



Development of a Population PK-PD Model for Tapentadol to Assess Postoperative Pain in Children Aged 6 to <12 using Nonlinear Mixed-Effects Modelling

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Introduction and Objectives

- **Postoperative pain** in children is often managed using opioid drugs.
- McGrath's **Colour Analog Scale (CAS)**, measures the self-reported pain intensity of participants aged **above 6 years old**.
- Literature on PK-PD models utilising paediatric pain scale scores is **scarce**, mainly due to pain assessment **challenges** and opioid side effects concerns [1].
- Focusing on the PD component is key to linking opioid treatment with pain score assessment.
- PK and PD data, comprising Tapentadol **plasma concentrations**, CAS-derived **pain scores** (0-10), and respective **time points**, were obtained from the **NCT01729728 Clinical Trial** (<https://clinicaltrials.gov/study/NCT01729728>)

Objectives:

- To characterise the **kinetics** describing **postoperative acute pain** upon oral administration of **Tapentadol**, by developing a novel **PK-PD population model**.
- Identify which **coupling mechanisms** are more adept in encapsulating the observed pain indications applying the CAS as a measure.

Tapentadol's Drug Mechanism

Tapentadol has a **dual** mechanism of action:

1. Acts as a **μ -opioid receptor**, reducing pain perception.
2. **Inhibits noradrenaline reuptake**, regulating the pain pathways.

