Supplement to "*Pharmacokinetic interactions and dosing rationale for antiepileptic drugs in adults and children*"

Contents

1. Introduction

Here we describe 1) the validation procedures used to ensure accurate implementation of the models previously published for each anti-epileptic drugs; 2) the concentration vs. time profiles obtained from the simulations for each drug after administration of different dose levels as monotherapy or in combination with add-on drugs, which provided the basis for the evaluation of the impact of pharmacokinetic drug-drug interactions (DDIs), and 3) a discussion of the simulation results with regard to the peak and trough concentrations. Results of peak and trough concentrations are discussed in this supplemental material, whereas the main article focusses on average steady-state concentrations (Css).

1.1. Validation procedures for PK model implementations

Pharmacokinetic models of 11 anti-epileptic drugs from the published literature were selected based on the parameterization of covariate effects describing the impact of co-medication on drug disposition. Some of the models were derived from data on Caucasian and Asian populations. All models were implemented in the statistical software NONMEM[1]. Often omega values (describing the variance of eta) were reported as % CV or sd and mean. Such values correspond to each other, as shown by the following conversion rule:

$$\omega = \frac{standard\ deviation}{mean} = \frac{coefficient\ of\ variation\ (\%)}{100\%}$$

where ω^2 is used in NONMEM as the measure of variability under $OMEGA.

Subject identification (ID), time (TIME), and covariates such as weight (WT), age (AGE), etc. were provided to NONMEM in the input dataset. If SUBROUTINE option was used in the original publication, that option was also used for the validation procedures and in subsequent simulations with NONMEM. In other cases, where a standard 1 or 2 compartment model was reported, the corresponding $SUBROUTINE based on the chosen parameters was implemented in NONMEM. User defined models were implemented using $PRED option in NONMEM. PsN[2] version 3.5.3 was used to manage runs in NONMEM. Data set manipulation, statistical and graphical summaries were performed in R[3] v3.1.1. Fixed seeds were used in R (5) and NONMEM (1234567890) to ensure reproducibility.

Each model was validated by performing simulations of 500 subjects. Patients' ages were randomly sampled from a uniform distribution using the age range described in the original papers. Weight was based on age according to the formulae reported in table 1 (as according to Luscombe & Owens in Arch Dis Child - 2007). Where of relevance, genetic polymorphisms were randomly simulated based on the frequencies reported in the original papers. Where available, observed vs predicted plots from the original paper are compared to simulated concentrations distributions. If the observed vs. predicted concentration plots were not reported in the paper, the reported observed concentrations distribution (mean, SD) was used to generate a plot in R based on such distribution characteristics, to compare to the simulated concentration distribution. Steady state concentrations were simulated for 12 hour intervals, assuming a twice daily dosing. Mean doses from the original papers are used in the form of mg/kg/day or μg/kg/day were available, or calculated by using mean dose and mean weight, to make sure very young simulated patients do not receive adult doses.

Table 1. Population demographics used for the model implementation validation procedures.

Population	Adult	Paediatric
Age (years)*	18-95	1-18
Mean weight (kg)	75 (male) 65 (female)	3·Age+7 †
Coefficient of variance on weight	16 %	10 %
Dose interval (hr)	12	12
Number of simulated subjects per model implementation	500	

* Minimum age found in the population PK studies was 1 year old, maximum age was 95 years old (see table 2). In these validation exercises, virtual subjects of age up to 18 were considered to still adhere to the weight-for-age rule of three times age plus seven kilograms. From age 18 and upwards, virtual subjects were considered to be roughly fully grown and thus be part of the normal adult population weight distributions as dependent on sex. In the actual dosing and drug-drug interaction simulation scenarios, only populations of children aged 4-14 and adults aged 18-65 years were considered. † The formula that gives weight for age, a subject's age is multiplied by 3 and 7 is added,

2. Model implementation validation results

2.1. Carbamazepine – Jiao et al. 2003[4]

Jiao reports carbamazepine (CBZ) concentrations ranging 1.1-14.6 mg/L after administration of 1.18-80 mg/kg/day (mean: 9.85) in patients aged 1-85 years with weight 5-115 kg (mean: 53). This model was defined as follows:

$$CL = \theta_1 \cdot \left(\frac{DD}{WT}\right)^{\theta_2} \cdot WT^{\theta_3} \cdot {\theta_4}^{PHT} \cdot {\theta_5}^{PHB} \cdot {\theta_6}^{VPA} \cdot {\theta_7}^{ELD} \cdot e^{\eta_1}$$

$$V = \theta_8 \cdot WT \cdot e^{\eta_2}$$

$$Ka = \theta_9$$

$$C_t = \frac{D}{V}\frac{k_a}{k_a - \frac{CL}{V}}\left(\frac{e^{-\frac{CL}{V}(t-t_D)}}{1-e^{-\frac{CL}{V}\tau}} - \frac{e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}}\right) + \varepsilon_1$$

Where CL is clearance (L/h), V is volume (L), Ka is absorption rate constant (h^{-1}), and D is the given dose in mg. DD is daily dose in mg. WT is weight in Kg. PHT (phenytoin), PHB (phenobarbital), VPA (valproic acid), ELD (older than 65) are binary values of 1 for true, 0 for false. A value of 1 will result in the change in CL being effected (i.e. x^1 = x), a value of 0 results in no change (i.e. x^0 = 1). Eta (η) is a random variable sampled from a normal distribution with mean 0 and variance of the omega squared of the corresponding number. Epsilon (ε) is a random variable sampled from a normal distribution with mean 0 and variance of the sigma squared of the corresponding number. T_D is time after dose (here always 0). Tau (τ) is the dosing interval. C_t is the simulated concentration (mg/L) at time *t*.

#	Theta (θ)	Omega squared (ω^2)	Sigma squared (σ^2)
1	0.0734	0.0254	0.975
2	0.406	0.01	
3	0.694		
4	1.45		
5	1.17		
6	1.21		
7	0.849		
8	1.91		
9	1.2		

Based on this information, we simulated a dosing of 10 mg/kg/day (5 mg/kg/12 hours) in patients aged 1-85 years.

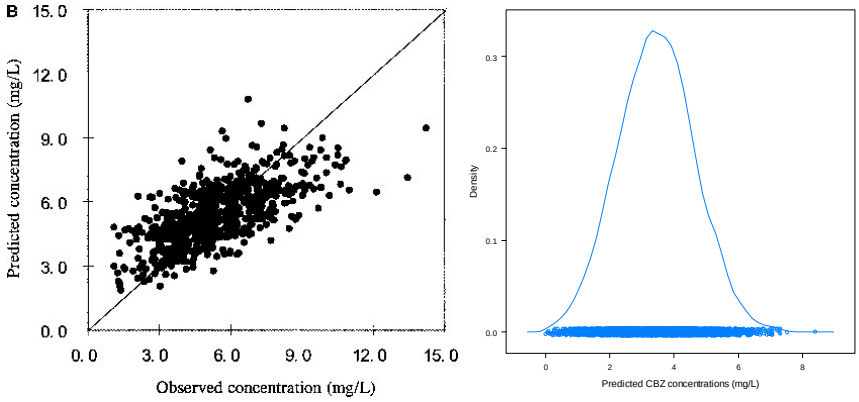

Figure 1. CBZ concentrations from the Jiao paper (left) and our simulations (right)

It seems that our simulations provide a similar concentration range (most concentrations centred around 4 mg/L), although not as many concentrations above 8 mg/L, probably due to some outliers in their doses (upper limit 80 mg/kg/day).

2.2. Clobazam – Saruwatari et al. 2014[5]

We thank Mr. Saruwatari for sending us his NONMEM control stream, which allows us to be certain of the correct implementation. Regardless, a validation of the model implementation is performed here. Saruwatari reports clobazam (CLB/CLBZ) concentrations of 20-700 µg/L after administration of 2-55 µg/day (mean: 21.2, sd: 12.6) in a population of 1-52 years with weight 8-102 kg (mean: 46, sd: 22.5). This model was defined as follows:

$$Ka = \theta_1 \cdot e^{\eta_1}$$

$$V = \theta_2 \cdot WT^{\theta_3} \cdot e^{\eta_3}$$

$$CL = \theta_4 \cdot WT^{\theta_5} \cdot \theta_6{}^{ZNS} \cdot \theta_7{}^{PHB} \cdot \theta_8{}^{PHT} \cdot \theta_9{}^{CYP2C19hetEM} \cdot \theta_{10}{}^{CYP2C19PM} \cdot \theta_{11}{}^{POR28CT} \cdot \theta_{12}{}^{POR28TT} \cdot e^{\eta_2}$$

$$S = 1000$$

$$C_t = \frac{D}{V}\frac{k_a}{k_a - \frac{CL}{V}}\left(\frac{e^{-\frac{CL}{V}(t-t_D)}}{1-e^{-\frac{CL}{V}\tau}} - \frac{e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}}\right) \cdot S \cdot (1+\varepsilon_1)$$

Where CL is clearance (L/h), V is volume (L), Ka is absorption rate constant (h^{-1}), and D is the given dose in mg. WT is weight in Kg. ZNS (zonisamide), PHB (phenobarbital), PHT (phenytoin), CYP2C19hetEM (heterozygote extended metaboliser in CYP2C19), CYP2C19PM (poor metaboliser in CYP2C19), POR28CT (CT polymorphism in POR28), POR28TT (TT polymorphism in POR28) are binary values of 1 for true, 0 for false. A value of 1 will result in the change in CL being effected (i.e. x^1 = x), a value of 0 results in no change (i.e. x^0 = 1). Eta (η) is a random variable sampled from a normal distribution with mean 0 and variance of the omega squared of the corresponding number. Epsilon (ε) is a random variable sampled from a normal distribution with mean 0 and variance of the sigma squared of the corresponding number. T_D is time after dose (here always 0). Tau (τ) is the dosing interval. C_t is the simulated concentration (µg/L) at time *t*. S is the scaling factor for translation between mg and µg. CYP2C19 and POR28 mutations were simulated to the proportions as they occurred in Saruwatari's data.

#	Theta (θ)	Omega squared (ω^2)	Sigma squared (σ^2)
1	0.0594	0.0000191	0.107
2	13.3	0.669	
3	0.136	0.00000000360	
4	0.511		
5	0.54		
6	0.484		
7	1.66		
8	1.93		
9	0.944		
10	0.819		
11	1.02		
12	1.44		

Based on this information, we simulated a dosing of 0.5 µg/kg/day (0.25 µg/kg/12 hours) in patients aged 1-52 years.

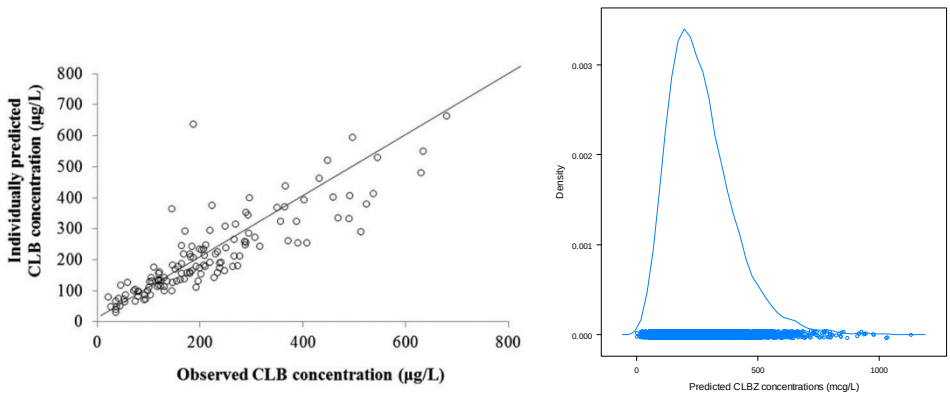

Figure 2. CLBZ concentrations from the Saruwatari paper (left) and our simulations (right)

Our simulations seem to reflect Saruwatari's concentrations (centred around 200 µg/L), although we predict some concentrations above 800 µg/L, which were never observed by Saruwatari. This is probably due to the higher clearance when using comedication (only 3 patients on monotherapy in Saruwatari's data), while our simulations only included monotherapy.

2.3. Clonazepam – Yukawa et al. 2002[6]

Yukawa reports clonazepam (CLNZ) concentrations of 2.9-41.8 µg/L after administration of 5.5-76.9 µg/kg/day (mean: 33.6, sd: 19.9) in a population of 0.3-21 years with weight 5.5-66.8 kg (mean: 31.3, sd: 16.9). This model was defined as follows:

$$CL = \theta_1 \cdot WT^{\theta_2} \cdot \theta_3{}^{VPA} \cdot e^{\eta_1}$$

$$S = 1000$$

$$C_{ss} = \frac{1}{24} \cdot \frac{DD}{CL} \cdot S + \varepsilon_1$$

Where CL is clearance (L/h), and DD is daily dose in mg. WT is weight in Kg. VPA (valproic acid), is a binary values of 1 for true, 0 for false. A value of 1 will result in the change in CL being effected (i.e. x^1 = x), a value of 0 results in no change (i.e. x^0 = 1). Eta (η) is a random variable sampled from a normal distribution with mean 0 and variance of the omega squared of the corresponding number. Epsilon (ε) is a random variable sampled from a normal distribution with mean 0 and variance of the sigma squared of the corresponding number. T_D is time after dose (here always 0). Tau (τ) is the dosing interval. C_{ss} is the simulated average steady-state concentration (µg/L) at any time. S is the scaling factor for translation between mg and µg.

#	Theta (θ)	Omega squared (ω^2)	Sigma squared (σ^2)
1	0.144	0.0404	0.0346
2	0.828		
3	1.14		

Based on this information, we simulated a dosing of 35 µg/kg/day (17.5 µg/kg/12 hours) in patients aged 1-21 years.

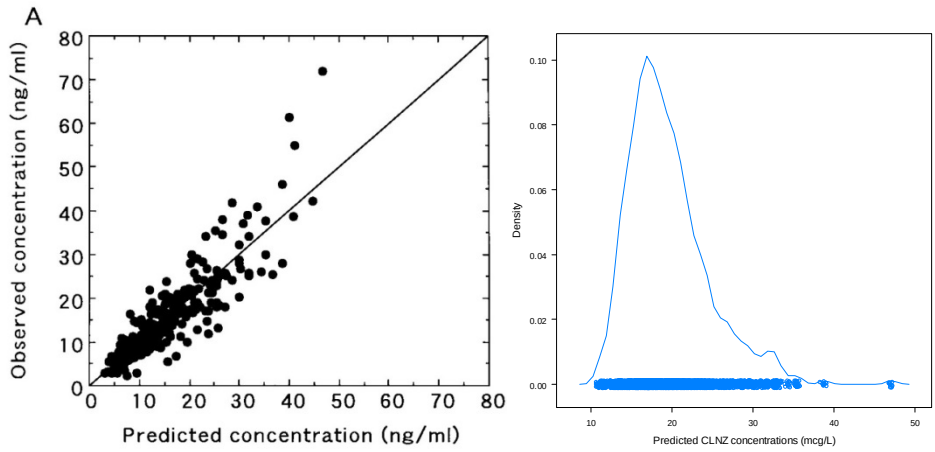

Figure 3. CLNZ concentrations from the Yukawa paper (left) and our simulations (right)

Our CLNZ simulations seem to reflect Yukawa's observations well, although the lower limit of simulated concentrations is above 10 µg/L, while concentrations as low as 2.9 µg/L were observed. This is possibly due to our dose being far above their lower limit of dosing (5 µg/kg/day).

2.4. Lamotrigine – Children – He et al. 2012[7]

He reports lamotrigine (LMT/LTG) concentrations of ~1-21 mg/L (based on left plot in figure 4) after administration of 12.5-525 mg/day (mean of 135 mg/day) in a population of 0.5-17 years with weight 8-85 kg (mean: 27.87). Here we will assume that the relation between weight and clearance has been derived well and that no maturation occurs after the age of 17. This model was defined as follows:

$$CL = \theta_1 \cdot \left(\frac{WT}{27.87}\right)^{\theta_2} \cdot e^{\theta_3 * VPA} \cdot e^{\theta_4 * CBZ} \cdot e^{\theta_5 * PHB} \cdot e^{\eta_1}$$

$$V = \theta_6 \cdot WT$$

$$Ka = \theta_7$$

$$C_t = \frac{D}{V} \frac{k_a}{k_a - \frac{CL}{V}} \left(\frac{e^{-\frac{CL}{V}(t - t_D)}}{1 - e^{-\frac{CL}{V}\tau}} - \frac{e^{-k_a(t - t_D)}}{1 - e^{-k_a \tau}} \right) \cdot (1 + \varepsilon_1)$$

Where CL is clearance (L/h), V is volume (L), Ka is absorption rate constant (h^{-1}), and D is the given dose in mg. WT is weight in Kg. VPA (valproic acid), CBZ (carbamazepine), PHB (phenobarbital) are binary values of 1 for true, 0 for false. A value of 1 will result in the change in CL being effected (i.e. x^1 = x), a value of 0 results in no change (i.e. x^0 = 1). Eta (η) is a random variable sampled from a normal distribution with mean 0 and variance of the omega squared of the corresponding number. Epsilon (ε) is a random variable sampled from a normal distribution with mean 0 and variance of the sigma squared of the corresponding number. T_D is time after dose (here always 0). Tau (τ) is the dosing interval. C_t is the simulated concentration (mg/L) at time *t*.

#	Theta (θ)	Omega squared (ω^2)	Sigma squared (σ^2)
1	1.01	0.067	0.045
2	0.635		
3	-0.753		
4	0.868		
5	0.633		
6	16.7		
7	1		

Based on this information, we simulated a dosing of 5 mg/kg/day (2.5 mg/kg/12 hours) in patients aged 4-17.

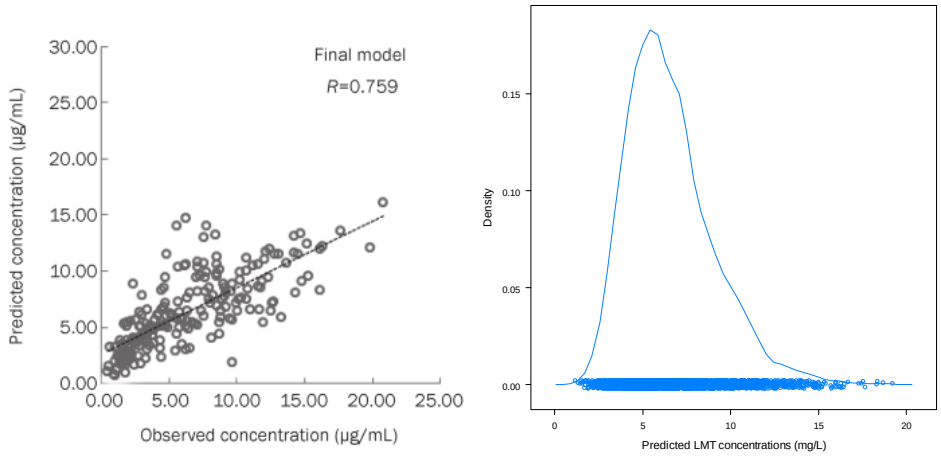

Figure 4. LMT concentrations from the He paper (left) and our simulations (right)

These simulations seem to reflect He's observations well.

