Table S1: Overview of morphine PK population models

Covariate Usage

	Holford[4]	Anand	Knibbe	Wang1	Wang2	Knosgaard[4]
Pub.	2012	2008	2009	2013	2013	2016
Comp	2	1	2	2	2	1
Type	Mechanistic	Mechanistic	Empiric	Empiric (BDE)	Empiric (BDE)	Mechanistic
Output[3]	M, M3G, M6G	M	M	M	M, M3G	M, M3G, M6G
CL	Bw, Pma, F[1]	Bw, Pma, F[1]	Bw	Bw	Bw	Bw, Pma
V1	Bw, Pna, F[2]	Bw, Pna, F[2]	Bw	Bw	Bw	Bw
Q	Bw	-	-	Bw	Bw	-
V2	Bw, Pna, F[2]	-	Bw	Bw	Bw	-
CL_{MxG}	Bw, Pna	-	-	-	Bw	Bw, Pna
V_{MxG}	Bw, Pna	-	-	-	Bw	Bw, Pna

[1] Also includes a group factor (FDEVCL) modeling the effect of mechanical ventilation

[2] Also includes a group factor (FDEVV) discriminating between preterm and term neonates

[3] MxG levels can only be simulated if the following parameters are given: fm, CL_{MxG} and V_{MxG}

[4] Uses the Bouwmeester (2004) metabolite model

Symbols

Bw	Bodyweight
Pma	Post meanstrual age
Pna	Post natal age
BDE	Bodyweight dependent exponent
M	Morphine concentration
M3G	Morphine-3-glucuronide concentration
M6G	Morphine-6-glucuronide concentration
CL	Morphine elimination clearance
V1	Morphine volume of central compartment
Q	Morphine distribution clearance
V2	Morphine volume of peripheral compartment
CL_{MxG}	Morphine-x-glucuronide elimination clearance
V_{MxG}	Morphine-x-glucuronide volume of distribution

Table S1. Modeling details in terms of model structure, tasks and validation.

The defined PKPD models consist of the following sub-models:
A1) Structural model (number of compartments, routes of administration and routes of elimination)
A2) Error model (uncertainty of PK parameters as described by its statistical distribution)
A3) Covariate model (modulation of PK parameters by physiological patient variables)

The PK model can be used for the following tasks:
B1) Simulation: Prediction of concentration for a given set of parameters and dosage regimen.
B2) Fitting: Estimation of parameters for a given set of concentrations (observations) and dosage regimen(s).
B3) Dose calculation: estimation of a dosage regimen for given set of exposure targets and parameters.

The correctness of a PKPD model can be established using two types of validation which respect to B1, B2 and B3.

C1) Model performance in clinical practice (predictive performance).
C2) General correctness of the PKPD modeling software (comparative performance).
C3) Correctness of the implementation of a particular model in a software application.

The C1 validation is performed by the authors presenting their model(s) in their papers. It is our concern, but was not reanalyzed.

The C2 validation is performed by the manufacturer. The correctness of the Edsim++ PK-Engine used for representing PKPD models in NeoRelief with respect to model aspects A1 and A2 has been extensively tested by the manufacturer of the Edsim++ software. This was done by implementing identical models in different software packages and comparing results/output of tasks B1, B2 and B3. In this project the Edsim++ PK engine was compared with MwPharm DOS, Berkeley Madonna and R (RxODE package).

For this project we performed C3 validation for covariate model aspects (A3). We checked the correctness of the effect of covariate values on PK parameter estimates. This was accomplished by implementing the mathematical description of the covariate model in two different software platforms. The covariate model as implemented in the NeoRelief PK-engine was compared with the covariate model implemented as simple equations in MS Excel. This will identify any coding errors, but not interpretation errors.