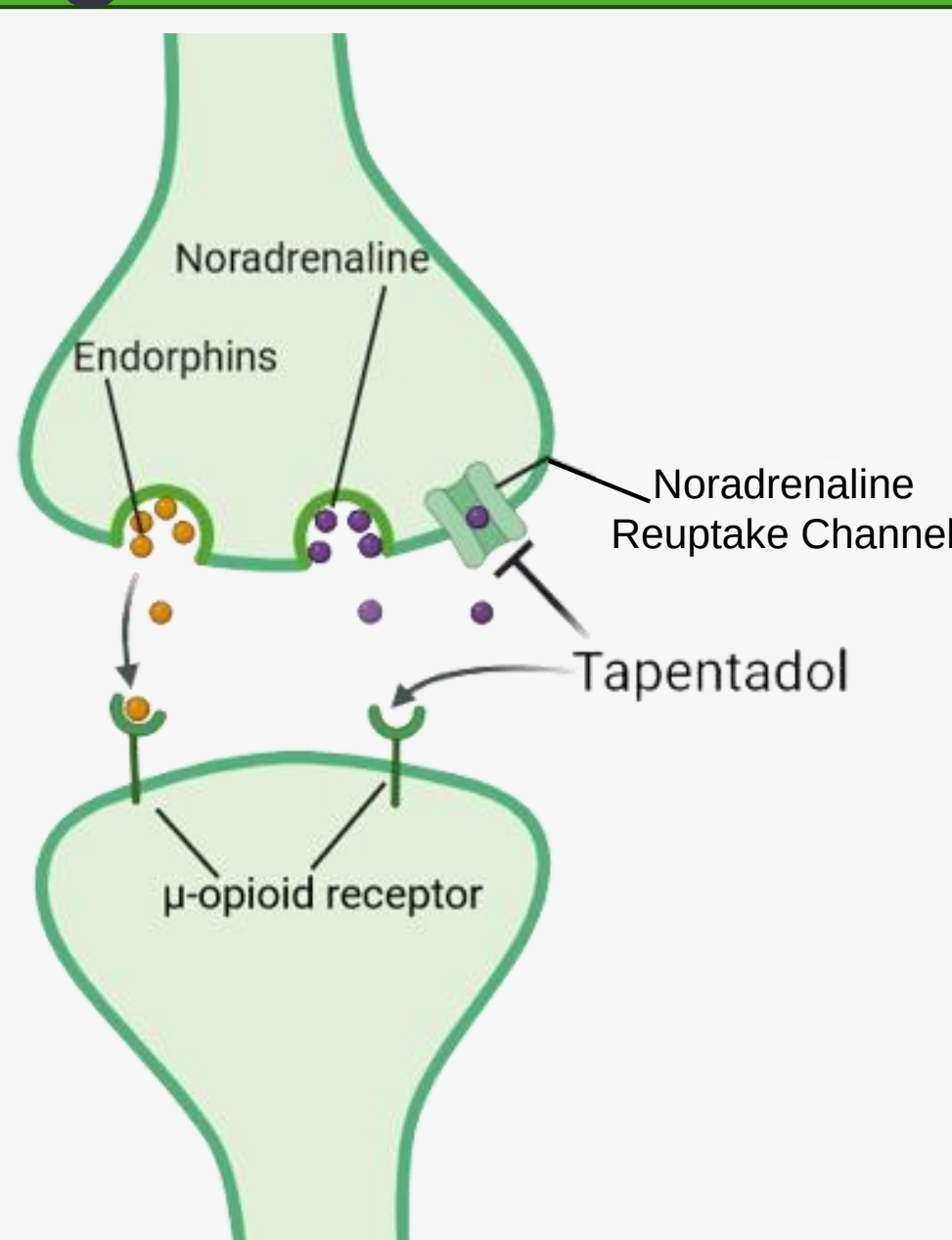


Figure 1: Drug mechanism of Tapentadol [2]

McGrath's Colour Analog Scale

- The CAS consists of a 145 mm long triangular strip of plastic, varying in width and hue [3].
 - Bottom (no pain): 1 mm wide & light pink hue
 - Top (most pain): 3 mm wide & deep red hue
- Children **slide a marker** along the coloured scale to indicate their perceived level of pain.
- **Numerical scores** on the back of the scale, allow healthcare providers to record the reported pain level.