2.5. Lamotrigine – Adults – Rivas et al. 2008[8]

Rivas reports lamotrigine (LMT/LTG) concentrations of ~1-25 mg/L (based on left plot in figure 5) after administration of 100-500 mg/day (mean of ~200-350 mg/day) in a population of 32-51 years with weight ~62-85 kg (mean: ~70-76). This model was defined as follows:

if(∑(CBZ,PHB,PHT)<2) $CL = \theta_1 \cdot WT \cdot e^{\theta_2 * VPA} \cdot e^{\theta_3 * PHT} \cdot e^{\theta_4 * PHB} \cdot e^{\theta_5 * CBZ} \cdot e^{\eta_1}$

else $CL = \theta_1 \cdot WT \cdot e^{\theta_2 * VPA} \cdot e^{\theta_6 * IND} \cdot e^{\eta_1}$

$V = \theta_7 \cdot WT$

$Ka = \theta_8$

$$C_t = \frac{D}{V} \frac{k_a}{k_a - \frac{CL}{V}} \left(\frac{e^{-\frac{CL}{V}(t-t_D)}}{1-e^{-\frac{CL}{V}\tau}} - \frac{e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}} \right) + \varepsilon_1$$

Where CL is clearance (L/h), V is volume (L), Ka is absorption rate constant (h^{-1}), and D is the given dose in mg. WT is weight in Kg. VPA (valproic acid), CBZ (carbamazepine), PHB (phenobarbital), IND (two or more inducers (CBZ/PHT/PHB)) are binary values of 1 for true, 0 for false. A value of 1 will result in the change in CL being effected (i.e. x^1 = x), a value of 0 results in no change (i.e. x^0 = 1). Eta (η) is a random variable sampled from a normal distribution with mean 0 and variance of the omega squared of the corresponding number. Epsilon (ε) is a random variable sampled from a normal distribution with mean 0 and variance of the sigma squared of the corresponding number. T_D is time after dose (here always 0). Tau (τ) is the dosing interval. C_t is the simulated concentration (mg/L) at time *t*.

#	Theta (θ)	Omega squared (ω^2)	Sigma squared (σ^2)
1	0.028	0.07285	1.25
2	-0.713		
3	0.663		
4	0.588		
5	0.467		
6	0.864		
7	1.5		
8	1.3		

Based on this information, we simulated a dosing of 5 mg/kg/day (2.5 mg/kg/12 hours) in patients aged 32-51.

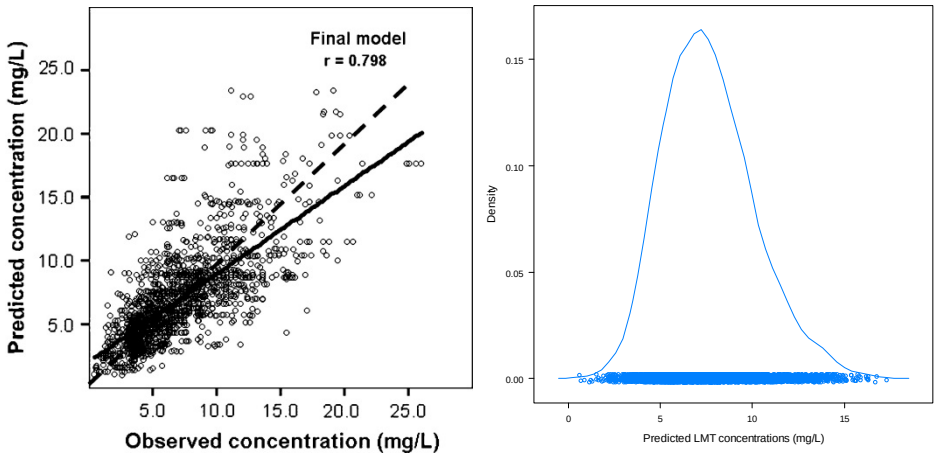

Figure 5. LMT concentrations from the Rivas paper (left) and our simulations (right)

These simulations seem to reflect Rivas' observations well.

2.6. Levetiracetam – Toublanc et al. 2014[9]

Toublanc reports levetiracetam (LEV/LVT) concentrations of ~1-100 mg/L (based on left plot in figure 6) after administration of 1000-3000 mg/day (we assume a mean of: 2000) in a population of 4.3-55.4 years with weight 13.8-107 kg (mean: 51.6, sd: 17.2). This model was defined as follows:

$$CL = \theta_1 \cdot \left(\frac{WT}{32}\right)^{0.75} \cdot {\theta_2}^{CO} \cdot e^{\eta_1}$$

$$V = \theta_4 \cdot \frac{WT}{32} \cdot e^{\eta_2}$$

$$Ka = \theta_3 \cdot e^{\eta_3}$$

$$C_t = \frac{D}{V} \frac{k_a}{k_a - \frac{CL}{V}} \left(\frac{e^{-\frac{CL}{V}(t-t_D)}}{1-e^{-\frac{CL}{V}\tau}} - \frac{e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}} \right) \cdot (1+\varepsilon_1)$$

Where CL is clearance (L/h), V is volume (L), Ka is absorption rate constant (h^{-1}), and D is the given dose in mg. WT is weight in Kg. CO (comedication with any of CBZ (carbamazepine) / VPA (valproic acid) / PHT (phenytoin)) is a binary value of 1 for true, 0 for false. A value of 1 will result in the change in CL being effected (i.e. x^1 = x), a value of 0 results in no change (i.e. x^0 = 1). Eta (η) is a random variable sampled from a normal distribution with mean 0 and variance of the omega squared of the corresponding number. Epsilon (ε) is a random variable sampled from a normal distribution with mean 0 and variance of the sigma squared of the corresponding number. T_D is time after dose (here always 0). Tau (τ) is the dosing interval. C_t is the simulated concentration (mg/L) at time *t*.

#	Theta (θ)	Omega squared (ω^2)	Correlation between omegas 1 & 2	Sigma squared (σ^2)
1	2.10	0.0396	0.0182	0.0357
2	1.22	0.149		
3	2.56	0.736		
4	20.4			

Based on this information, we simulated a dosing of 40 mg/kg/day (20 mg/kg/12 hours) in patients aged 4-55 years.

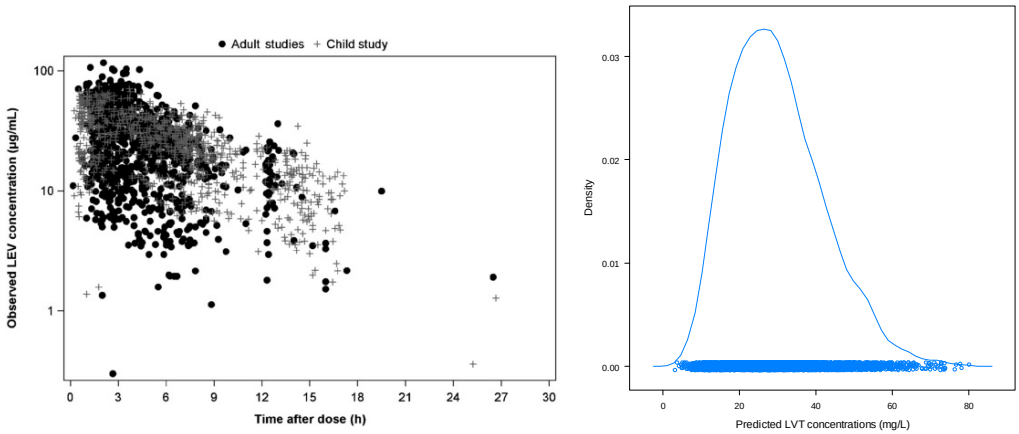

Figure 6. LVT concentrations from the Toublanc paper (left) and our simulations (right)

These simulations seem to reflect Toublanc's observations well, although no concentrations were predicted above 80 mg/L, probably due to our dosing never reaching 3000 mg/day, which did occur in the Toublanc populations.

2.7. Oxcarbazepine – Park et al. 2012[10]

Park reports oxcarbazepine (OXC/MHD) concentrations of 0.2-49.9 mg/L after administration of a mean weight-adjusted dose of 16.22 mg/kg/day in a population of 3-80 years with weight 10.1-95 kg (mean: 62.8). This model was defined as follows:

$$CL = \theta_1 \cdot \left(\frac{WT}{62.8}\right)^{\theta_2} \cdot (1 + \theta_5 \cdot EIAED) \cdot e^{\eta_1}$$

$$Ka = \theta_3$$

$$V = \theta_4 \cdot \frac{WT}{62.8}$$

$$C_t = \frac{D}{V} \frac{k_a}{k_a - \frac{CL}{V}} \left(\frac{e^{-\frac{CL}{V}(t-t_D)}}{1-e^{-\frac{CL}{V}\tau}} - \frac{e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}} \right) \cdot (1 + \varepsilon_1) + \varepsilon_2$$

Where CL is clearance (L/h), V is volume (L), Ka is absorption rate constant (h^{-1}), and D is the given dose in mg. WT is weight in Kg. EIAED (comedication with any of CBZ (carbamazepine) / PHB (phenobarbital) / PHT (phenytoin)) is a binary value of 1 for true, 0 for false. A value of 1 will result in the change in CL being effected (i.e. x^1 = x), a value of 0 results in no change (i.e. x^0 = 1). Eta (η) is a random variable sampled from a normal distribution with mean 0 and variance of the omega squared of the corresponding number. Epsilon (ε) is a random variable sampled from a normal distribution with mean 0 and variance of the sigma squared of the corresponding number. T_D is time after dose (here always 0). Tau (τ) is the dosing interval. C_t is the simulated (MHD) concentration (mg/L) at time *t*.

#	Theta (θ)	Omega squared (ω^2)	Sigma squared (σ^2)
1	2.13	0.077	0.057
2	0.666		2.83
3	0.598		
4	49		
5	0.312		

Based on this information, we simulated a dosing of 15 mg/kg/day (7.5 mg/kg/12 hours) in patients aged 3-80 years.

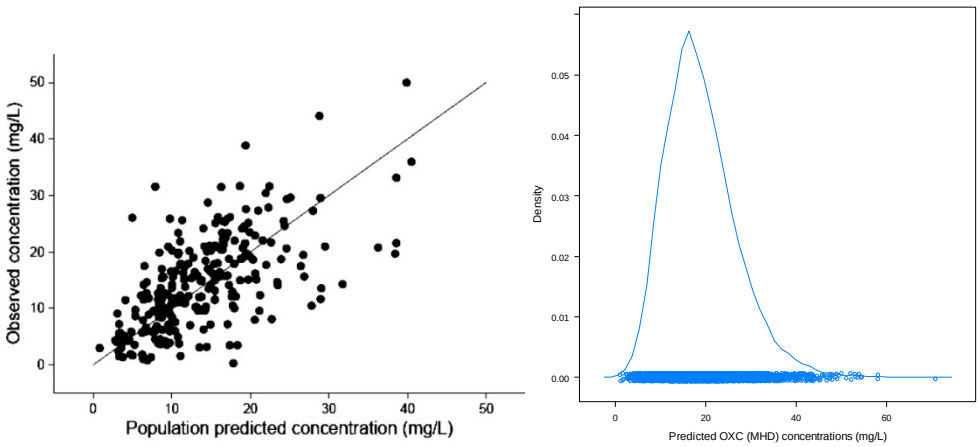

Figure 7. OXC (MHD) concentrations from the Park paper (left) and our simulations (right)

Our OXC simulations seem to reflect Park's observations well, although mean concentrations seem to lie slightly higher than expected and our simulations include more concentrations above 40 mg/L.

2.8. Phenobarbital – Goto et al. 2007[11]

Goto reports phenobarbital (PHB) concentrations of 3.6-36.7 mg/L after administration of 30-235 mg/day (mean: 86.3, sd: 29.8) in a population of 0.8-43.8 years with weight 8.5-80.2 kg (mean: 35.4, sd: 18.1). Based on this information, we simulated a dosing of 3 mg/kg/day (1.5 mg/kg/12 hours) in patients aged 1-44 years. This model was defined as follows:

$$CL = \theta_1 \cdot \left(\frac{WT}{40}\right)^{\theta_2} \cdot {\theta_3}^{VPA} \cdot {\theta_4}^{PHT} \cdot (1 + \eta_1)$$

$$V = \theta_5 + \eta_2$$

$$Ka = \theta_6$$

$$C_t = \frac{D}{V} \frac{k_a}{k_a - \frac{CL}{V}} \left(\frac{e^{-\frac{CL}{V}(t - t_D)}}{1 - e^{-\frac{CL}{V}\tau}} - \frac{e^{-k_a(t - t_D)}}{1 - e^{-k_a\tau}} \right) + \varepsilon_1$$

Where CL is clearance (L/h), V is volume (L), Ka is absorption rate constant (h^{-1}), and D is the given dose in mg. WT is weight in Kg. EIAED (comedication with any of CBZ (carbamazepine) / PHB (phenobarbital) / PHT (phenytoin)) is a binary value of 1 for true, 0 for false. A value of 1 will result in the change in CL being effected (i.e. x^1 = x), a value of 0 results in no change (i.e. x^0 = 1). Eta (η) is a random variable sampled from a normal distribution with mean 0 and variance of the omega squared of the corresponding number. Epsilon (ε) is a random variable sampled from a normal distribution with mean 0 and variance of the sigma squared of the corresponding number. T_D is time after dose (here always 0). Tau (τ) is the dosing interval. C_t is the simulated concentration (mg/L) at time *t*.

#	Theta (θ)	Omega squared (ω^2)	Sigma squared (σ^2)
1	0.23	0.03	12.2
2	0.21	2.93	
3	0.68		
4	0.85		
5	14.78		
6	2		

No plots of concentrations were provided by Goto and thus a density plot was generated using 500 randomly generated concentrations of a normal distribution based on their reported mean 20 and sd 9 mg/L.

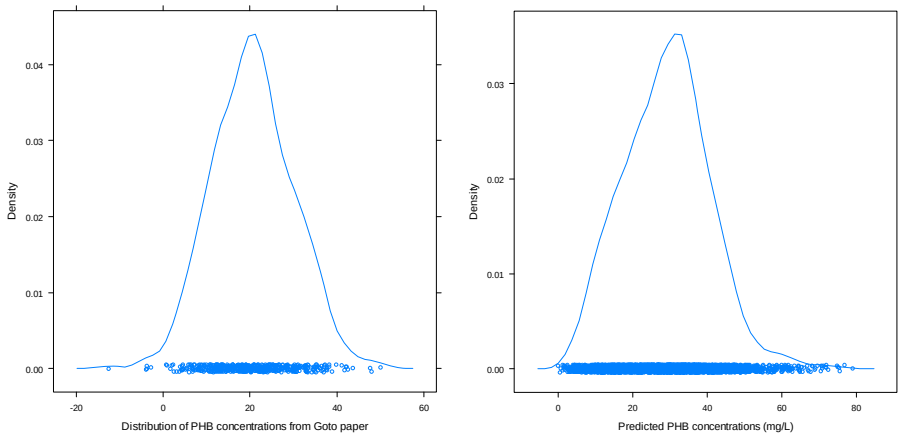

Figure 8. PHB concentrations based on the Goto paper (left) and from our simulations (right)

Our simulations seem to reflect Goto's observations well, although the upper limit of simulated concentrations is higher than those reported by Goto, which is explained in the conclusions.

2.9. Phenytoin - Odani et al. 1996[12]

Odani reports phenytoin (PHT) concentrations of 0.1-45 mg/L after administration of 0.5-9 mg/kg/day (mean: 200, sd: 64) (concentrations and doses based on left plot in figure 9) in a population of 1-37 years with weight mean 42.4 and sd 16.9 kg. This model was defined as follows:

$$SIZE = 42 \cdot \left(\frac{WT}{42}\right)^{\theta_4}$$

$$VM = \theta_1 \cdot SIZE \cdot e^{\eta_1}$$

$$V = \theta_3 \cdot SIZE \cdot e^{\eta_3}$$

$$KM = \theta_2 \cdot {\theta_5}^{ZNS} \cdot e^{\eta_2}$$

$$CL = \frac{VM - \frac{D}{\tau}}{KM}$$

$$C_{ss} = \frac{D}{V} \cdot \frac{e^{-\frac{CL}{V}(t-t_D)}}{1 - e^{-\frac{CL}{V}\tau}} \cdot (1 + \varepsilon_1)$$

This dose-dependent clearance model (DDCL) is in essence a collapsed version of the regular one compartment model, due to the lack of absorption. VM is the maximum metabolic capacity Vmax (mg/day), V is the volume of distribution (L), KM is the michaelis menten constant (concentration of PHT in mg/L at which 50% of the maximum metabolic capacity has been reached). CL is clearance (L/h), D is the dose in mg, WT is weight in Kg. ZNS (zonisamide), is a binary values of 1 for true, 0 for false. A value of 1 will result in the change in CL being effected (i.e. x^1 = x), a value of 0 results in no change (i.e. x^0 = 1). Eta (η) is a random variable sampled from a normal distribution with mean 0 and variance of the omega squared of the corresponding number. Epsilon (ε) is a random variable sampled from a normal distribution with mean 0 and variance of the sigma squared of the corresponding number. T_D is time after dose (here always 0). Tau (τ) is the dosing interval. C_t is the simulated concentration (mg/L) at time *t*.

#	Theta (θ)	Omega squared (ω^2)	Sigma squared (σ^2)
1	9.80	0.023	0.033
2	9.19	0.098	
3	1.23	0.206	
4	0.463		
5	1.16		

Based on this information, we simulated a dosing of 5 mg/kg/day (2.5 mg/kg/12 hours) in patients aged 1-37 years.

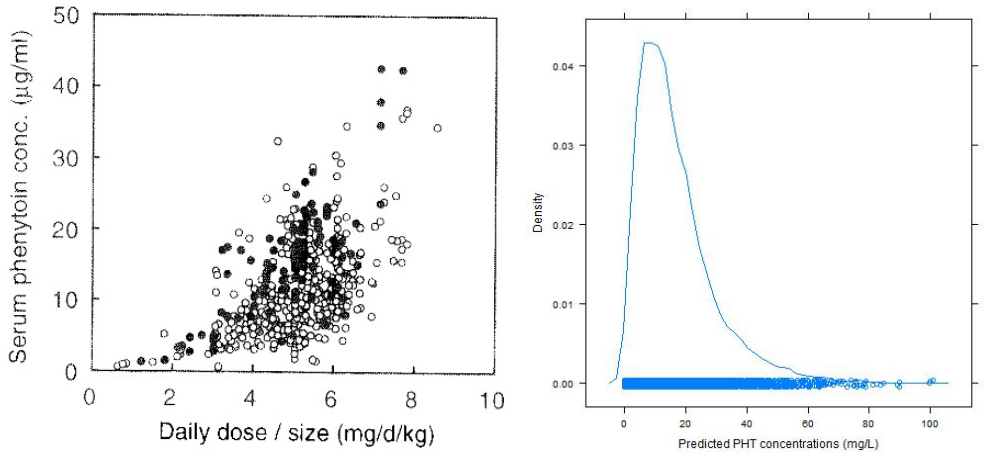

Figure 9. PHT concentrations from the Odani paper (left) and our simulations (right)

Our simulations seem to reflect Odani's observations well, except for the longer tail towards higher concentrations, which is explained in the conclusions.

