogenic withdrawal= ‘brought forth by healer’
 - Analgesics and sedatives
- How to achieve optimal weaning?
 - Heterogenous population, difficult to study
- Model available data, then simulate ‘what if’ scenarios

Pharmacometrics 1.0



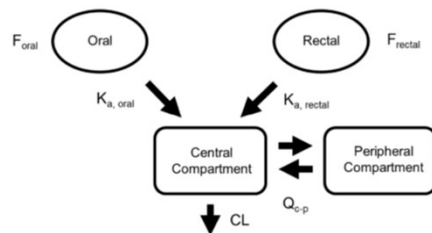
- Concentration important 'tool' to predict effect
 - Especially in children
- Dose → concentration well characterized, concentration → effect often unknown

Clinical data

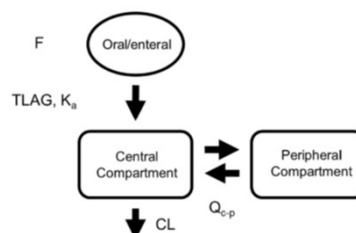
- Observation study (Ista et al.)
 - Sophia Children's hospital in Rotterdam
 - N=81 patients, 1 month to 17 years old
 - Drug administration history during intensive care stay
- Data: 1782 withdrawal assessments
 - Nurse score withdrawal severity (0 – 10)
- Problem: no concentration data
 - Ethical constraints for blood sampling in children
 - Patients receive multiple drugs simultaneously