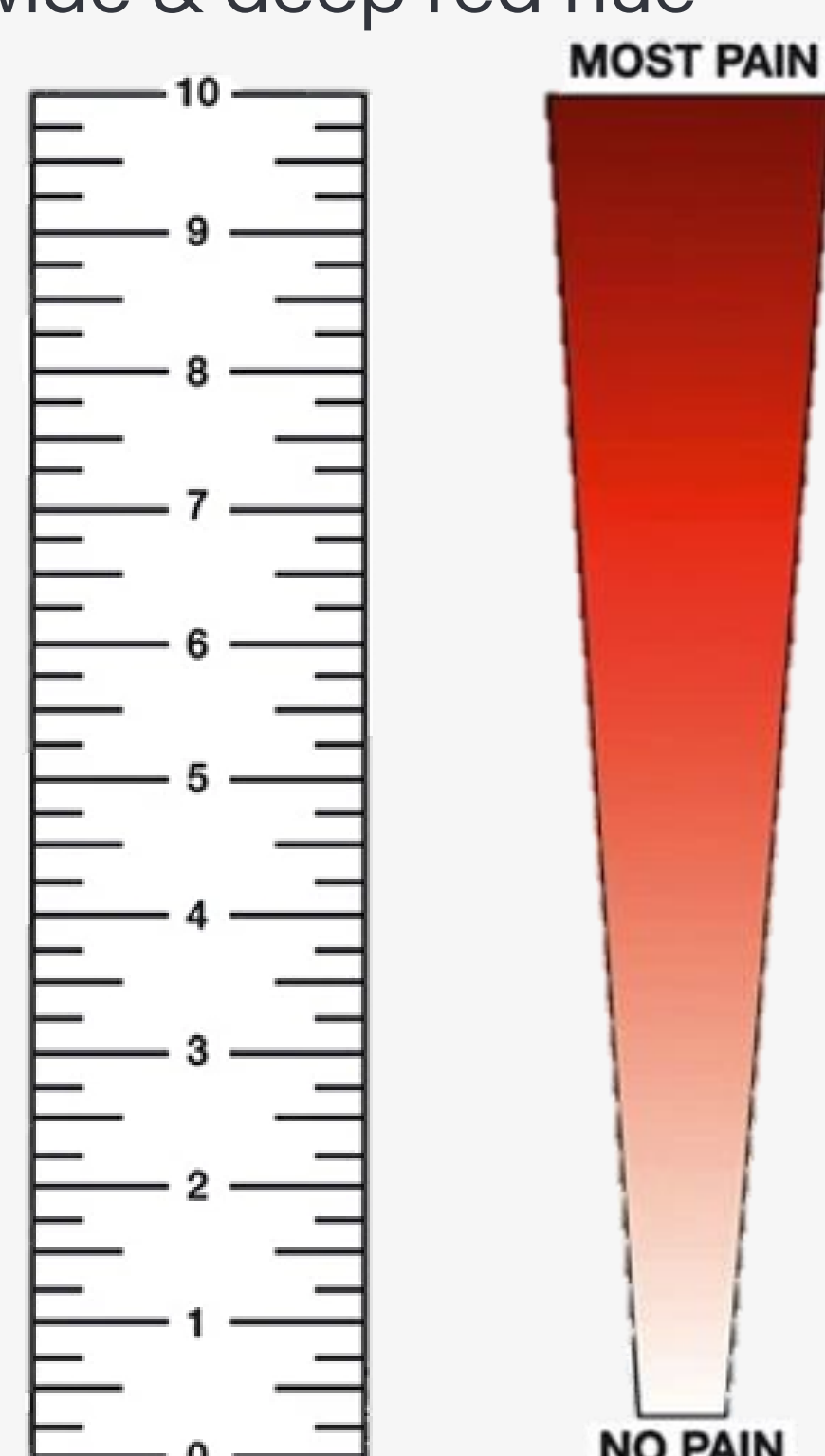


Figure 2: McGrath's CAS staff side (left) and child side (right) [3]

PK-PD Compartmental Model

- The **PK** model developed to characterise **Tapentadol** kinetics was adopted and modified from [4] and consists of **1 compartment** with linear oral absorption and clearance (**Fig. 3**):
- The **PD** model developed to characterise the **CAS** response follows an **indirect Effect** formulation with a K_{in} and K_{out} (**Fig. 3**):