2.10. Topiramate – Girgis et al. 2010[13]

Girgis does not report topiramate (TPM) concentrations and thus our simulations will be validated against their plot of simulated Cmin concentrations for a typical patient of 10 years old (left plot in figure 10). Their population received target TPM doses of 100-800 mg/day in a population of 2-85 years with no reported weight. This model was defined as follows:

$$CL = \theta_1 \cdot (1 + \theta_2 \cdot ADJ) \cdot \left(\frac{WT}{69.9}\right)^{\theta_3} \cdot e^{\theta_4 \cdot (AGE - 31.4)} \cdot {\theta_5}^{INMD} \cdot {\theta_6}^{VPA} \cdot {\theta_7}^{NEMD} \cdot e^{\eta_1}$$

$$V_1 = \theta_8 \cdot \left(\frac{WT}{69.9}\right)^{\theta_9} \cdot e^{\eta_2}$$

$$Ka = \theta_{10} \cdot e^{\eta_3}, \qquad K_{12} = \theta_{11}, \qquad K_{21} = \theta_{12}$$

$$\alpha = \frac{K_{21}\frac{CL}{V_1}}{\beta}, \qquad \beta = \frac{1}{2}\left(K_{12} + K_{21} + \frac{CL}{V_1} - \sqrt{(K_{12} + K_{21} + \frac{CL}{V_1})^2 - 4K_{21}\frac{CL}{V_1}}\right), \qquad A = \frac{k_a}{V_1}\frac{K_{21} - \alpha}{(k_a - \alpha)(\beta - \alpha)}, \qquad B = \frac{k_a}{V_1}\frac{K_{21} - \beta}{(k_a - \beta)(\alpha - \beta)}$$

$$C_t = D\left(\frac{Ae^{-\alpha(t-t_D)}}{1-e^{-\alpha\tau}} + \frac{Be^{-\beta(t-t_D)}}{1-e^{-\beta\tau}} - \frac{(A+B)e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}}\right) \cdot (1 + \varepsilon_1) + \varepsilon_2$$

Where CL is clearance (L/h), V is volume (L), Ka is absorption rate constant (h^{-1}), K_{12} and K_{21} are intercompartimental elimination constants (h^{-1}), and D is the given dose in mg. WT is weight in Kg. INMD (any comedication with CBZ/PHB/PHT), VPA (valproic acid), NEMD (comedication with zonisamide) are binary values of 1 for true, 0 for false. A value of 1 will result in the change in CL being effected (i.e. x^1 = x), a value of 0 results in no change (i.e. x^0 = 1). Eta (η) is a random variable sampled from a normal distribution with mean 0 and variance of the omega squared of the corresponding number. Epsilon (ε) is a random variable sampled from a normal distribution with mean 0 and variance of the sigma squared of the corresponding number. T_D is time after dose (here always 0). Tau (τ) is the dosing interval. C_t is the simulated concentration (mg/L) at time *t*.

#	Theta (θ)	Omega squared (ω^2)	Sigma squared (σ^2)
1	1.21	0.0744	0.0648
2	0.479	1.35	0.0323
3	0.453	0.0499	
4	-0.00306		
5	1.94		
6	0.686		
7	0.635		
8	4.61		
9	1.14		
10	0.105		
11	0.577		
12	0.0586		

Based on this information, we simulated a dosing of 10 mg/kg/day (5 mg/kg/12 hours) in patients aged 10 years, to be validated against their predictions for such patients.

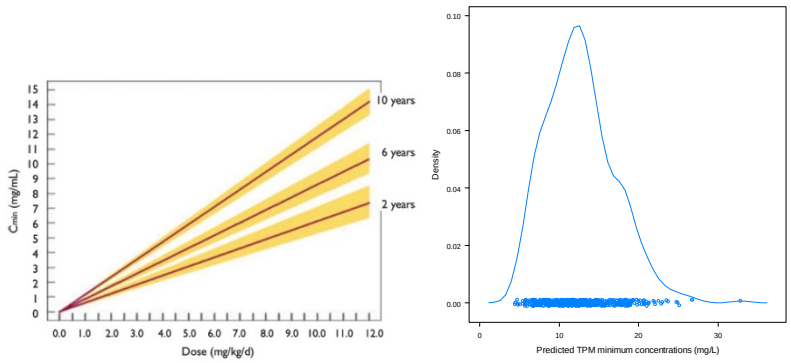

Figure 10. TPM predicted minimum concentrations from the Girgis paper (left) and our simulations (right)

Our predictions seem to correspond well with their model-based predictions of 10 mg/kg/day in a 10-year old patient.

2.11. Valproic Acid – Children – Blanco-Serrano et al. 1999[14]

Blanco-Serrano reports valproic acid (VPA) concentrations of 25.7-157 mg/L (mean: 65.3) after administration of 15.7-50 mg/kg/day (mean: 24.2) in a population of 0.1-14 years with weight 4.0-74 kg (mean: 31.3). Based on this information, we simulated a dosing of 25 mg/kg/day (12.5 mg/kg/12 hours) in patients aged 1-14 years. This model was defined as follows:

$$CL = \theta_1 \cdot WT^{\theta_2} \cdot DDMGKG^{\theta_3} \cdot (1 + \theta_4 * CBZ) \cdot e^{\eta_1}$$

$$Ka = \theta_5$$

$$V = \theta_6 \cdot WT$$

$$C_t = \frac{D}{V} \frac{k_a}{k_a - \frac{CL}{V}} \left(\frac{e^{-\frac{CL}{V}(t-t_D)}}{1-e^{-\frac{CL}{V}\tau}} - \frac{e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}} \right) \cdot (1 + \varepsilon_1)$$

Where CL is clearance (L/h), V is volume (L), Ka is absorption rate constant (h^{-1}), and D is the given dose in mg. DDMGKG is the daily dose in mg/kg. WT is weight in Kg. CBZ (carbamazepine) is a binary value of 1 for true, 0 for false. A value of 1 will result in the change in CL being effected (i.e. x^1 = x), a value of 0 results in no change (i.e. x^0 = 1). Eta (η) is a random variable sampled from a normal distribution with mean 0 and variance of the omega squared of the corresponding number. Epsilon (ε) is a random variable sampled from a normal distribution with mean 0 and variance of the sigma squared of the corresponding number. T_D is time after dose (here always 0). Tau (τ) is the dosing interval. C_t is the simulated concentration (mg/L) at time *t*.

#	Theta (θ)	Omega squared (ω^2)	Sigma squared (σ^2)
1	0.012	0.046255	0.1556
2	0.715		
3	0.306		
4	0.359		
5	1.9		
6	0.24		

No plots of concentrations were provided by Blanco-Serrano and thus a density plot was generated using their reported mean VPA concentration 65.3 mg/L and an estimated sd of 20 (based on trial-and-error random sampling with varying sd until a range was derived similar to that reported in their paper).

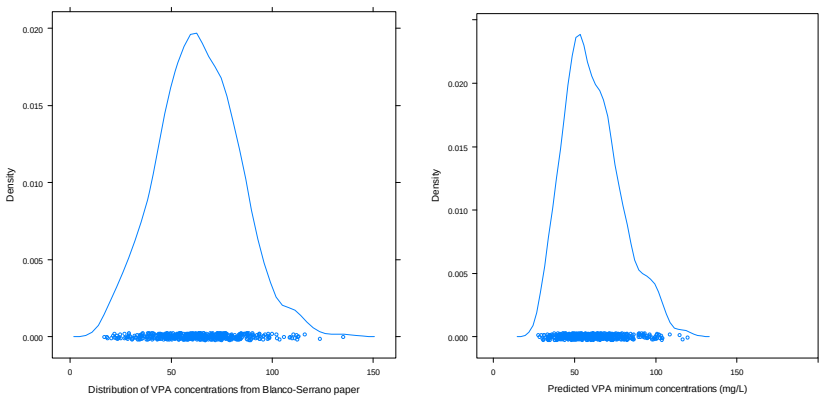

Figure 11. VPA concentrations based on the Blanco-Serrano paper (left) and from our simulations (right)

These simulations seem to correspond well to Blanco-Serrano's observations.

2.12. Valproic Acid – Adults – Blanco-Serrano et al. 1999[15]

Blanco-Serrano reports valproic acid (VPA) concentrations of 21-123 mg/L after administration of a mean weight-adjusted dose of 17.2 mg/kg/day in a population of 14-95 years with weight 27-100 kg (mean: 64.1). This model was defined as follows:

$$CL = \theta_1 \cdot WT \cdot DDMGKG^{\theta_2} \cdot (1 + \theta_3 * CBZ) \cdot (1 + \theta_4 * PHT) \cdot (1 + \theta_5 * PHB) \cdot e^{\eta_1}$$

$$Ka = \theta_6$$

$$V = \theta_7 \cdot WT$$

$$C_t = \frac{D}{V} \frac{k_a}{k_a - \frac{CL}{V}} \left(\frac{e^{-\frac{CL}{V}(t-t_D)}}{1-e^{-\frac{CL}{V}\tau}} - \frac{e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}} \right) + \varepsilon_1$$

Where CL is clearance (L/h), V is volume (L), Ka is absorption rate constant (h^{-1}), and D is the given dose in mg. DDMGKG is the daily dose in mg/kg. WT is weight in Kg. CBZ (carbamazepine), PHT (phenytoin), PHB (phenobarbital) are binary values of 1 for true, 0 for false. A value of 1 will result in the change in CL being effected (i.e. x^1 = x), a value of 0 results in no change (i.e. x^0 = 1). Eta (η) is a random variable sampled from a normal distribution with mean 0 and variance of the omega squared of the corresponding number. Epsilon (ε) is a random variable sampled from a normal distribution with mean 0 and variance of the sigma squared of the corresponding number. T_D is time after dose (here always 0). Tau (τ) is the dosing interval. C_t is the simulated concentration (mg/L) at time *t*.

#	Theta (θ)	Omega squared (ω^2)	Sigma squared (σ^2)
1	0.004	0.0547	11.36
2	0.304		
3	0.363		
4	0.541		
5	0.397		
6	1.2		
7	0.2		

Based on this information, we simulated a dosing of 18 mg/kg/day (9 mg/kg/12 hours) in patients aged 14-95 years.

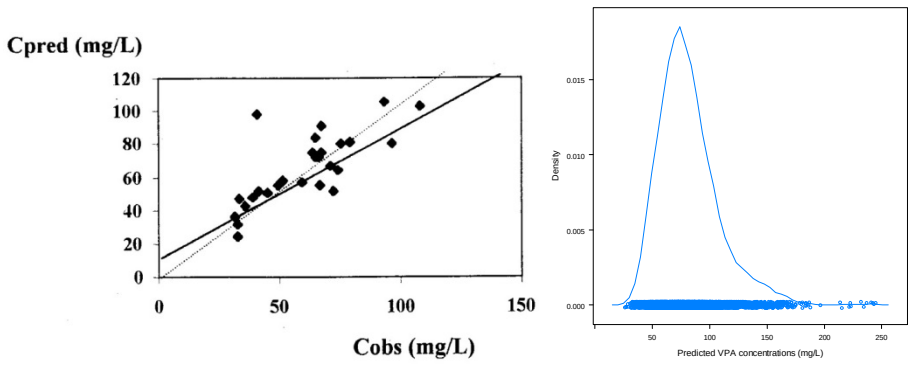

Figure 12. VPA concentrations from the Blanco-Serrano paper (left) and our simulations (right)

The majority of the simulated concentrations correspond with those reported by Blanco-Serrano. Blanco-Serrano only reported very few concentrations, which could explain why the range of simulated concentrations is larger, although another reason is explained in conclusions below. A small cluster of very high concentrations can be seen in the simulated concentrations, which were the result of sampling a very low clearance from the distribution of clearance, which is a chance finding and corresponds to outliers sometimes found in reality.

2.13. Zonisamide – Okada et al. 2008[16]

Okada reports zonisamide (ZNS) concentrations of 2-89 mg/L (mean: 24.4, sd: 16.1) after administration of 40-800 mg/day (mean: 251.2) in a population of 1.36-39.24 years with weight 10-117 kg (mean: 40.7). Based on this information, we simulated a dosing of 6 mg/kg/day (3 mg/kg/12 hours) in patients aged 1-40 years. This model was defined as follows:

$$CL = \theta_1 \cdot \left(\frac{WT}{44}\right)^{\theta_2} \cdot DD^{\theta_3} \cdot \theta_4{}^{CYP2C19hetEM} \cdot \theta_5{}^{CYP2C19PM} \cdot \theta_6{}^{CBZ} \cdot \theta_7{}^{PHT} \cdot \theta_8{}^{PHB} \cdot e^{\eta_1}$$

$$V = \theta_9 \cdot WT$$

$$Ka = \theta_{10}$$

$$C_t = \frac{D}{V} \frac{k_a}{k_a - \frac{CL}{V}} \left(\frac{e^{-\frac{CL}{V}(t-t_D)}}{1-e^{-\frac{CL}{V}\tau}} - \frac{e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}} \right) \cdot (1+\varepsilon_1)$$

Where CL is clearance (L/h), V is volume (L), Ka is absorption rate constant (h^{-1}), and D is the given dose in mg. DD is the daily dose in mg/day. WT is weight in Kg. ZNS (zonisamide), PHB (phenobarbital), PHT (phenytoin), CYP2C19hetEM (heterozygote extended metaboliser in CYP2C19), CYP2C19PM (poor metaboliser in CYP2C19), CBZ (carbamazepine), PHT (phenytoin), PHB (phenobarbital) are binary values of 1 for true, 0 for false. A value of 1 will result in the change in CL being effected (i.e. x^1 = x), a value of 0 results in no change (i.e. x^0 = 1). Eta (η) is a random variable sampled from a normal distribution with mean 0 and variance of the omega squared of the corresponding number. Epsilon (ε) is a random variable sampled from a normal distribution with mean 0 and variance of the sigma squared of the corresponding number. T_D is time after dose (here always 0). Tau (τ) is the dosing interval. C_t is the simulated concentration (mg/L) at time *t*.

#	Theta (θ)	Omega squared (ω^2)	Sigma squared (σ^2)
1	1.22	0.076	0.05
2	0.77		
3	-0.17		
4	0.84		
5	0.70		
6	1.24		
7	1.28		
8	1.29		
9	1.23		
10	2		

No plots of concentrations were provided by Okada and thus a density plot was generated using 500 randomly generated concentrations of a normal distribution using their reported mean and sd of ZNS concentrations.

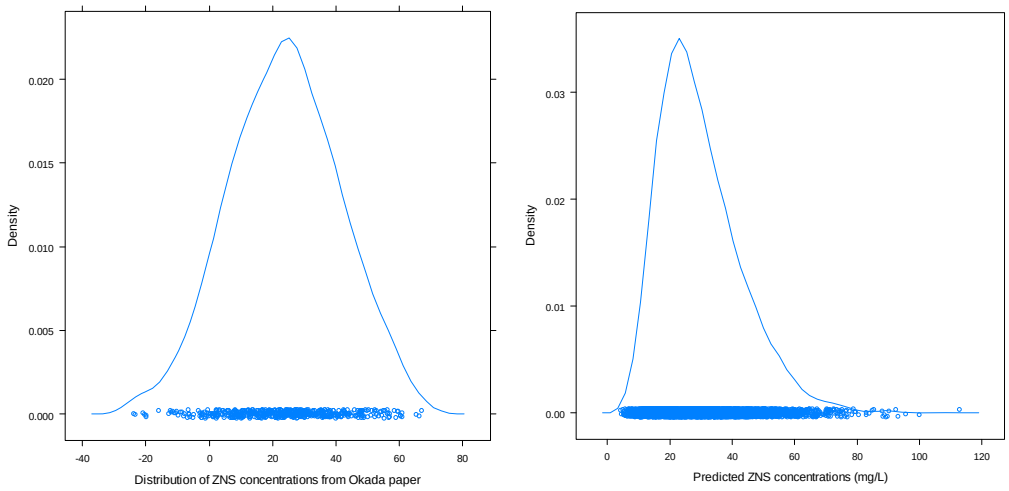

Figure 13. ZNS concentrations based on the Okada paper (left) and from our simulations (right)

Due to the large sd relating to the Okada concentrations, some of the randomly sampled concentrations end up in the negative, a result of the normal distribution which allows this. Apart from this discrepancy, predicted concentrations roughly correspond with those reported, although higher concentrations are included in the predicted, a possible reason for this is further explained in the conclusions.

3. Points to consider based on the evaluation of individual model performance

All models yielded reasonably similar predictions compared to their original data for model building, although a consistent difference in mean and peak predicted concentrations was found for most models. After multiple reviews of the implementation of the models, we have concluded that the models were implemented correctly. However, as AED concentrations are often sampled at time-points after the absorption and distribution phases have occurred, discrepancies were observed due to the lack of a frequent sampling schedule.

4. Results of simulations of concentrations over time for each scenario

In this section we report the simulation results of each mono- and polytherapy simulation scenario per anti-epileptic drug, with regard to the adult (4.1) and paediatric (4.2) populations. Results for the paediatric population are discussed in terms of agreement or disagreement with those in the adult population. Findings are depicted as median and 95% prediction interval of concentrations over time during the dosing interval, and they are discussed in brief with regard to the therapeutic window. An overview (summary graphs and discussion) of peak (Cmax) and trough (Cmin) concentrations per simulation scenario is presented in the final section (5).

4.1. Adults

4.1.1 Carbamazepine (CBZ)

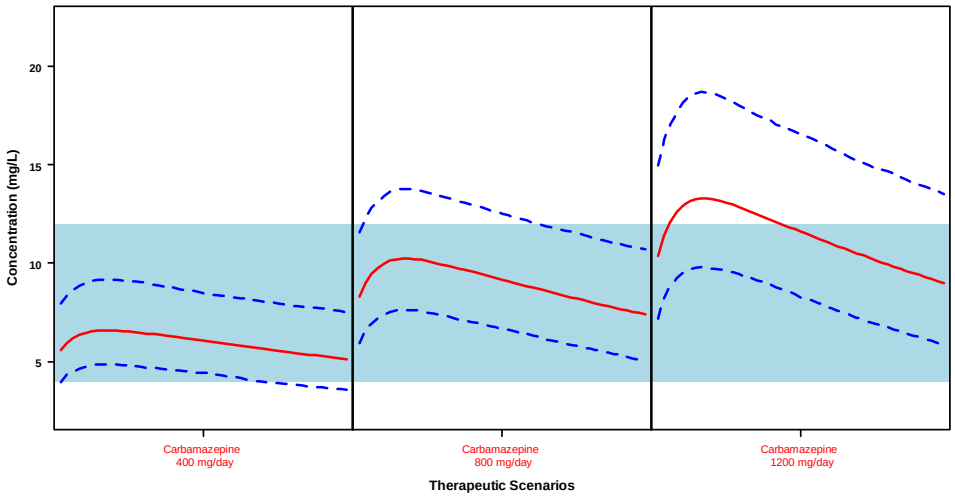

Figure 14. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of carbamazepine concentrations at steady-state resulting from doses of 400, 800, and 1200 mg/day. Each panel corresponds to the dosing interval time window of 12 hours.