Solution: use existing models

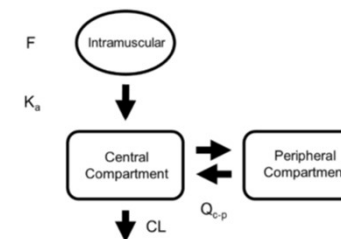
Morphine



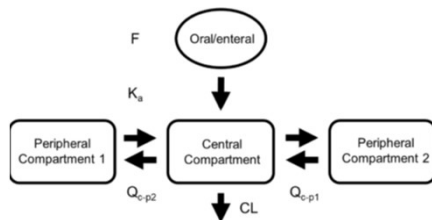
Clonidine



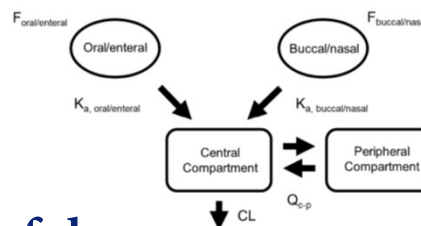
Ketamine



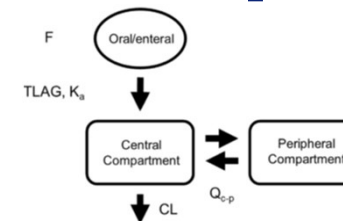
Methadone



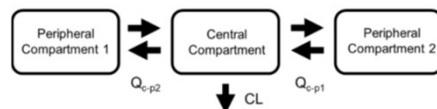
Midazolam



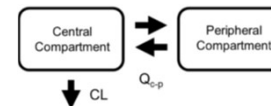
Lorazepam



Propofol



Fentanyl

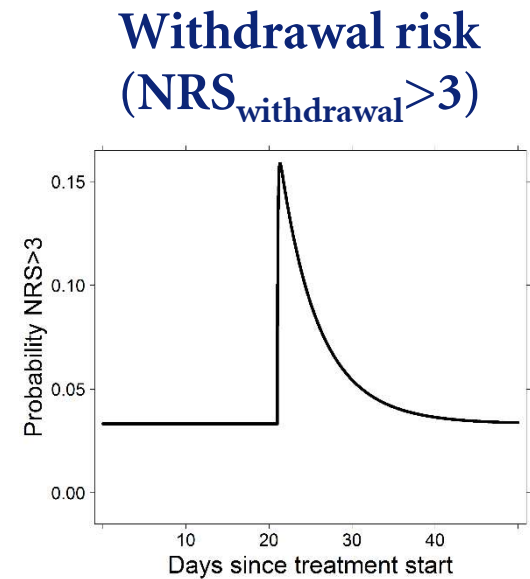
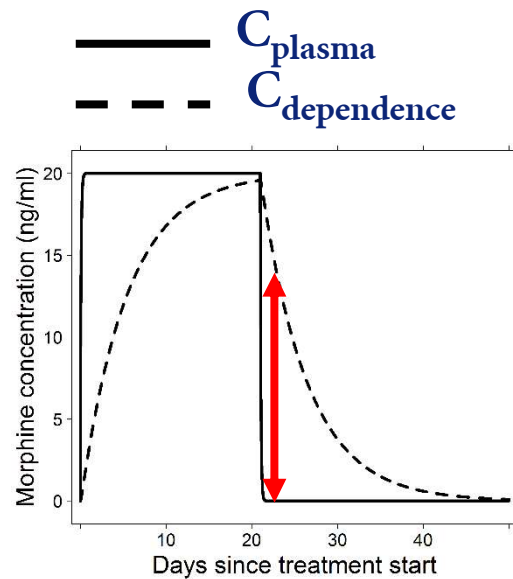
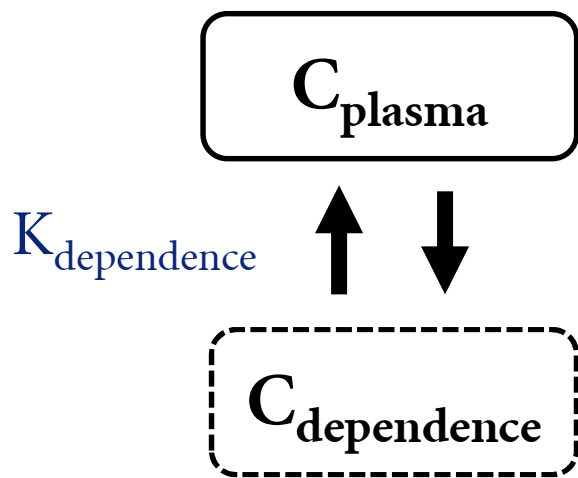


How to model withdrawal symptoms?



Existing models to link concentration to effect failed!

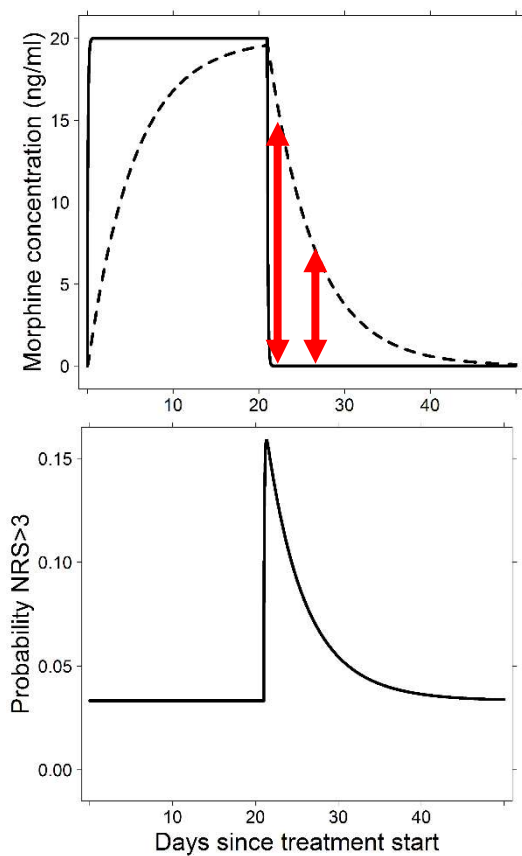
Illustration withdrawal model



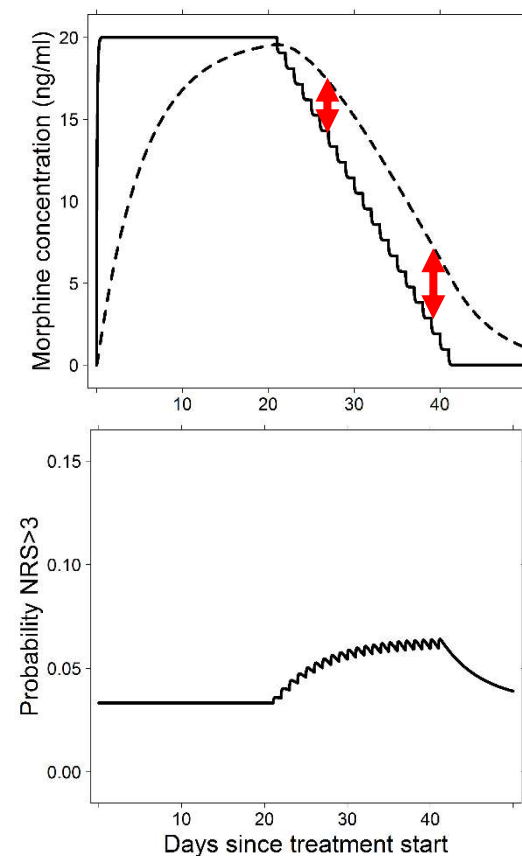
Withdrawal dynamics quantified for:
morphine, ketamine and fentanyl