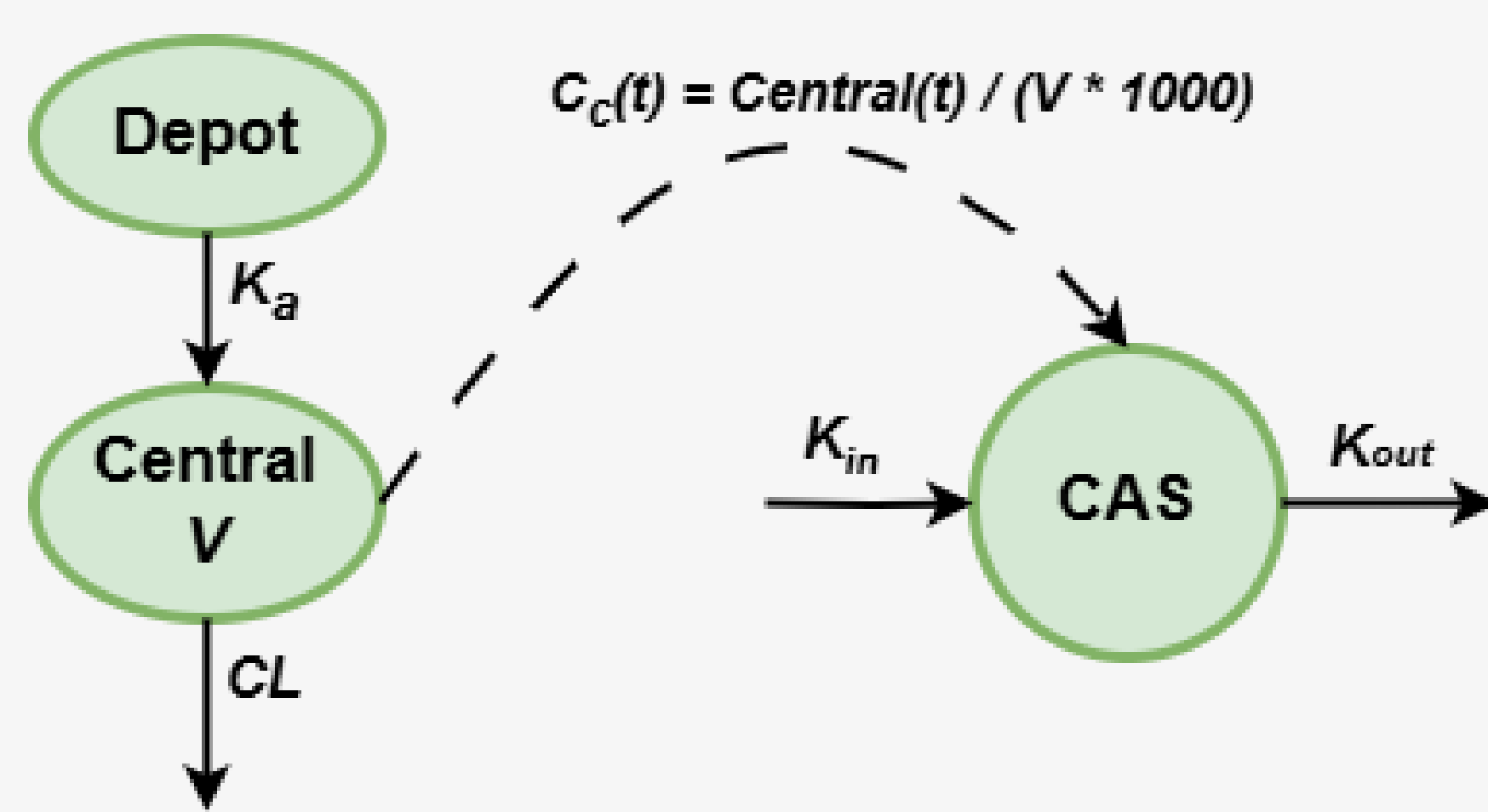


Figure 3: Compartmental model for Tapentadol

Here: K_a : Absorption rate constant from the depot to the central compartment (h^{-1}), CL : Clearance from the central compartment to the external environment (L/h), K_{in} : Production rate of pain (h^{-1}), K_{out} : Degradation rate of pain (h^{-1}), $Central$: Tapentadol quantity in the central compartment (mg/kg), C_c : Tapentadol concentration in central compartment (ng/mL) and V : Volume of distribution in the central compartment (L)

PK Model Equations

Linear model ODEs (Units are amounts in mg/kg):

$$\frac{dDepot(t)}{dt} = -K_a \cdot Depot(t)$$

$$\frac{dCentral(t)}{dt} = K_a \cdot Depot(t) - \frac{CL}{V \cdot 1000} \cdot Central(t)$$

Observation: $C_c(t) = \frac{Central(t)}{V \cdot 1000}$
Initial conditions: $Depot(0) = Dose = 1 \frac{mg}{kg}$ per B.W.
 $Central(0) = 0 \frac{mg}{kg}$

PD Model Equations

$$\frac{dCAS}{dt} = K_{in} \cdot (1 - Eff(t)) - K_{out} \cdot CAS$$

Michaelis-Menten Formulation	Hill Formulation ($n = 3$)
$Eff(t) = \frac{I_{max} C_c}{IC50 + C_c}$	$Eff(t) = \frac{I_{max} C_c^3}{IC50 + C_c^3}$
$\frac{dCAS}{dt} = K_{in} \cdot \left(1 - \frac{I_{max} C_c}{IC50 + C_c}\right) - K_{out} \cdot CAS$	$\frac{dCAS}{dt} = K_{in} \cdot \left(1 - \frac{I_{max} C_c^3}{IC50 + C_c^3}\right) - K_{out} \cdot CAS$

Table 1: ODE model formulations considered to characterise CAS-derived pain intensity in PK-PD analysis

Model Parameterisation

- Population parameter estimation analysis was conducted in Monolix, employing the **SAEM algorithm** (Stochastic Approximation Expectation-Maximisation) [5] via a Non-Linear Mixed Effects (**NLME**) modelling approach, yielding the following PK and PD parameter estimates:

Modelling formulations	Estimated Parameters (units)	Pop. Value	S.E.	R.S.E. (%)	AIC	BIC
PK model	K_a (h^{-1})	2.48	0.71	28.6	-703.3	-693.97
	CL (L/h)	102.48	4221.11	4.12		
	V (L)	430.86	25.6	5.94		
PK-PD Michaelis-Menten	K_{in} (h^{-1})	490.83	49.82	10.2	627.78	638.44
	K_{out} (h^{-1})	133.01	14.15	10.6		
	$IC50$ (ng/mL)	140.83	46.69	33.2		
PK-PD Hill ($n = 3$)	I_{max}	1	-	-	663.82	674.48
	K_{in} (h^{-1})	3.1	0.23	7.31		
	K_{out} (h^{-1})	0.86	0.085	9.85		
	$IC50$ (ng/mL)	211.01×10^3	193.06×10^3	91.5		
	I_{max}	1	-	-		