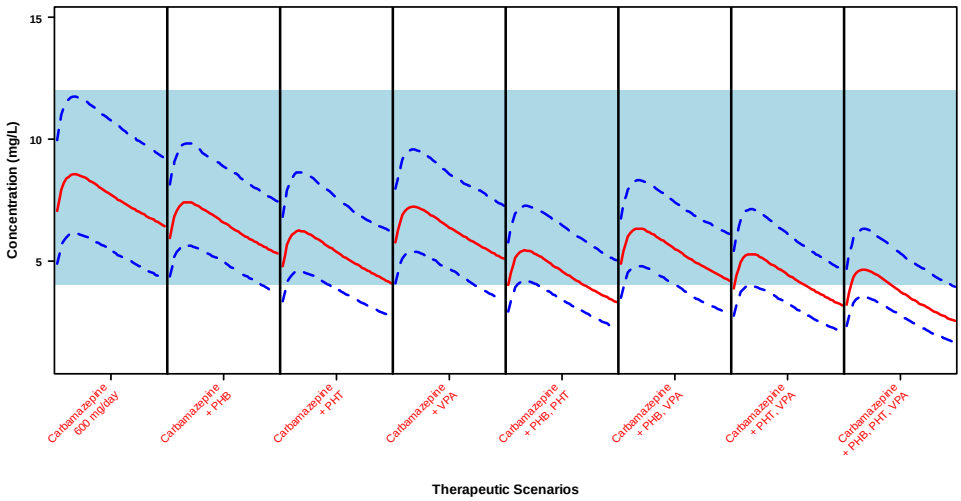

Figure 15. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of carbamazepine concentrations at steady-state resulting from a 600 mg/day carbamazepine dose and comedication with phenobarbital (PHB), and/or phenytoin (PHT), and/or valproic acid (VPA). Each panel corresponds to the dosing interval time window of 12 hours.

The auto-induction involved in CBZ PK (CBZ dose as a covariate on CBZ clearance) results in larger peak/trough differences when the dose is increased (figure 14), whereas such changes are not observed when introducing comedication with PHB, PHT, or VPA (figure 15). Whether this is an intended result of the manner in which the model was coded is unclear. It is possible that an induction of CBZ clearance by any of the comedications would interact with CBZ auto-induction, thereby leading to some non-linearity in the dose-exposure relationship. All DDIs, implemented in a multiplicative fashion in the model, resulted in increased CBZ clearance, thereby reducing exposure. While comedication with PHB or VPA alone still leads to adequate CBZ exposure, two or more comedications can lead to trough concentrations below the therapeutic minimum.

4.1.2 Clobazam

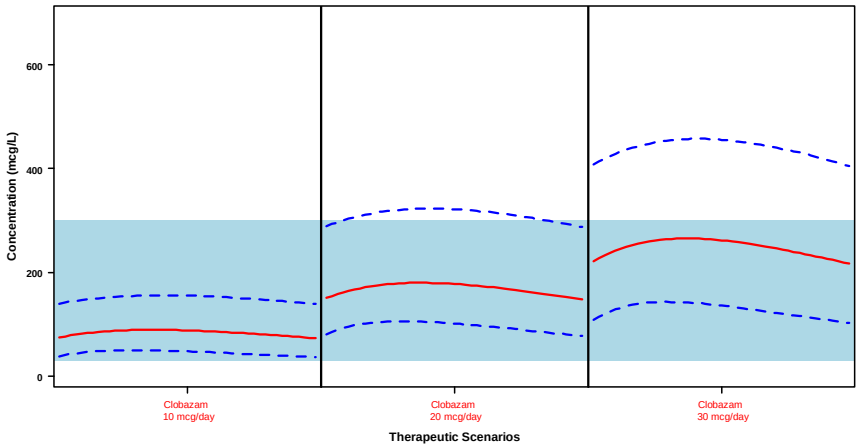

Figure 16. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of clobazam concentrations at steady-state resulting from doses of 10, 20, and 30 µg/day. Each panel corresponds to the dosing interval time window of 12 hours.

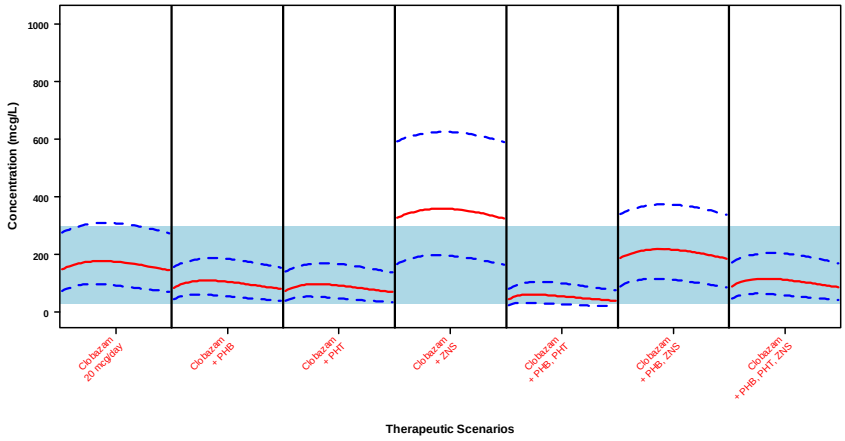

Figure 17. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of clobazam concentrations at steady-state resulting from a 20 µg/day clobazam dose and comedication with phenobarbital (PHB), and/or phenytoin (PHT), and/or zonisamide (ZNS). Each panel corresponds to the dosing interval time window of 12 hours.

Clobazam is absorbed slowly, leading to relatively small peak/trough differences. Depending on dose, variability in PK profiles increases quite much (figure 16). Regardless, due to the small peak/trough differences, a dose of 20 µg/day results in therapeutic concentrations throughout the dosing interval without many patients experiencing peak or trough concentrations outside the therapeutic window. While single add-on medication of PHB or PHT will probably not result in supra or subtherapeutic peak/trough concentrations, total exposure is reduced, and when CLBZ is combined with both PHB and PHT, the PK profiles drop to the lower end of the therapeutic window. When CLBZ is given in combination with ZNS, clearance is greatly inhibited and most virtual subjects have a PK profile that is constantly above the therapeutic maximum.

4.1.3 Clonazepam

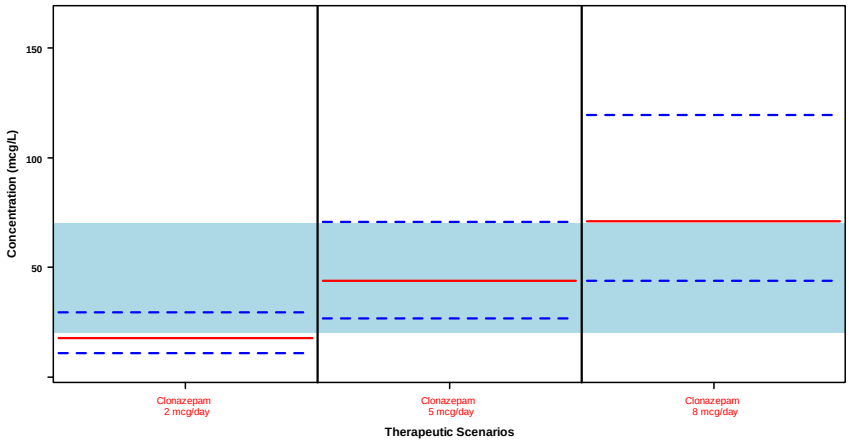

Figure 18. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of clonazepam concentrations at steady-state resulting from doses of 2, 5, and 8 μg/day. Each panel corresponds to the dosing interval time window of 12 hours.

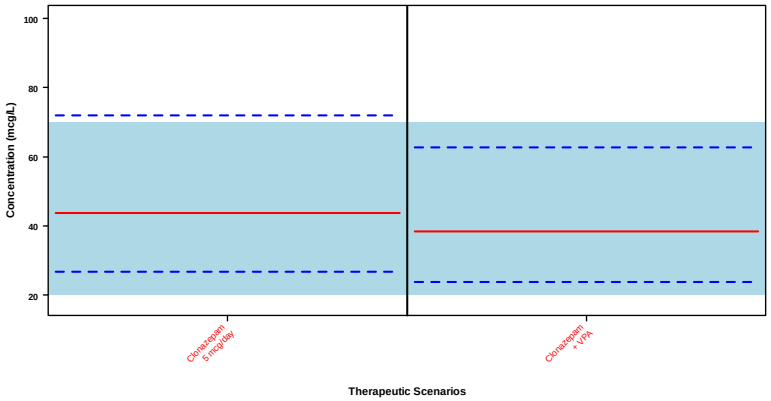

Figure 19. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of clonazepam concentrations at steady-state resulting from a 5 μg/day clonazepam dose and comedication with valproic acid (VPA). Each panel corresponds to the dosing interval time window of 12 hours.

The PK model of clonazepam does not take into account absorption and thus does not accurately represent peak and trough concentrations; while a 5 μg/day dose seems to result in concentrations mostly within the therapeutic window, in reality peak and trough concentrations may fall outside of this window. Changes in dose significantly change variability in PK profiles. An increase in dose of roughly 50% (5 to 8 μg/day) results in about 50% of the population attaining supratherapeutic concentrations where before most fell well within the therapeutic window. VPA increases CLNZ clearance by only 16%, which here did not have a large impact on concentrations within/outside the therapeutic window.

4.1.4 Lamotrigine

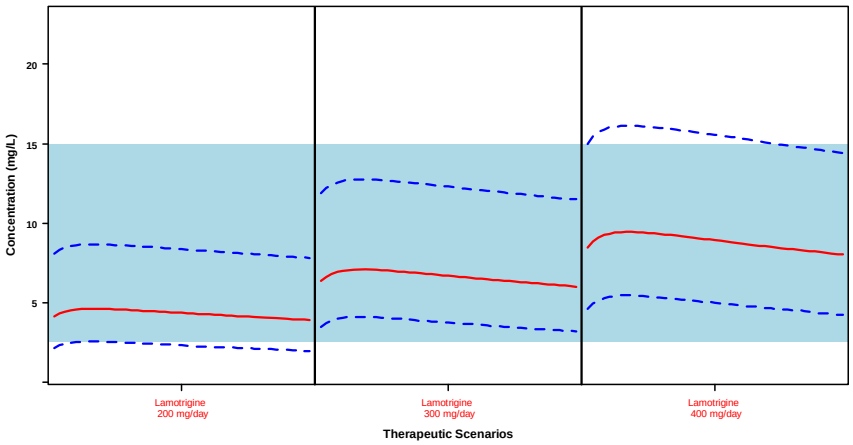

Figure 20. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of lamotrigine concentrations at steady-state resulting from doses of 200, 300, and 400 mg/day. Each panel corresponds to the dosing interval time window of 12 hours.

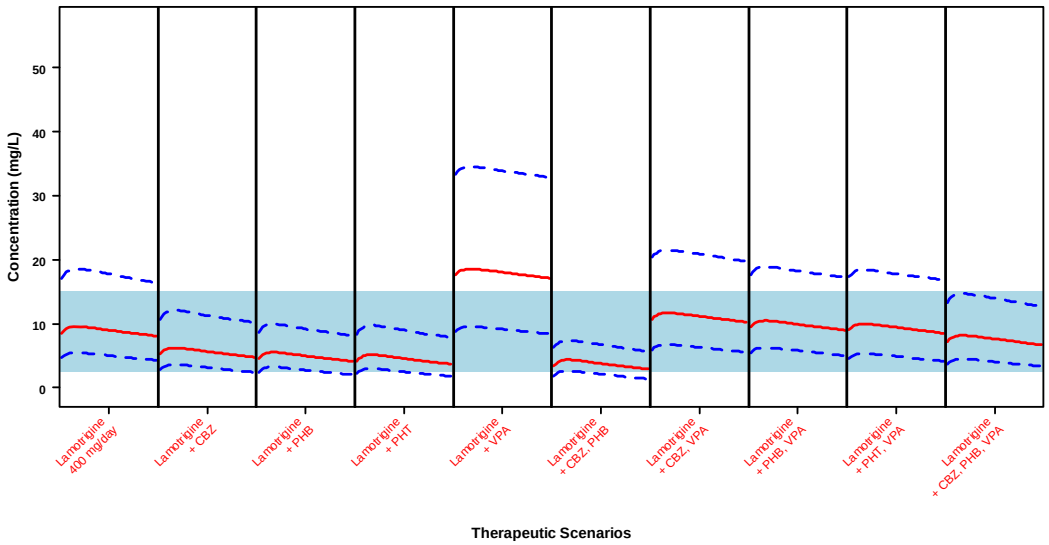

Figure 21. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of lamotrigine concentrations at steady-state resulting from a 400 mg/day lamotrigine dose and comedication with carbamazepine (CBZ), and/or phenobarbital (PHB), and/or phenytoin (PHT), and/or valproic acid (VPA). Each panel corresponds to the dosing interval time window of 12 hours.

Lamotrigine is rapidly absorbed and shows steady PK profiles, leading to relatively small peak/trough differences, and variability in PK profiles is fairly small relative to its therapeutic window (figure 20). LMT clearance is induced by CBZ, PHB, and PHT, each to a moderate degree, resulting in only mildly reduced exposure in single comedication addition, yet more pronounced changes when two or three are added. VPA reduces LMT clearance to a large degree, resulting in a large portion of the population attaining supratherapeutic concentrations. This drug-drug interaction with VPA can in part be cancelled out when one or more of the inducers are added (figure 21).

4.1.5 Levetiracetam

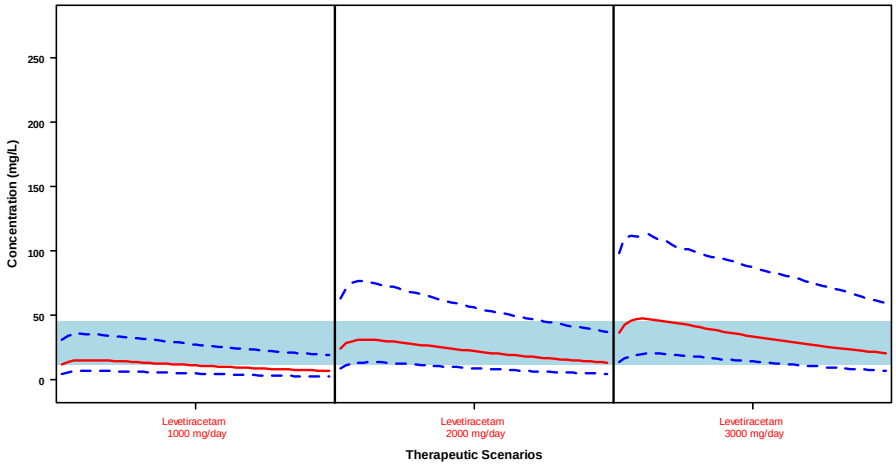

Figure 22. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of levetiracetam concentrations at steady-state resulting from doses of 1000, 2000, and 3000 mg/day. Each panel corresponds to the dosing interval time window of 12 hours.

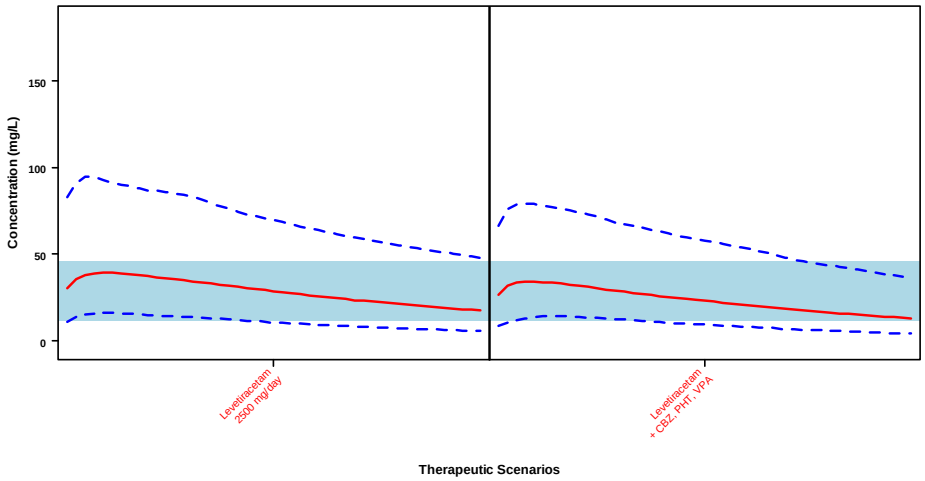

Figure 23. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of levetiracetam concentrations at steady-state resulting from a 2500 mg/day levetiracetam dose and comedication with an inducer (carbamazepine (CBZ), or phenytoin (PHT), or valproic acid (VPA)). Each panel corresponds to the dosing interval time window of 12 hours.

Although levetiracetam PK profiles are fairly stable over the dosing interval, its variability is large relative to its therapeutic window, resulting in a portion of the population achieving concentrations outside the therapeutic window for the simulated LVT doses (figure 22). When an inducer is added as comedication (any out of CBZ, PHT or VPA), only very small changes in PK profiles are observed (figure 23).

5.1.6 Oxcarbazepine

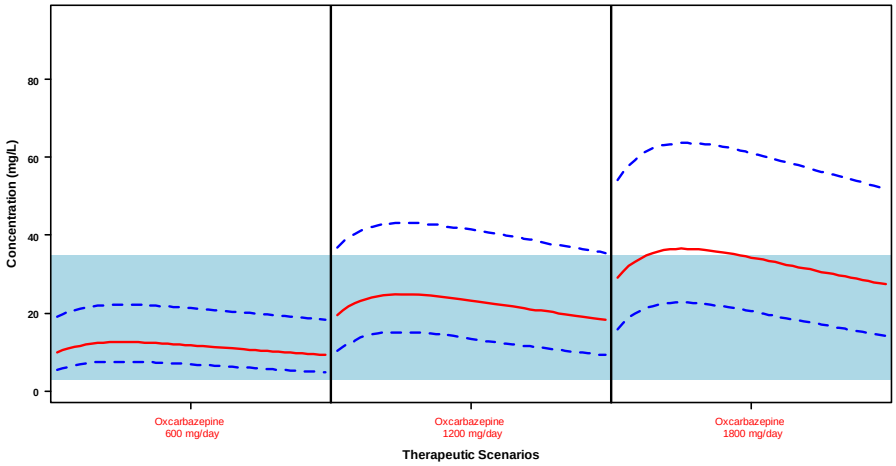

Figure 24. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of MHD concentrations at steady-state resulting from oxcarbazepine doses of 600, 1200, and 1800 mg/day. Each panel corresponds to the dosing interval time window of 12 hours.

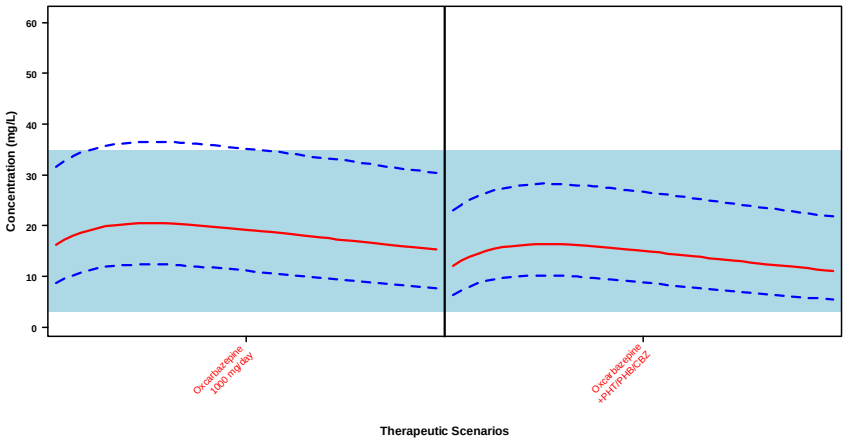

Figure 25. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of MHD concentrations at steady-state resulting from a 1000 mg/day oxcarbazepine dose and comedication with an inducer (phenytoin (PHT), or phenobarbital (PHB), or carbamazepine (CBZ)). Each panel corresponds to the dosing interval time window of 12 hours.