Explore weaning strategies (morphine)

No weaning



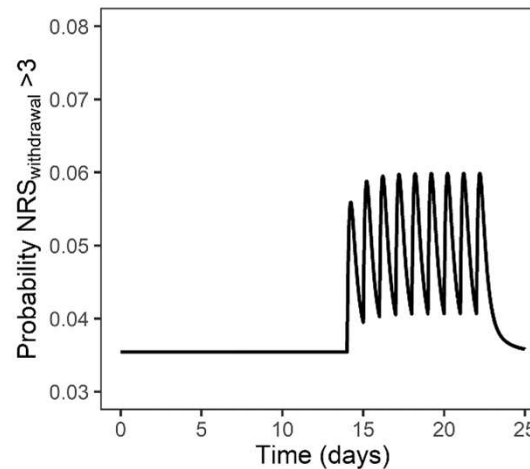
Weaning
(3 weeks)



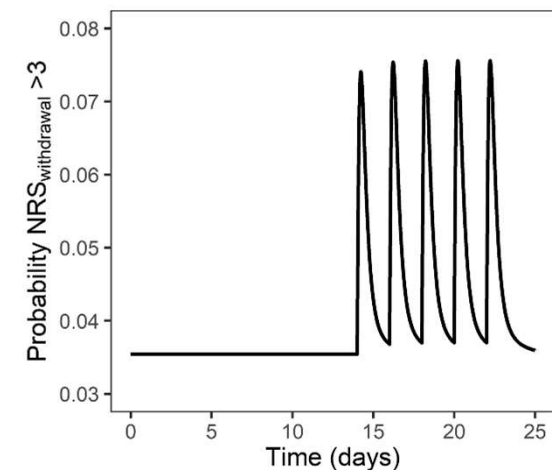
Slow but steady wins the race for fentanyl?

- Lower peak withdrawal with more frequent but smaller steps for fentanyl
- Fentanyl reported to be more likely to cause withdrawal compared to morphine

Small weaning steps
every 24h



Large weaning steps
every 48h



Discussion

- Available literature models allowed pharmacometric modelling despite lack of concentration data
 - Applications to real-world data?
- New model able to link drug concentration profiles to withdrawal risk in children
- Simulations generating new clinical hypotheses on optimal weaning strategies