Table 2: Summary of the estimated PK-PD parameters along with statistical metrics

Model Evaluation

- Model evaluation was performed using goodness-of-fit plots:

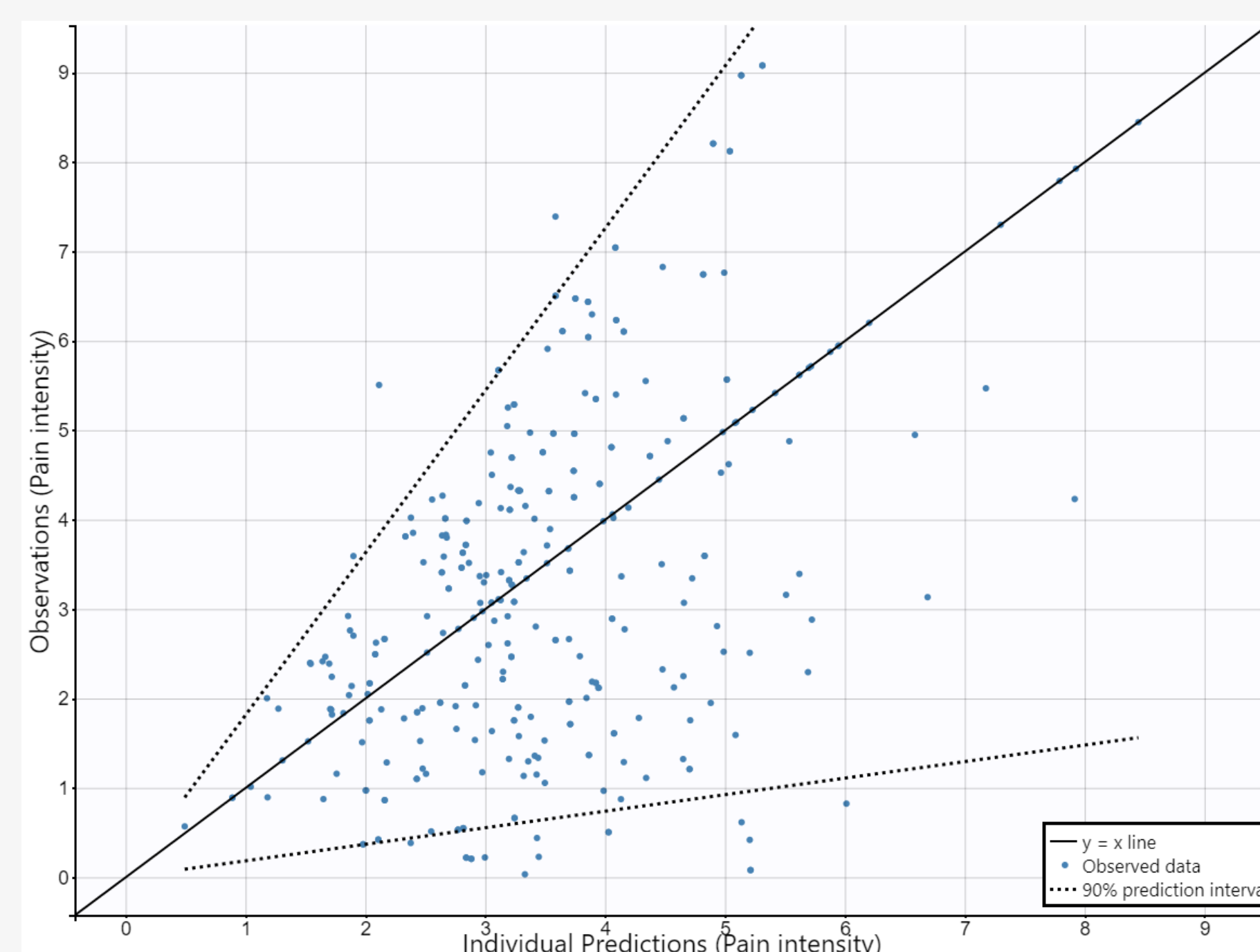
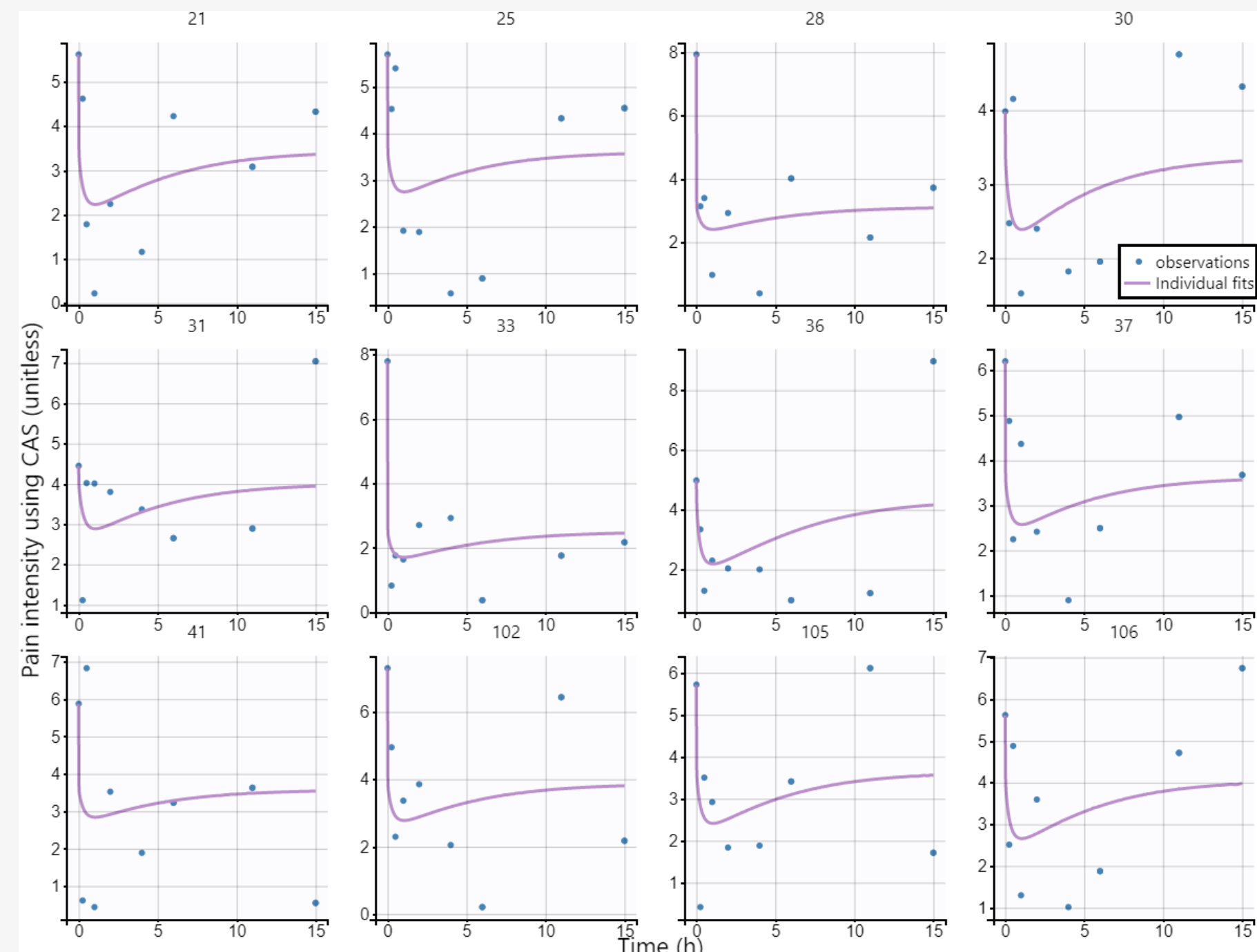


Figure 4: Goodness-of-fit plot for Hill formulation

Individual Fit Plots

- Postoperative pain intensity population data from children aged 6 to < 12 years, who received a 1 mg/kg oral dose of Tapentadol, have been evaluated:

Michaelis-Menten:



Hill ($n = 3$):