When oxcarbazepine is absorbed, it is subsequently almost completely converted into its active metabolite monohydroxy-derivative (MHD) during the first pass through the liver. This process results in smooth PK curves, thereby reducing peak/trough differences, whereas changes in the dose increase these peak/trough differences (figure 24). The addition of any of the inducers PHT, PHB, or CBZ increases MHD clearance by roughly 30%, yet this does not lead to large apparent changes in the PK profiles, although overall exposure is still affected (figure 25).

4.1.7 Phenobarbital

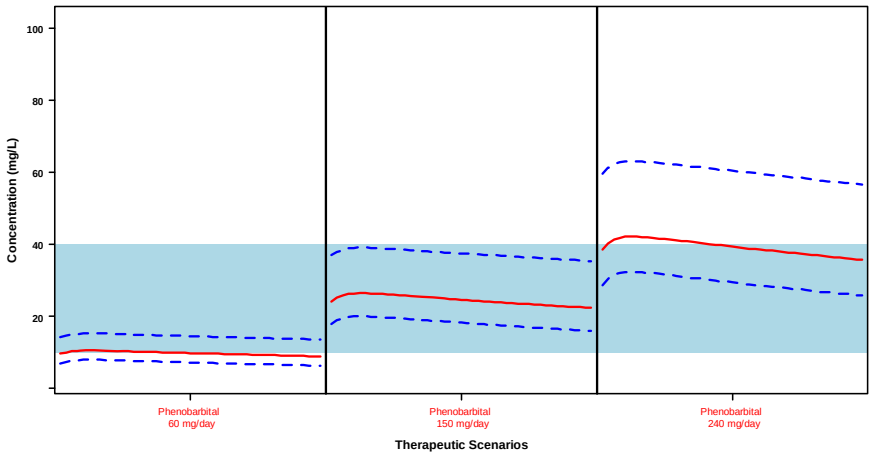

Figure 26. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of phenobarbital concentrations at steady-state resulting from doses of 60, 150, and 240 mg/day. Each panel corresponds to the dosing interval time window of 12 hours.

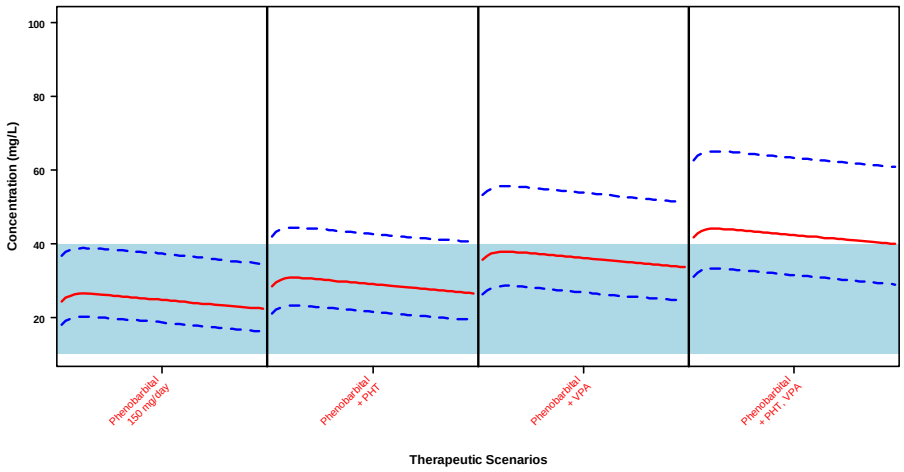

Figure 27. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of phenobarbital concentrations at steady-state resulting from a 150 mg/day phenobarbital dose and comedication with phenytoin (PHT), and/or valproic acid (VPA). Each panel corresponds to the dosing interval time window of 12 hours.

Phenobarbital is rapidly absorbed with only moderate peaks and a subsequent slow elimination slope, and thus small peak/trough concentration differences. Concentrations in the simulated dose range may often be found outside the therapeutic window for a significant portion of the population (figure 26). The addition of comedication PHT results in only a mild reduction in PHB clearance, and thereby increases in PHB concentrations, with a small portion of the population attaining supratherapeutic concentrations. Comedication with VPA however decreases PHB clearance to a larger degree, resulting in a more significant portion of the population achieving supratherapeutic concentrations, which is further attenuated when PHT is added on top of it (figure 27).

4.1.8 Phenytoin

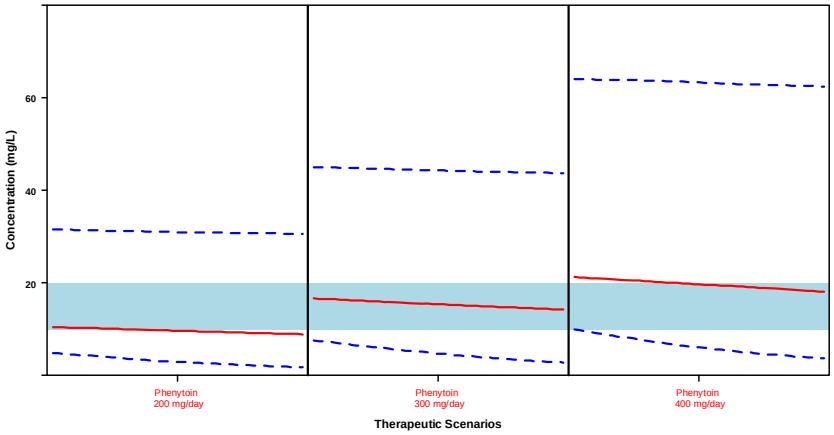

Figure 28. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of phenytoin concentrations at steady-state resulting from doses of 200, 300, and 400 mg/day. Each panel corresponds to the dosing interval time window of 12 hours.

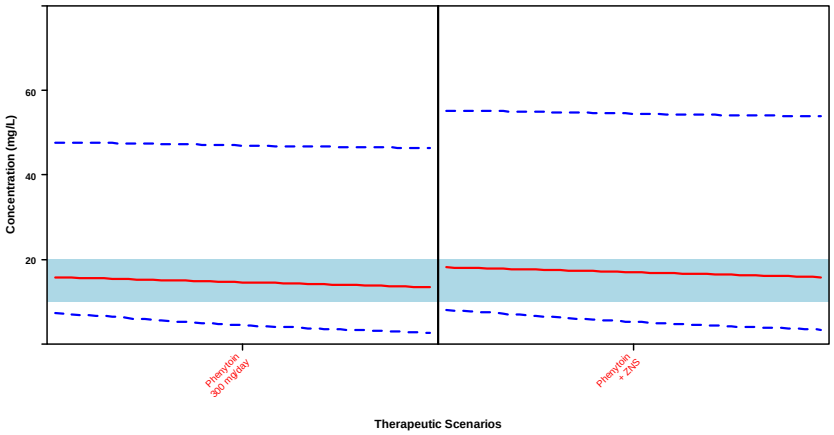

Figure 29. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of phenytoin concentrations at steady-state resulting from a 300 mg/day phenytoin dose and comedication with zonisamide (ZNS). Each panel corresponds to the dosing interval time window of 12 hours.

Phenytoin is the only AED in these simulations for which no dose can be chosen at which at least 95% of the population achieves steady-state concentrations within the therapeutic window, due to its large variability and relatively narrow therapeutic window. The model that is used does not take into account absorption processes, meaning that peak concentrations may be higher than shown here. Comedication with ZNS decreases PHT clearance by only 16%, and does not lead to a large impact on the steady-state concentrations (figure 29).

4.1.9 Topiramate

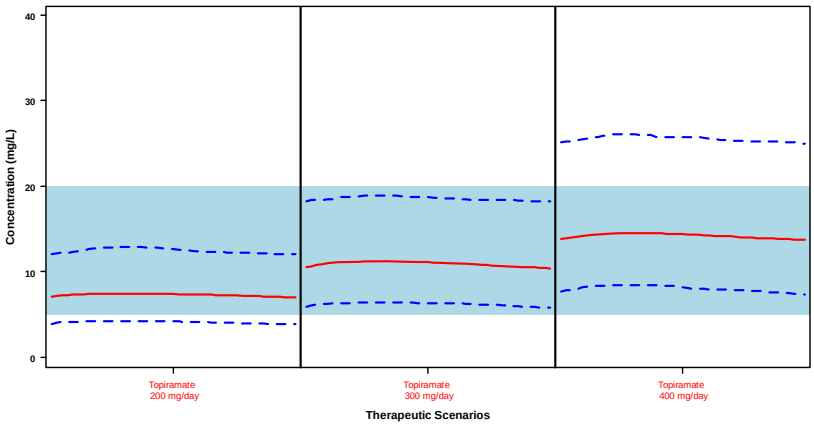

Figure 30. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of topiramate concentrations at steady-state resulting from doses of 200, 300, and 400 mg/day. Each panel corresponds to the dosing interval time window of 12 hours.

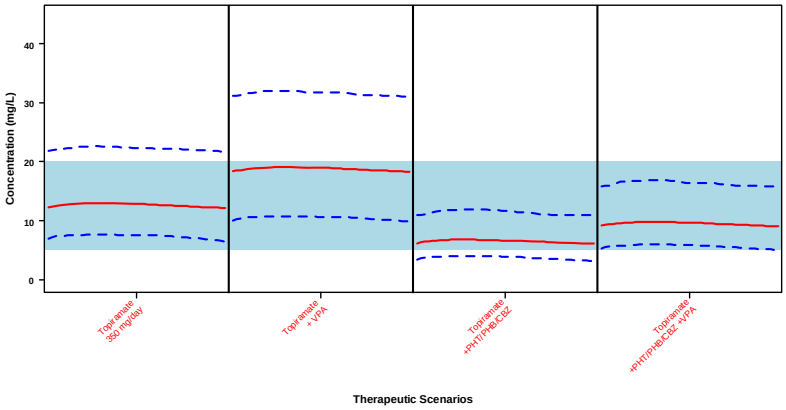

Figure 31. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of topiramate concentrations at steady-state resulting from a 350 mg/day topiramate dose and comedication with valproic acid (VPA), and/or phenytoin (PHT) or phenobarbital (PHB) or carbamazepine (CBZ). Each panel corresponds to the dosing interval time window of 12 hours.

The PK profiles of topiramate show its slow absorption and corresponding smooth PK curves. Its PK variability allows a dose of 300 mg/day to result in steady-state concentrations over time to fit snugly within the therapeutic window (figure 30). The addition of VPA results in a large decrease in TPM clearance and thereby raises concentrations to supratherapeutic levels in roughly 50% of the population, which may be mitigated by the addition of any of the inducers PHT, PHB or CBZ (figure 31).

4.1.10 Valproic Acid

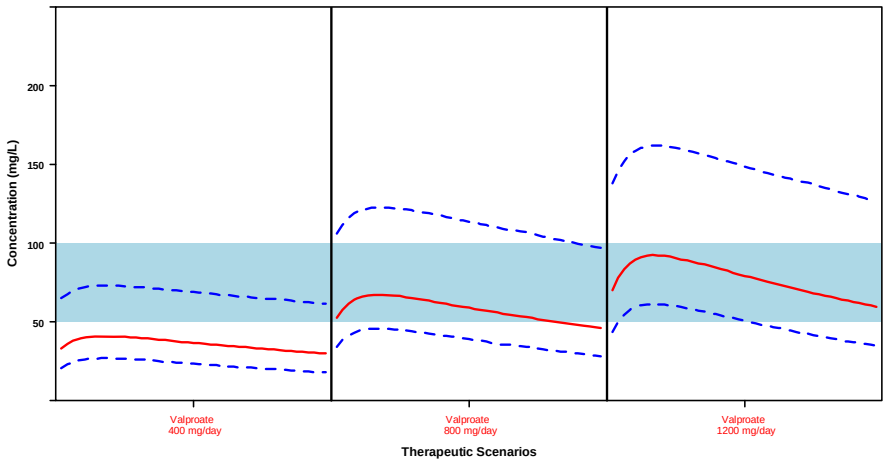

Figure 32. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of valproic acid concentrations at steady-state resulting from doses of 400, 800, and 1200 mg/day. Each panel corresponds to the dosing interval time window of 12 hours.

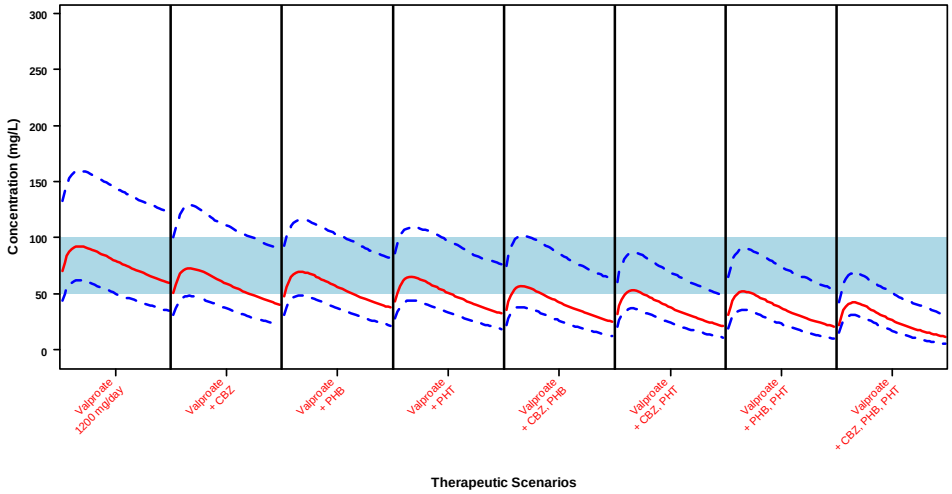

Figure 33. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of valproic acid concentrations at steady-state resulting from a 1200 mg/day valproic acid dose and comedication with carbamazepine (CBZ), and/or phenobarbital (PHB), and/or phenytoin (PHT). Each panel corresponds to the dosing interval time window of 12 hours.

The valproic acid PK model here includes auto-induction on its clearance, which leads to increased peak/trough concentration differences at increased dose levels. The variability in VPA PK curves is large relative to the therapeutic window, leading to a small portion of the population achieving concentrations outside the therapeutic window at any dose (figure 32). VPA clearance can be induced by CBZ, PHB and PHT, each of which proportionally “stacks”, i.e. each added comedication compounds the induced clearance by the other comedications, leading to subtherapeutic concentrations especially when two or more comedications are given (figure 33).

4.1.11 Zonisamide

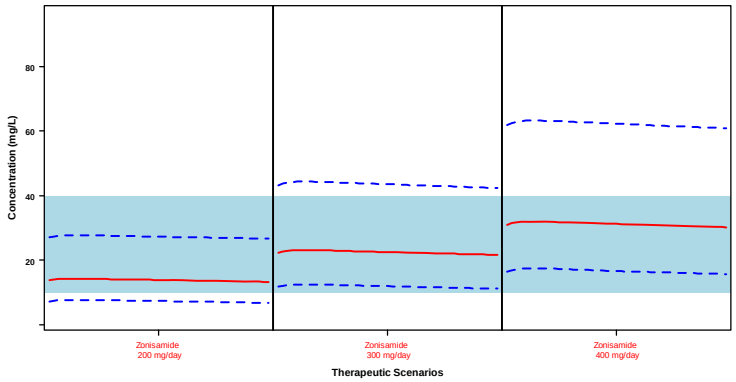

Figure 34. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of zonisamide concentrations at steady-state resulting from doses of 200, 300, and 400 mg/day. Each panel corresponds to the dosing interval time window of 12 hours.

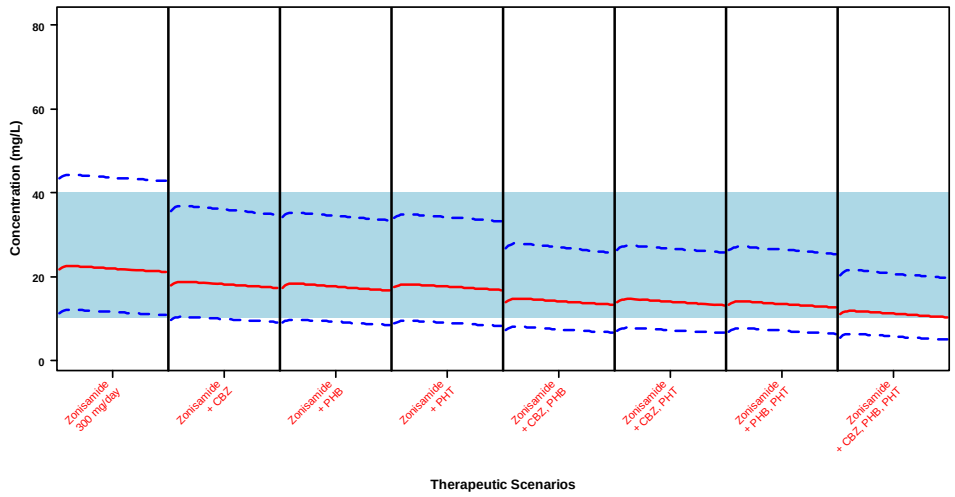

Figure 35. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of zonisamide concentrations at steady-state resulting from a 300 mg/day zonisamide dose and comedication with carbamazepine (CBZ), and/or phenobarbital (PHB), and/or phenytoin (PHT). Each panel corresponds to the dosing interval time window of 12 hours.

Zonisamide PK curves are very smooth, with small differences between peak and trough concentrations. Variability allows selecting a dose that results in concentrations within the therapeutic window for most of the population (figure 34). Comedications CBZ, PHB, and PHT induce ZNS clearance each by only a moderate degree, but when added in combination may result in subtherapeutic ZNS concentrations (figure 35).

4.2. Children

4.2.1 Carbamazepine

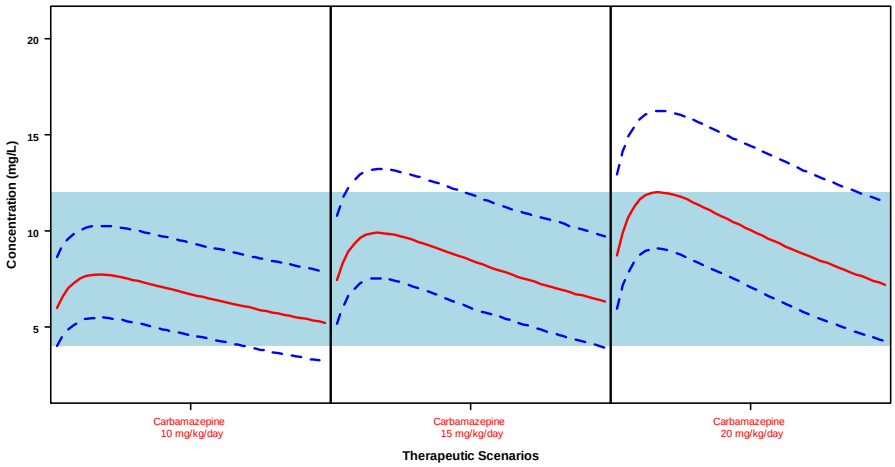

Figure 36. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of carbamazepine concentrations at steady-state resulting from doses of 10, 15, and 20 mg/kg/day. Each panel corresponds to the dosing interval time window of 12 hours.