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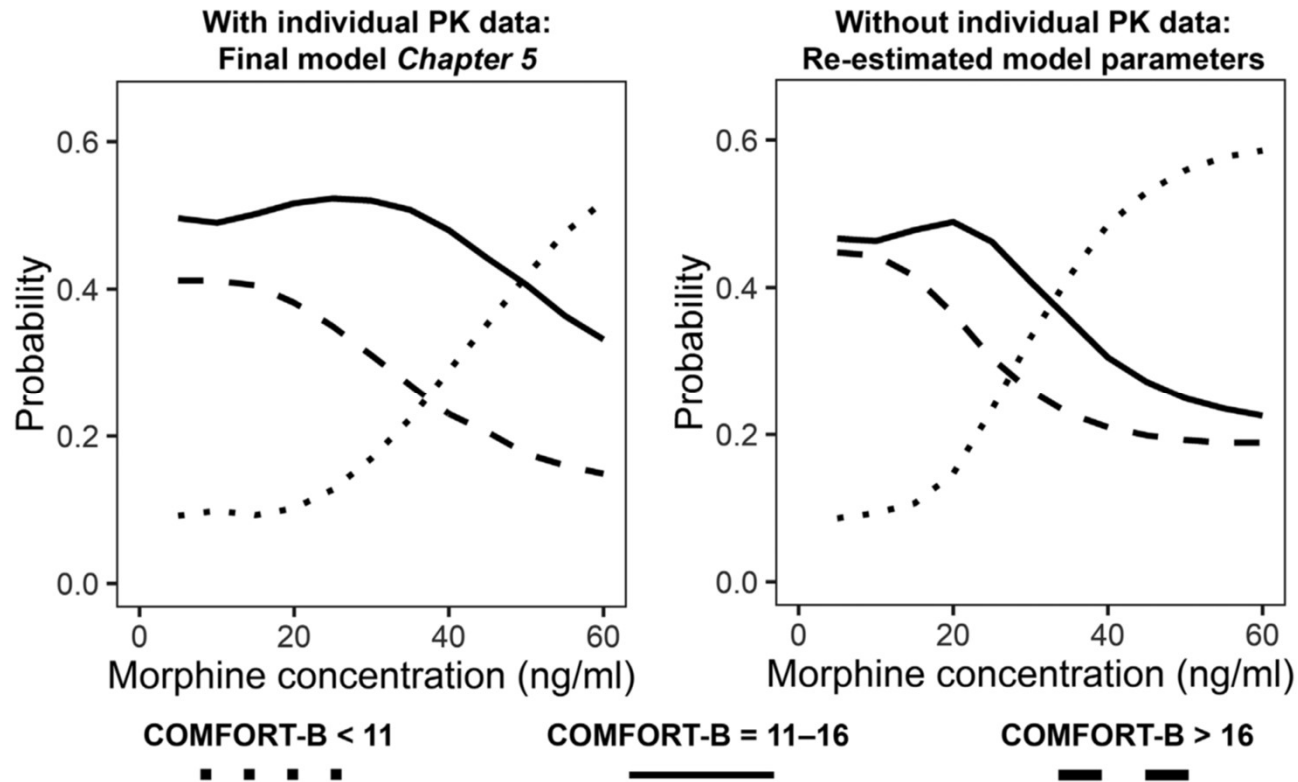


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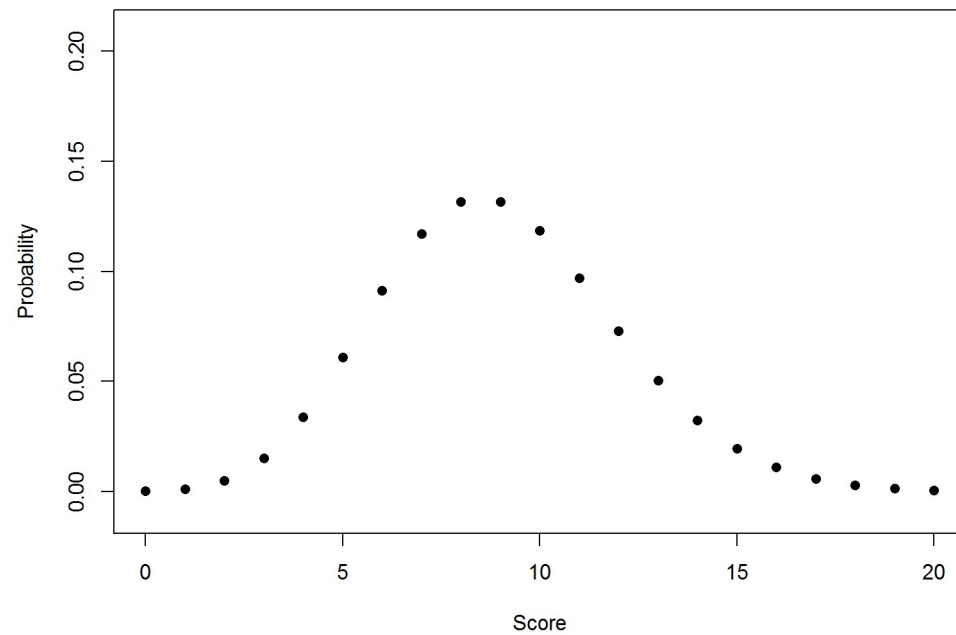
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Do we always need concentration data?