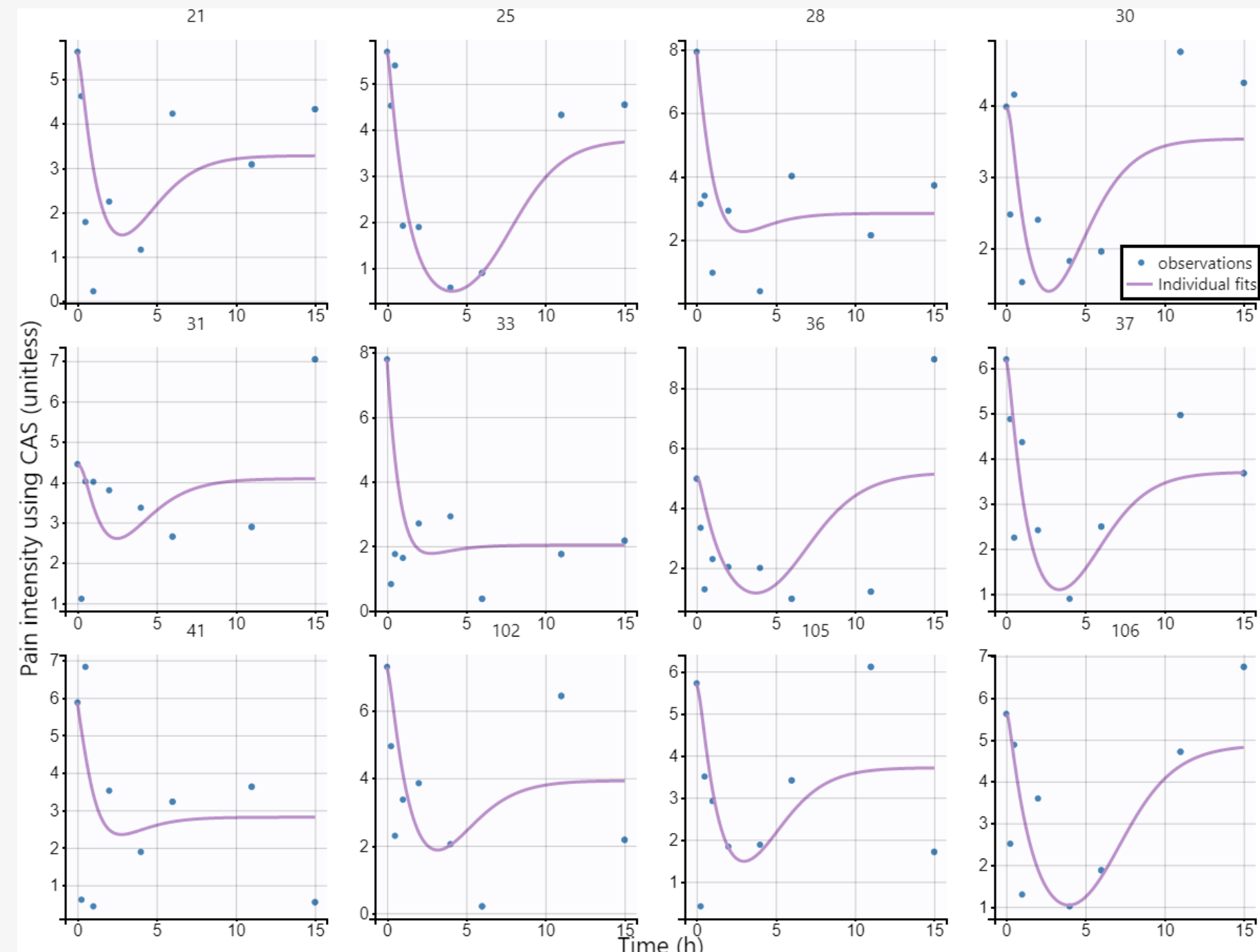


Figure 5: Individual fits of Pain intensity vs. Time (h) for both mathematical formulations

Conclusions and Future Work

- Coupling the **PK model** with a **Hill function** ($n = 3$) based on **cubed central concentration**, yielded more accurate results than the **Michaelis-Menten** formulation, which exhibited individual variations.
- Further work will focus on **extending** the PD model to better **characterise** the **pain pathway** in **paediatrics**.

References

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