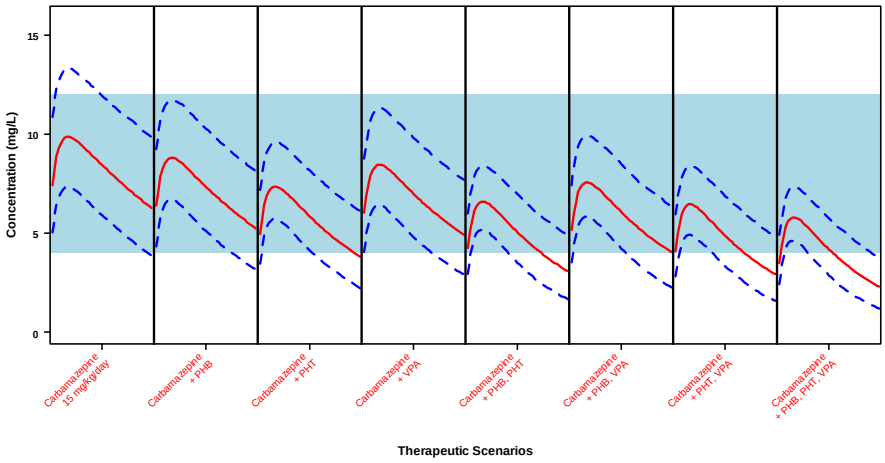

Figure 37. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of carbamazepine concentrations at steady-state resulting from a 15 mg/kg/day carbamazepine dose and comedication with phenobarbital (PHB), and/or phenytoin (PHT), and/or valproic acid (VPA). Each panel corresponds to the dosing interval time window of 12 hours.

The profiles in the paediatric population largely resemble those in adults. Peak/trough differences are slightly larger in children compared to adults, especially in the case of comedication (figure 15 vs 37). The impact of comedication shows no other discernible difference between adults and children.

4.2.2 Clobazam

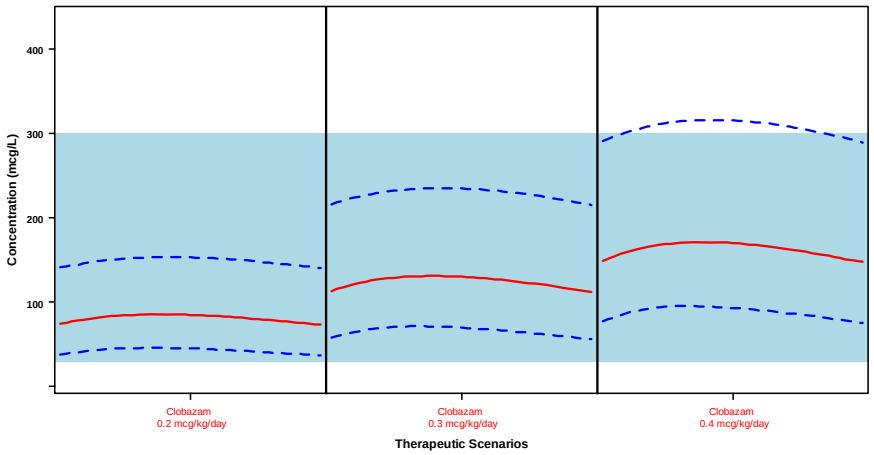

Figure 38. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of clobazam concentrations at steady-state resulting from doses of 0.2, 0.3, and 0.4 μg/kg/day. Each panel corresponds to the dosing interval time window of 12 hours.

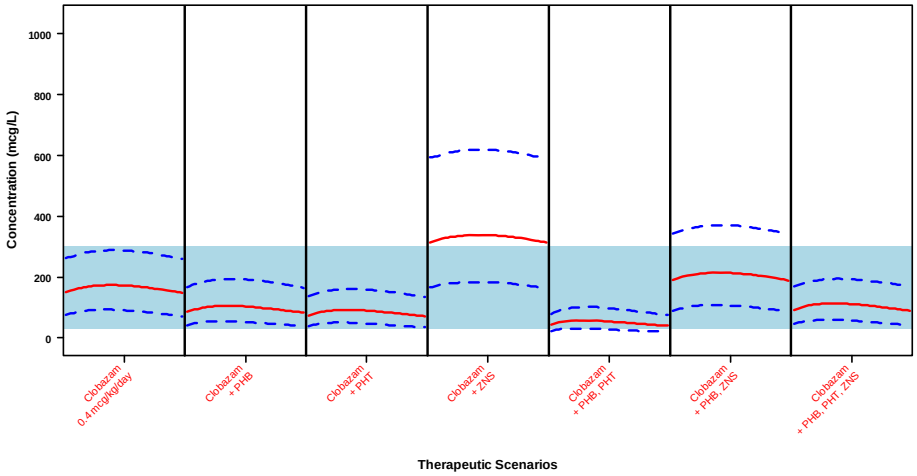

Figure 39. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of clobazam concentrations at steady-state resulting from a 0.4 μg/kg/day clobazam dose and comedication with phenobarbital (PHB), and/or phenytoin (PHT), and/or zonisamide (ZNS). Each panel corresponds to the dosing interval time window of 12 hours.

No differences between the results in adults and children can be observed.

4.2.3 Clonazepam

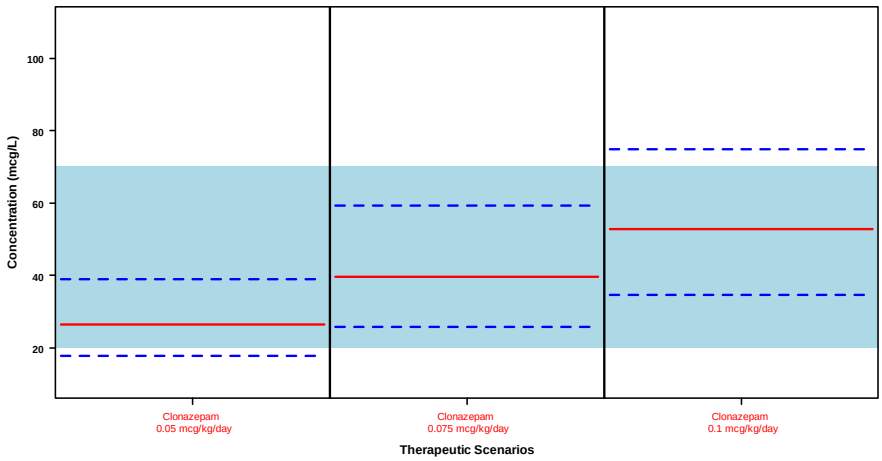

Figure 40. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of clonazepam concentrations at steady-state resulting from doses of 0.05, 0.075, and 0.1 μg/kg/day. Each panel corresponds to the dosing interval time window of 12 hours.

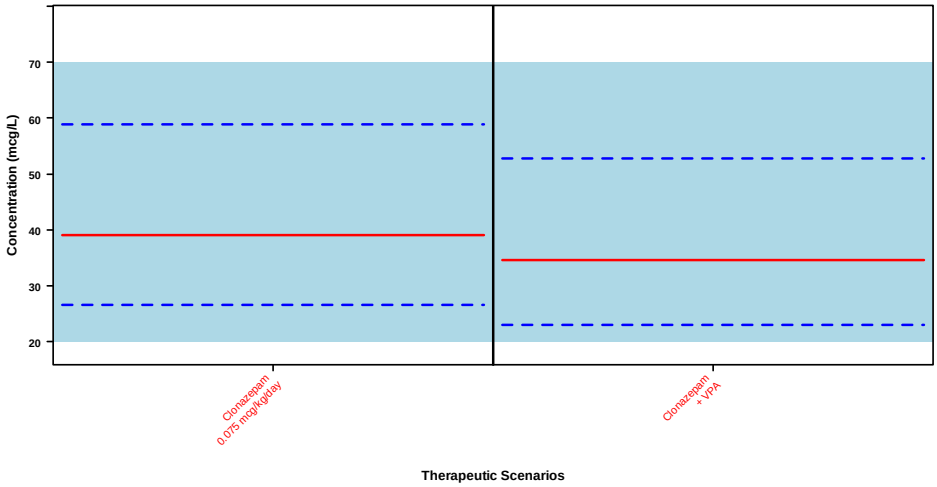

Figure 41. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of clonazepam concentrations at steady-state resulting from a 0.075 μg/kg/day clonazepam dose and comedication with valproic acid (VPA). Each panel corresponds to the dosing interval time window of 12 hours.

Clonazepam PK variability in children seems slightly smaller relative to its therapeutic window when compared to that in adults. Otherwise, no clear differences can be observed.

4.2.4 Lamotrigine

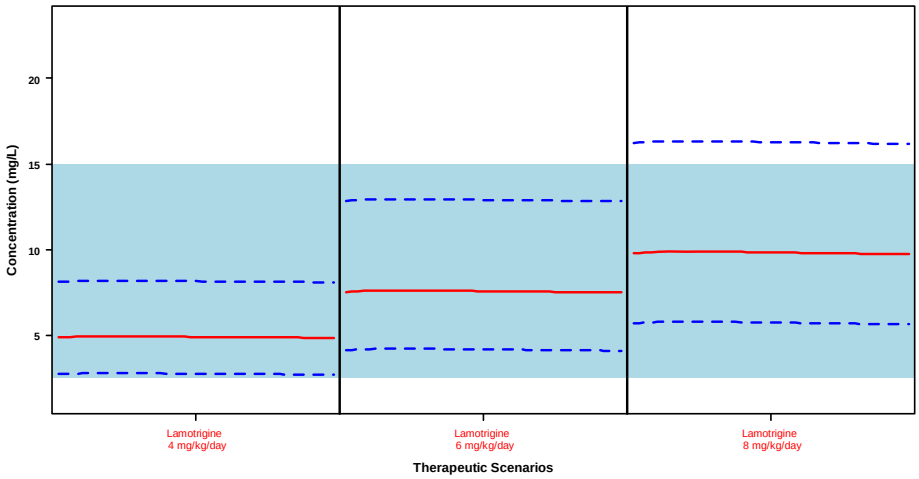

Figure 42. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of lamotrigine concentrations at steady-state resulting from doses of 4, 6, and 8 mg/kg/day. Each panel corresponds to the dosing interval time window of 12 hours.

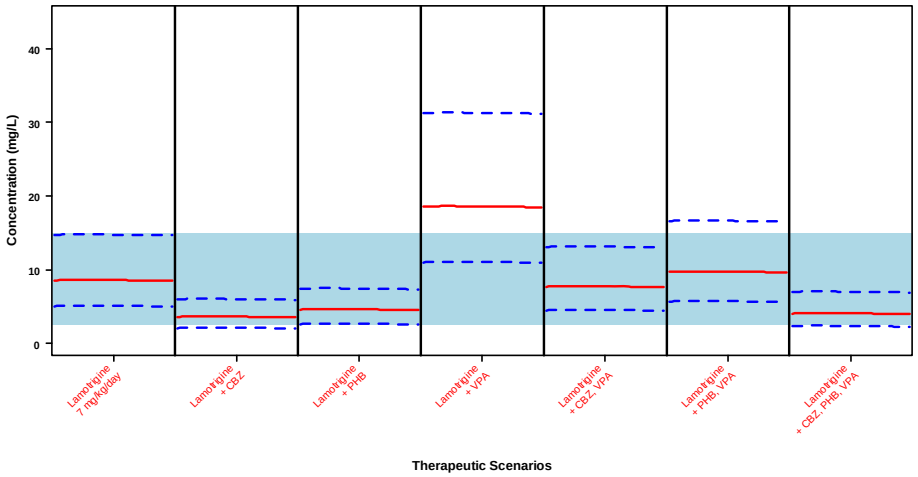

Figure 43. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of lamotrigine concentrations at steady-state resulting from a 7 mg/kg/day lamotrigine dose and comedication with carbamazepine (CBZ), and/or phenobarbital (PHB), and/or valproic acid (VPA). Each panel corresponds to the dosing interval time window of 12 hours.

Lamotrigine absorption in the paediatric PK model was a little slower (1 h^{-1} vs 1.3 h^{-1} in the adult model), resulting in much less pronounced peaks and even flatter curves. Otherwise, variability relative to the therapeutic window is roughly similar between adults and children. The paediatric model does not take into account drug-drug interactions with PHT, whereas the adult model does. The impact of CBZ comedication seems a bit larger in children, while that of PHB is similar to that in adults. Due to the difference in CBZ impact, the co-administration of all three comedications does not result in the same level of cancelling-out of clearance inducing and inhibiting effects.

4.2.5 Levetiracetam

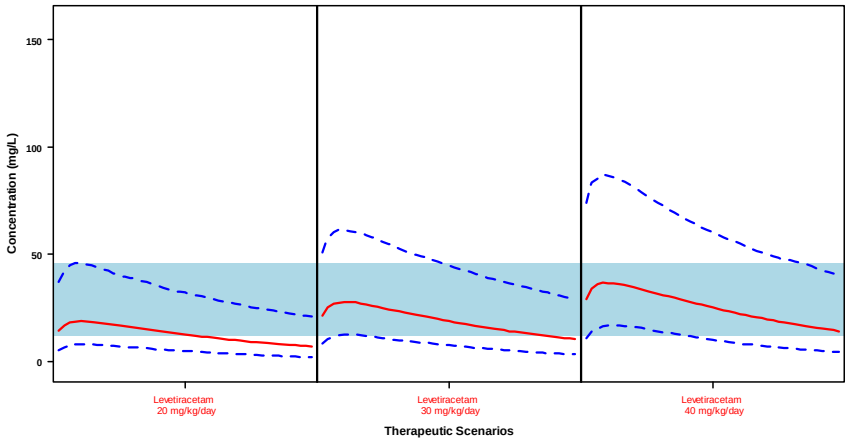

Figure 44. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of levetiracetam concentrations at steady-state resulting from doses of 20, 30, and 40 mg/kg/day. Each panel corresponds to the dosing interval time window of 12 hours.

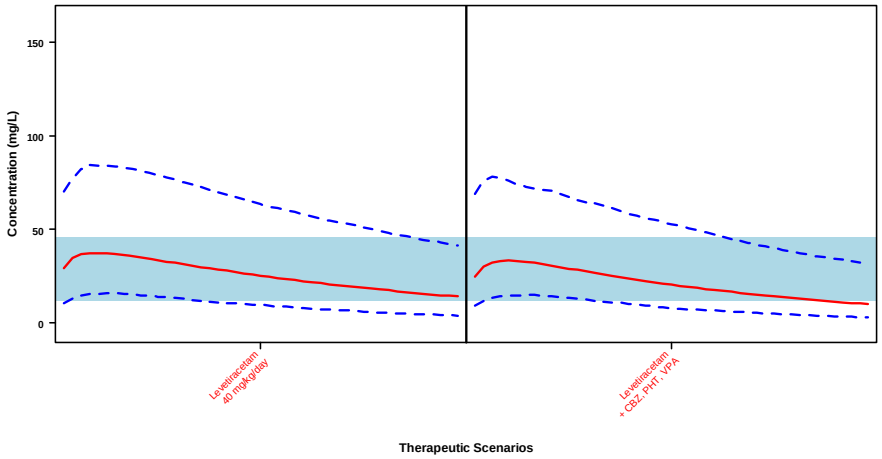

Figure 45. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of levetiracetam concentrations at steady-state resulting from a 40 mg/kg/day levetiracetam dose and comedication with an inducer (carbamazepine (CBZ), or phenytoin (PHT), or valproic acid (VPA)). Each panel corresponds to the dosing interval time window of 12 hours.

The levetiracetam simulation results in children are highly similar to those in adults.

4.2.6 Oxcarbazepine

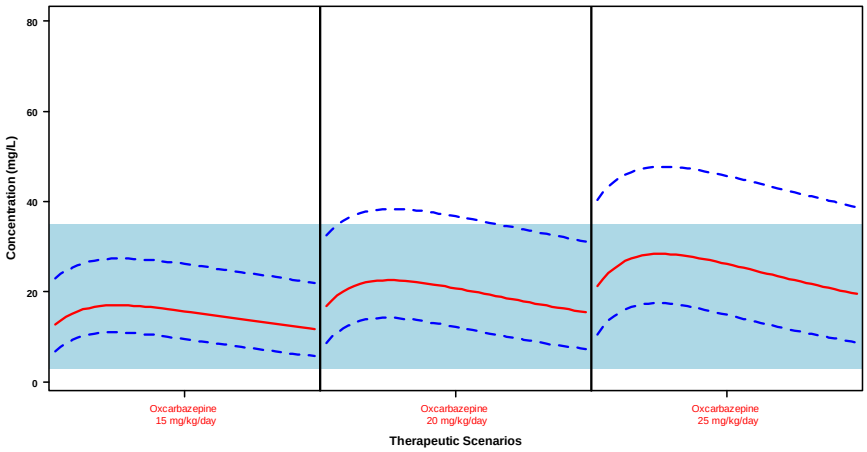

Figure 46. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of MHD concentrations at steady-state resulting from oxcarbazepine doses of 15, 20, and 25 mg/kg/day. Each panel corresponds to the dosing interval time window of 12 hours.

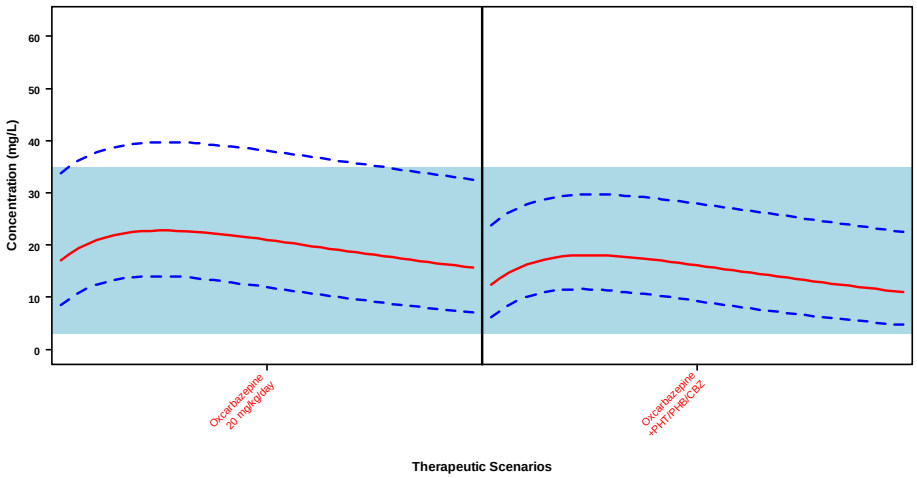

Figure 47. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of MHD concentrations at steady-state resulting from a 20 mg/kg/day oxcarbazepine dose and comedication with an inducer (phenytoin (PHT), or phenobarbital (PHB), or carbamazepine (CBZ)). Each panel corresponds to the dosing interval time window of 12 hours.

No clear differences between adults and children can be observed in the simulation results for oxcarbazepine.