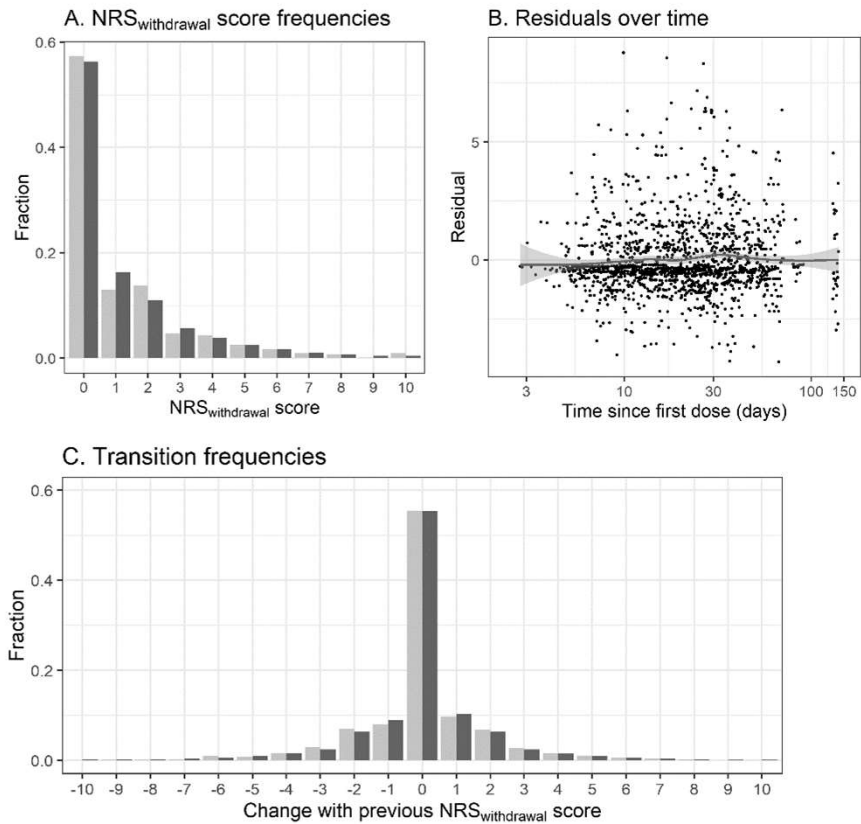


Truncated Poisson

- Markovian probability inflation to account for correlations of subsequent observations



Diagnostics



Panels A and C compare observed (light grey) vs simulated (dark grey) data.

Iatrogenic withdrawal symptoms

Autonomic dysfunction		
1	Tachycardia	<input type="checkbox"/> Yes if heart rate exceeds baseline value by $\geq 15\%$.
2	Tachypnea	<input type="checkbox"/> Yes if breathing rate exceeds baseline value by $\geq 15\%$.
3	Fever	<input type="checkbox"/> Yes if body temperature exceeded 38.4°C in past 4 hours.
4	Sweating	<input type="checkbox"/> Not caused by room temperature, clothing, swaddling e.g.
Central nervous system irritability		
5	Agitation	<input type="checkbox"/> Yes if child shows at least one of these signs: irritable, restless, agitated, fidgety.
6	Anxiety	<input type="checkbox"/> Unrest or anxious face (eyes wide open, eyebrows tense and raised). Behavior can vary from panicky to draw back.
7	Tremors: <i>(pick one)</i>	Slight, involuntary rhythmic movements of hand and/or feet.
	• Spontaneous	<input type="checkbox"/> <i>Note: please turn over for instructions.</i>
	• In response to environmental stimuli	<input type="checkbox"/>
8	Motor disturbance: <i>(pick one of four)</i>	
	Slight muscle jerks:	Involuntary, of forearms/lower legs, muscle twitching.
	• Spontaneous	<input type="checkbox"/>
	• In response to environmental stimuli	<input type="checkbox"/>
	Uncontrolled, robust movements:	Choreoathetosis of arms, legs and/or head.
	• Spontaneous	<input type="checkbox"/>
	• In response to environmental stimuli	<input type="checkbox"/>
9	Increased muscle tension	<input type="checkbox"/> Clenched fists or tense clenched toes.
10	Inconsolable crying	<input type="checkbox"/> Yes if child cannot be consoled by parents or by offering distraction, e.g. pacifier, food, or game playing for older children. Score silent crying in intubated children.
11	Grimacing	<input type="checkbox"/> Eyebrows contracted and lowered, nasolabial fold visible.
12	Sleeplessness	<input type="checkbox"/> Sleeps not more than 1 hour at a stretch.
13	Hallucinations	<input type="checkbox"/> During the past 4 hours child seems to see, hear or feel things that are not there.
Gastrointestinal dysfunction		
14	Vomiting	<input type="checkbox"/> At least once in past 4 hours, not related to feeding changes.
15	Diarrhea	<input type="checkbox"/> Watery stools, not related to feeding changes (do not score e.g. when the result of breastfeeding).