4.2.7 Phenobarbital

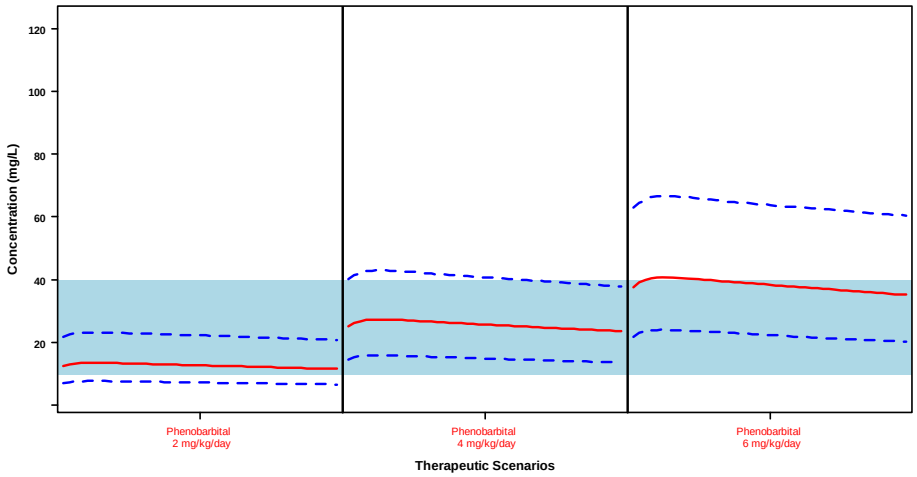

Figure 48. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of phenobarbital concentrations at steady-state resulting from doses of 2, 4, and 6 mg/kg/day. Each panel corresponds to the dosing interval time window of 12 hours.

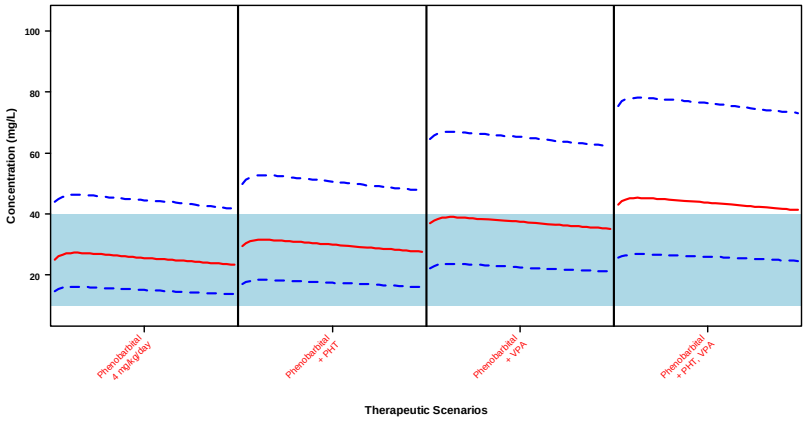

Figure 49. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of phenobarbital concentrations at steady-state resulting from a 4 mg/kg/day phenobarbital dose and comedication with phenytoin (PHT), and/or valproic acid (VPA). Each panel corresponds to the dosing interval time window of 12 hours.

Phenobarbital PK variability seems slightly larger in the paediatric population compared to that in adults (compare figure 26 vs 48, keep in mind the different scales). This also leads to a larger spread of supratherapeutic concentrations when it is given in combination with both PHT and VPA. No other clear differences between adults and children could be found.

4.2.8 Phenytoin

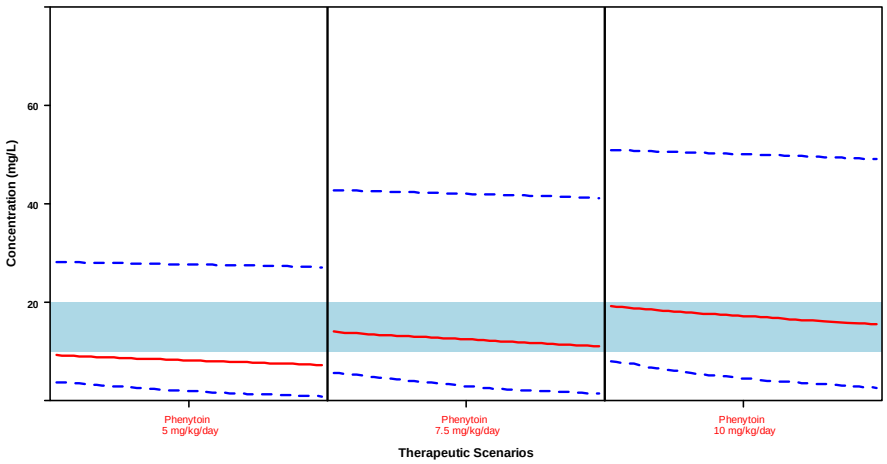

Figure 50. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of phenytoin concentrations at steady-state resulting from doses of 5, 7.5, and 10 mg/day. Each panel corresponds to the dosing interval time window of 12 hours.

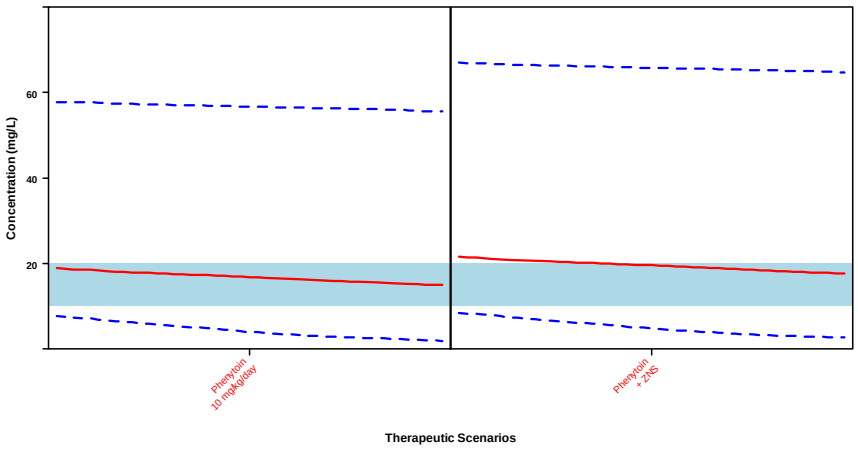

Figure 51. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of phenytoin concentrations at steady-state resulting from a 10 mg/kg/day phenytoin dose and comedication with zonisamide (ZNS). Each panel corresponds to the dosing interval time window of 12 hours.

No obvious differences between adults and children were found for the simulations of phenytoin.

4.2.9 Topiramate

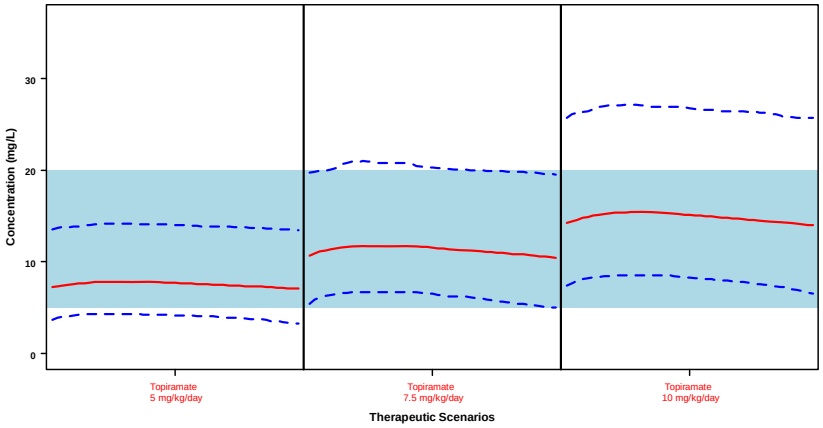

Figure 52. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of topiramate concentrations at steady-state resulting from doses of 5, 7.5, and 10 mg/kg/day. Each panel corresponds to the dosing interval time window of 12 hours.

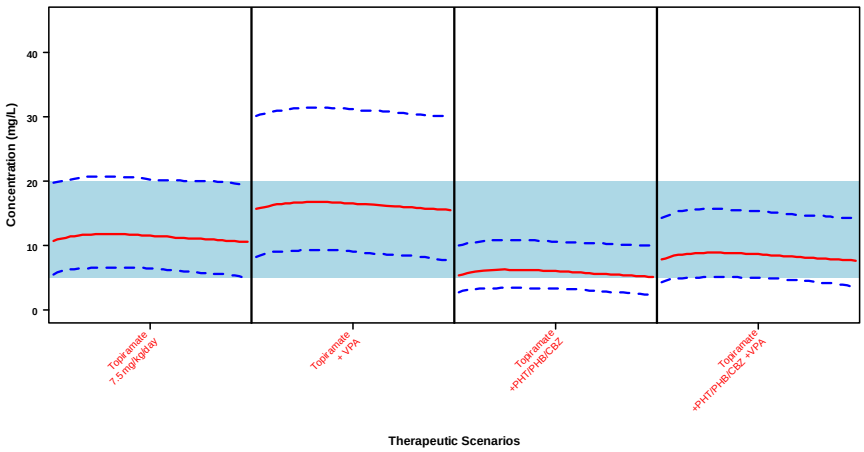

Figure 53. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of topiramate concentrations at steady-state resulting from a 7.5 mg/kg/day topiramate dose and comedication with valproic acid (VPA), and/or phenytoin (PHT) or phenobarbital (PHB) or carbamazepine (CBZ). Each panel corresponds to the dosing interval time window of 12 hours.

No clear differences were found in the topiramate simulation results between adults and children.

4.2.10 Valproic Acid

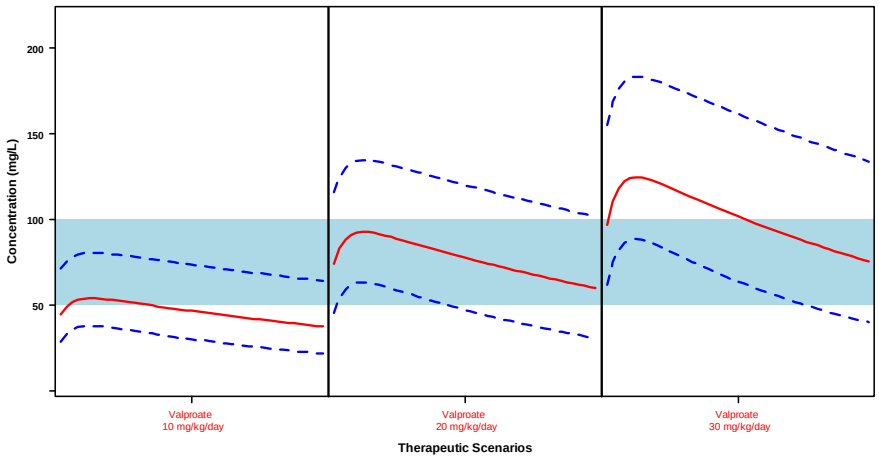

Figure 54. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of valproic acid concentrations at steady-state resulting from doses of 10, 20, and 30 mg/kg/day. Each panel corresponds to the dosing interval time window of 12 hours.

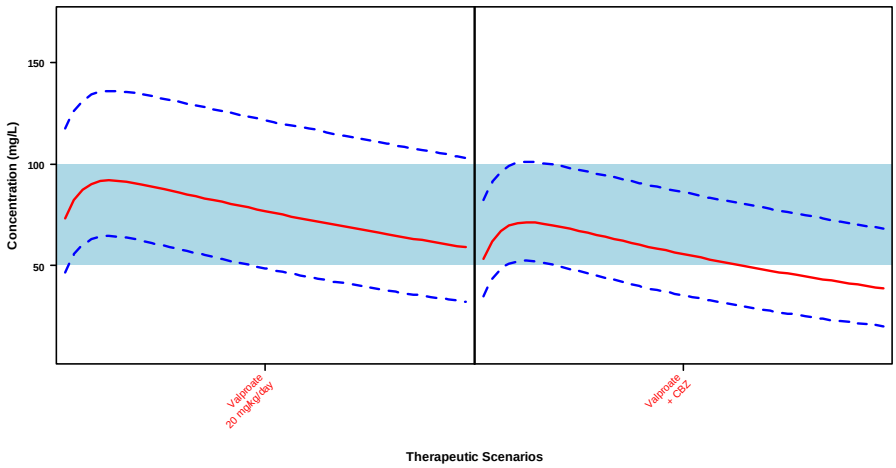

Figure 55. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of valproic acid concentrations at steady-state resulting from a 20 mg/kg/day valproic acid dose and comedication with carbamazepine (CBZ). Each panel corresponds to the dosing interval time window of 12 hours.

The paediatric PK model for valproic acid only includes the effect of CBZ as an inducer of VPA clearance. Although we use two different models for adults and children, both were built by the same first author and consist of highly similar parameter values. This is also reflected in the simulation results, where no clear differences between the adult and paediatric population can be observed.

4.2.11 Zonisamide

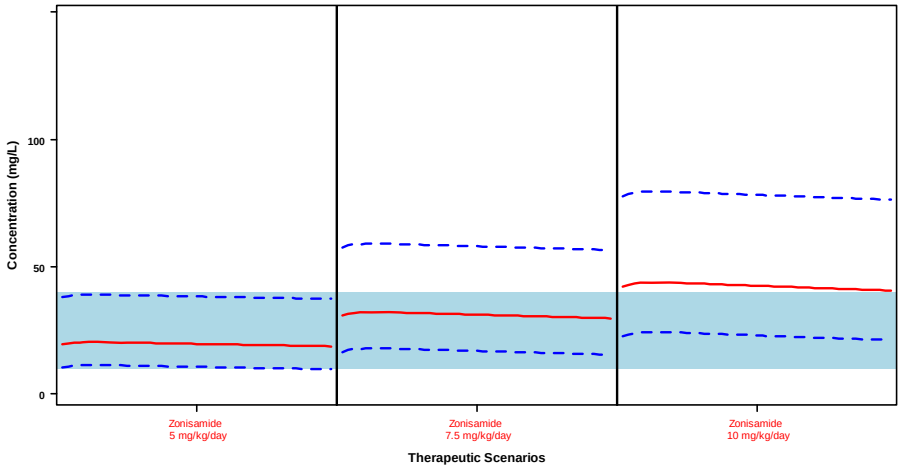

Figure 56. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of zonisamide concentrations at steady-state resulting from doses of 5, 7.5, and 10 mg/kg/day. Each panel corresponds to the dosing interval time window of 12 hours.

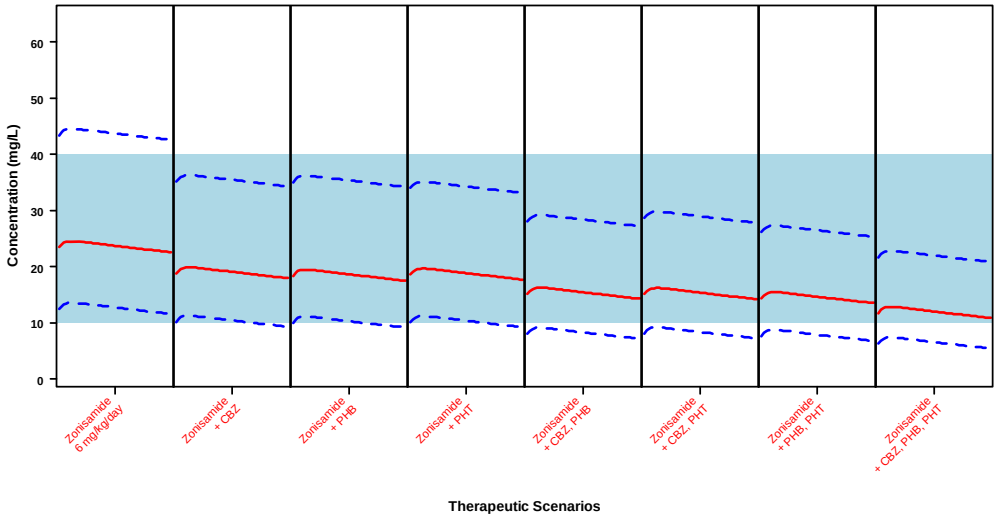

Figure 57. median (red uninterrupted line) and 95% prediction interval (blue dotted lines) of zonisamide concentrations at steady-state resulting from a 6 mg/kg/day zonisamide dose and comedication with carbamazepine (CBZ), and/or phenobarbital (PHB), and/or phenytoin (PHT). Each panel corresponds to the dosing interval time window of 12 hours.

The simulation results for zonisamide in adults and children are highly similar.

5. Discussion

5.1. Overview of peak and trough concentrations for all simulation scenarios

The following graphs represent an overview of the peak (Cmax) and trough (Cmin) concentrations expressed as a ratio with regard to the posited optimum average steady-state concentration. A positive value (e.g. 1.3) means that the observed peak or trough concentration is 30% above the aimed-at concentration. By comparing graphs corresponding to Cmax and Cmin, the overall variability across the dosing interval time window can be assessed, and doses can be avoided that result in either supratherapeutic (and thus possibly toxic) concentrations, or subtherapeutic (and thus inefficacious) concentrations.

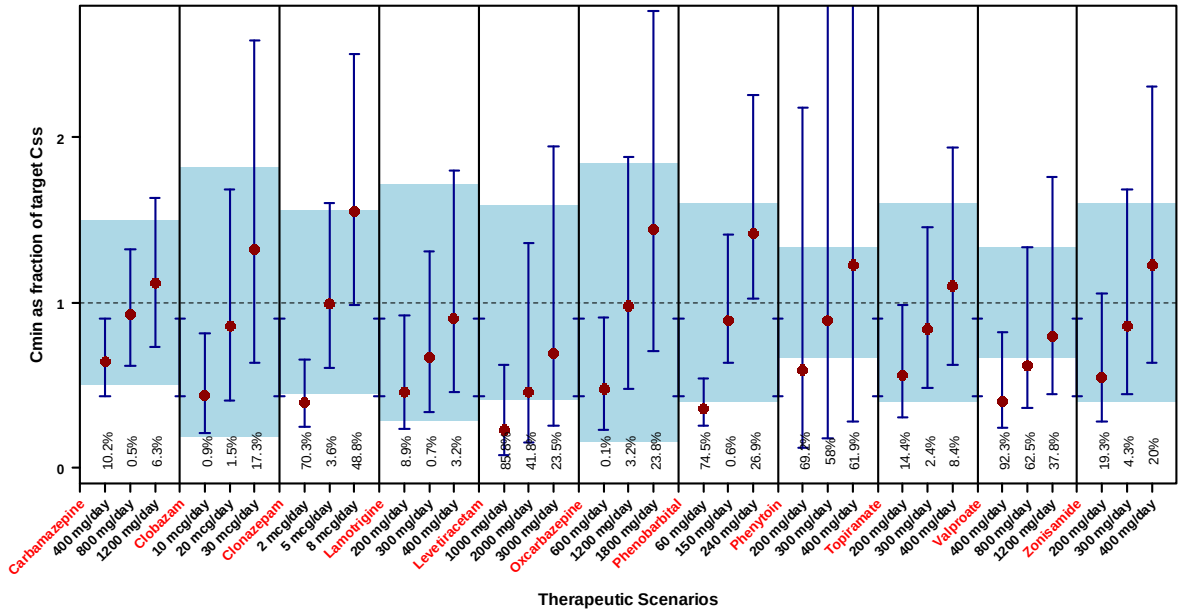

Figure 58. Overview of median (circles) and 95% prediction interval (bars) of peak drug concentrations (Cmax) in adults for different drugs and dosing scenarios. Shaded area represents the reference therapeutic range, numbers listed below the bars are percentages of the population with Cmax values outside the reference therapeutic range

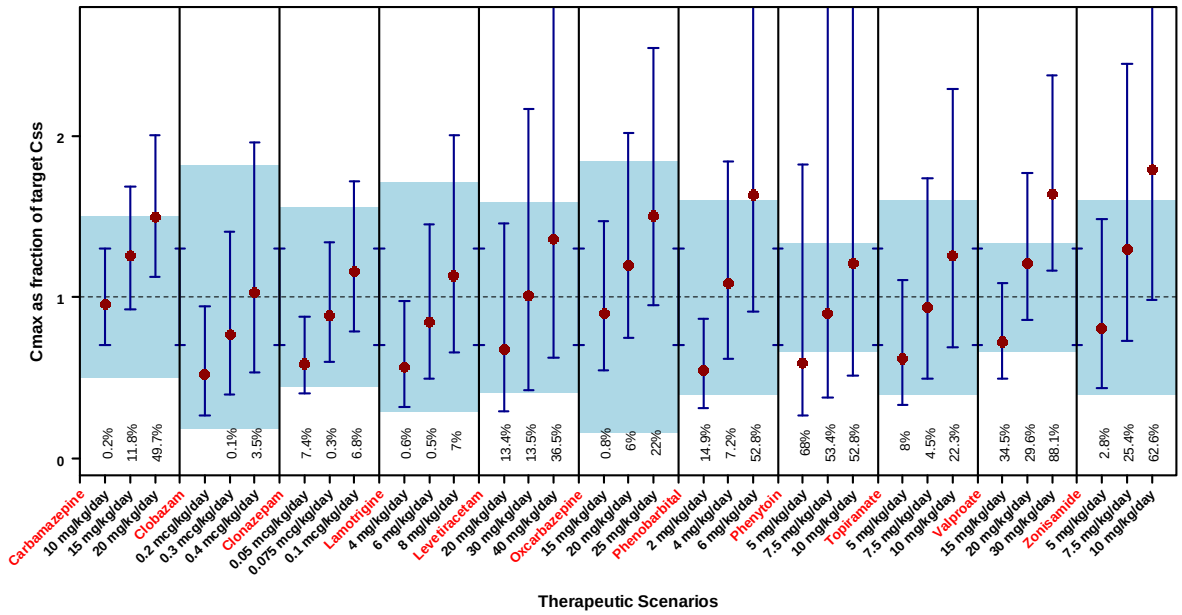

Figure 59. Overview of median (circles) and 95% prediction interval (bars) of peak drug concentrations (Cmax) in children for different drugs and dosing scenarios. Shaded area represents the reference therapeutic range, numbers listed below the bars are percentages of the population with Cmax values outside the reference therapeutic range

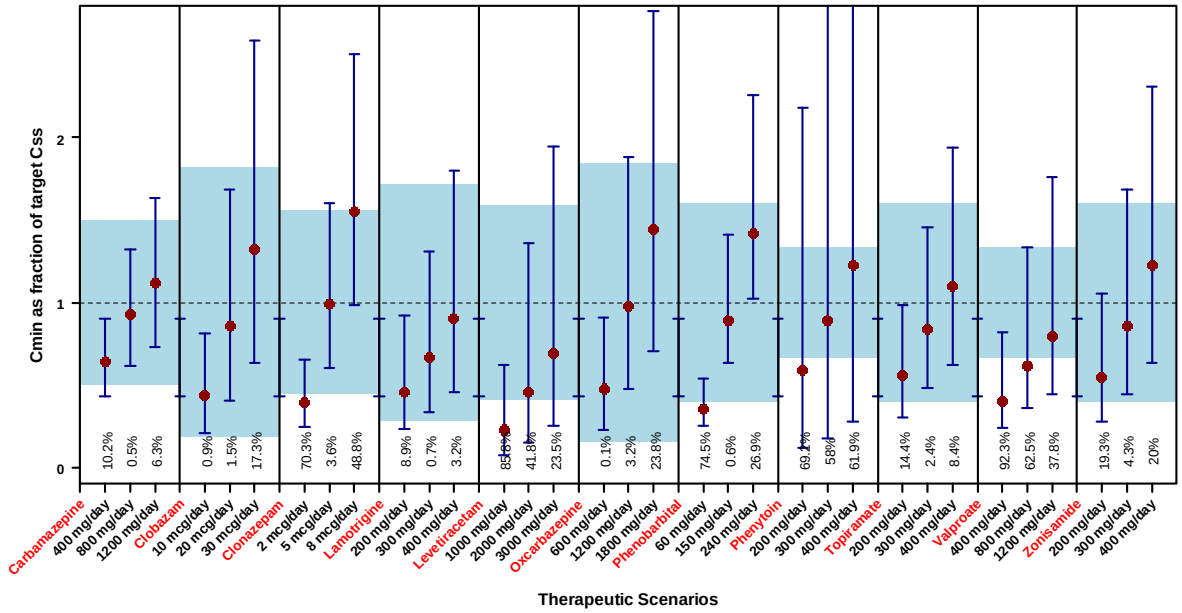

Figure 60. Overview of median (circles) and 95% prediction interval (bars) of trough drug concentrations (Cmin) in adults for different drugs and dosing scenarios. Shaded area represents the reference therapeutic range, numbers listed below the bars are percentages of the population with Cmin values outside the reference therapeutic range

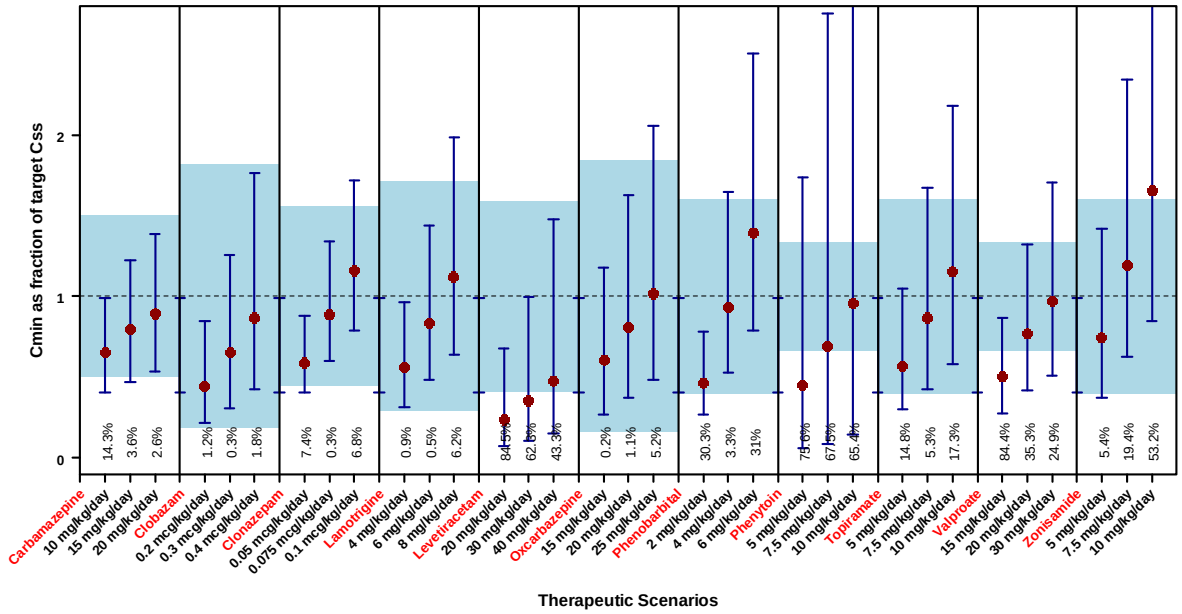

Figure 61. Overview of median (circles) and 95% prediction interval (bars) of trough drug concentrations (Cmin) in children for different drugs and dosing scenarios. Shaded area represents the reference therapeutic range, numbers listed below the bars are percentages of the population with Cmin values outside the reference therapeutic range

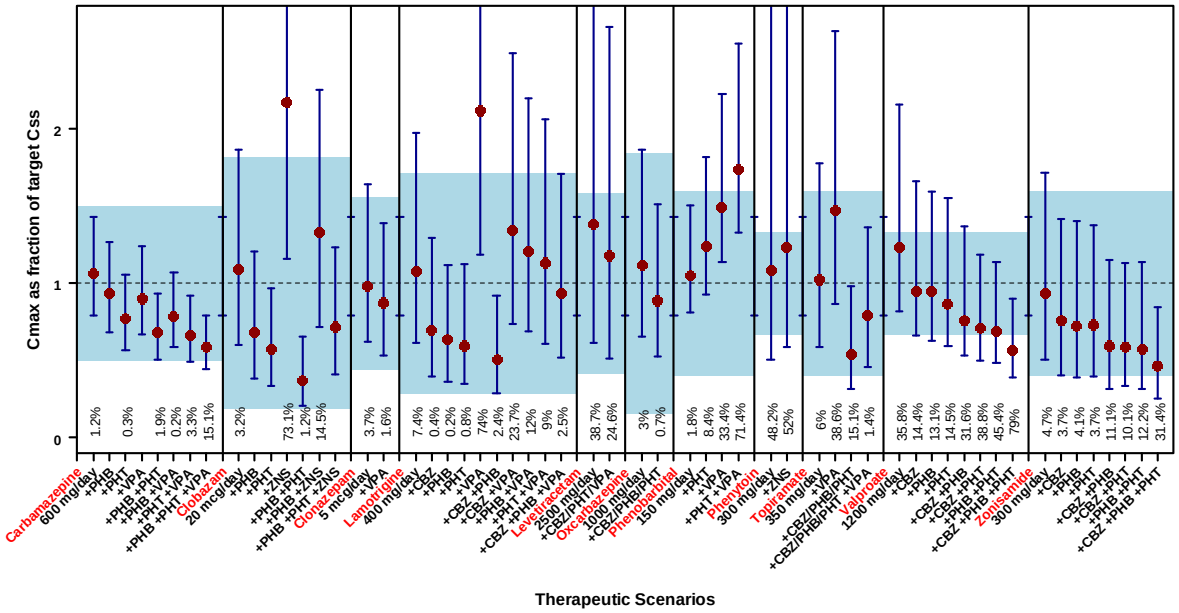

Figure 62. Overview of median (circles) and 95% prediction interval (bars) of peak drug concentrations (Cmax) in adults for different drugs and comedication scenarios. Shaded area represents the reference therapeutic range, numbers listed below the bars are percentages of the population with Cmax values outside the reference therapeutic range

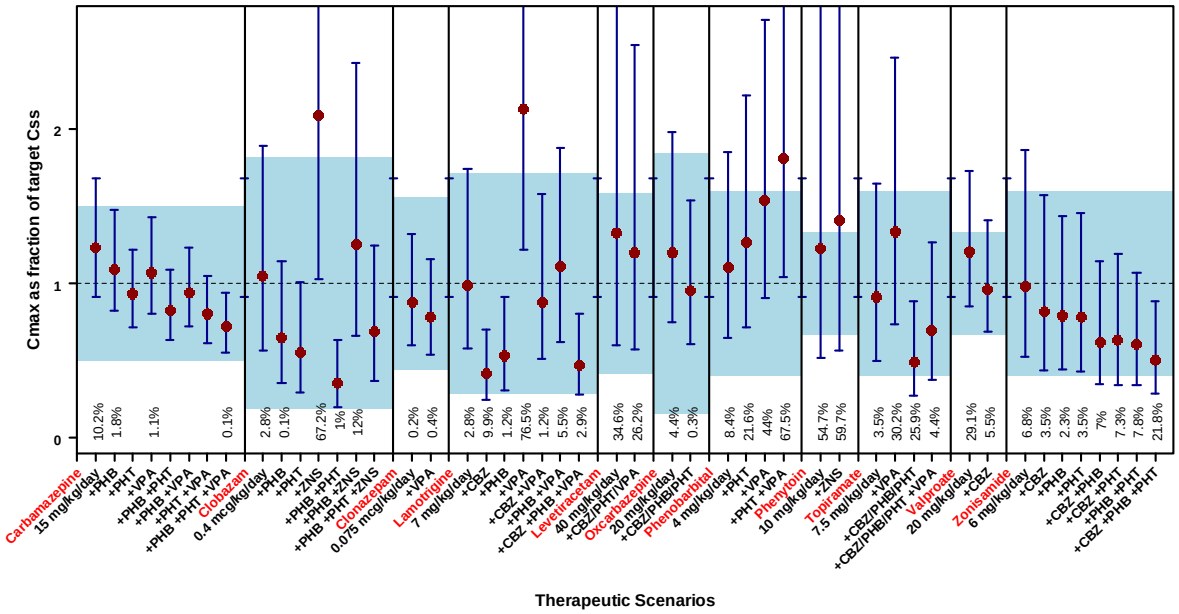

Figure 63. Overview of median (circles) and 95% prediction interval (bars) of peak drug concentrations (Cmax) in children for different drugs and comedication scenarios. Shaded area represents the reference therapeutic range, numbers listed below the bars are percentages of the population with Cmax values outside the reference therapeutic range

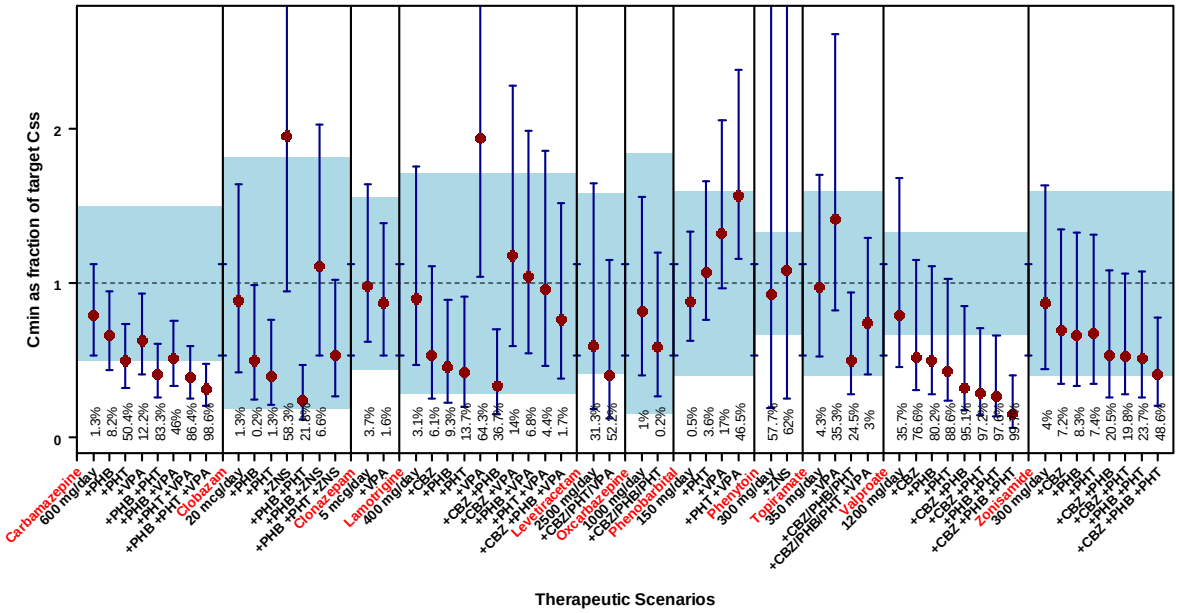

Figure 64. Overview of median (circles) and 95% prediction interval (bars) of trough drug concentrations (Cmin) in adults for different drugs and comedication scenarios. Shaded area represents the reference therapeutic range, numbers listed below the bars are percentages of the population with Cmin values outside the reference therapeutic range

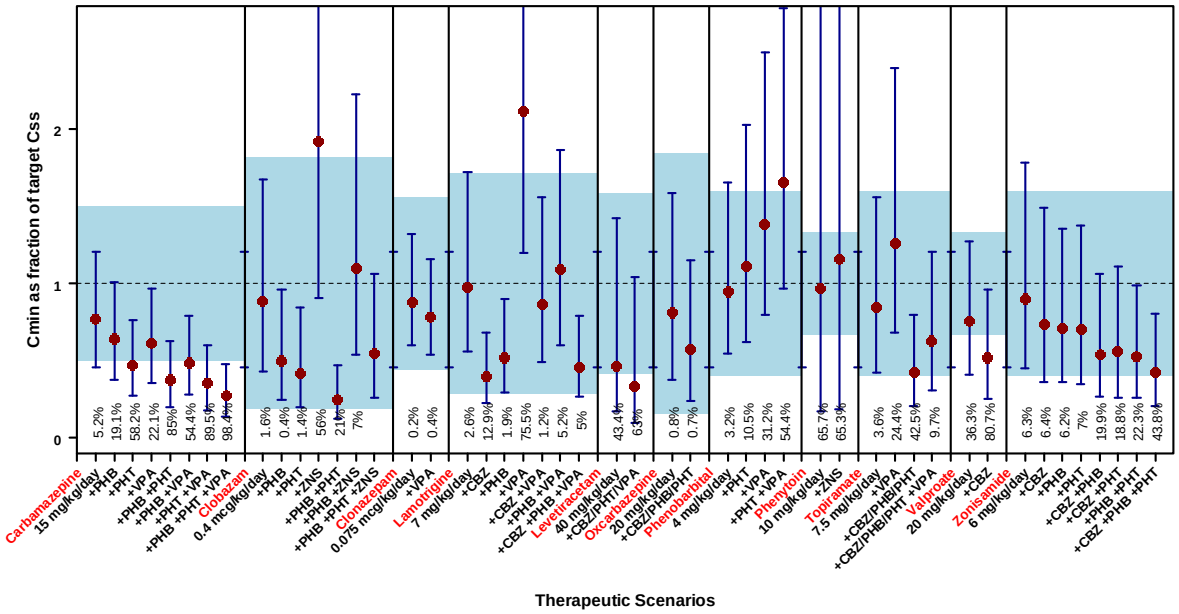

Figure 65. Overview of median (circles) and 95% prediction interval (bars) of trough drug concentrations (Cmin) in children for different drugs and comedication scenarios. Shaded area represents the reference therapeutic range, numbers listed below the bars are percentages of the population with Cmin values outside the reference therapeutic range

5.2. Discussion of simulation scenario results

The simulation results presented in the previous sections reveal that, although anti-epileptic drug (AED) doses can be selected for each population that may result in average steady-state concentrations (Css) within the therapeutic window for the majority of the population (shown in the main body of the article), it is impossible to select doses that at the same time also lead to peak (Cmax) and trough (Cmin) concentrations within the therapeutic window (shown in this supplement). In other words, no ideal dose exists. Auto-induction (carbamazepine, valproic acid) and michealis menten kinetics (phenytoin), result in changes in exposure that cannot be easily predicted without the use of pharmacokinetic (PK) models. Moreover, the impact of drug-drug interactions (DDIs) may be summarised by a simple percentage of increase or decrease in the first-line AED clearance, and thereby an inverse change in exposure, but part of the variability on clearance included in these models accounts for the inter-individual variability in DDIs. Given this inter-individual variability in DDIs, it is unpredictable how exposure will exactly change in the individual patient, without therapeutic drug monitoring (TDM) and model-based evaluation (i.e. parameter estimation). Current clinical practice deals with PK variability by ignoring it and navigate based on clinical outcome alone. Alternatively, it is possible to titrate up to an initial target maintenance dose that should result in the most optimal exposure across the three PK markers (Css, Cmax, Cmin), with subsequent optimisation based on TDM combined with model-based individualisation to quantitatively understand the source of drug efficacy and side-effects.

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