Pharmacokinetic interactions and dosing rationale for antiepileptic drugs in adults and children

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SUMMARY

Aim: Population pharmacokinetic modelling has been widely used across many therapeutic areas to identify sources of variability, which are incorporated into models as covariate factors. Despite numerous publications on pharmacokinetic (PK) drug-drug interactions (DDIs) between antiepileptic drugs (AEDs), such data are not used to support the dose rationale for polytherapy in the treatment of epileptic seizures. Here we assess the impact of DDIs on plasma concentrations and evaluate the need for AED dose adjustment.

Methods: Models describing the pharmacokinetics of carbamazepine, clobazam, clonazepam, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide in adult and paediatric patients were collected from the published literature and implemented in NONMEM v7.2. Taking current clinical practice into account, we explore simulation scenarios to characterise AED exposure in virtual patients receiving mono-, and polytherapy. Css, Cmax and Cmin were selected as parameters of interest for the purpose of this analysis.

Results: Our simulations show that DDIs can cause major changes in AED concentrations both in adults and children. When more than one AED is used, even larger changes are observed in the concentrations of the primary drug, leading to significant differences in Css between mono- and polytherapy for most AEDs. These results suggest that currently recommended dosing algorithms and titration procedures do not ensure attainment of appropriate therapeutic concentrations.

Conclusions: The effect of DDIs on AED exposure cannot be overlooked. Clinical guidelines must take into account such covariate effects and ensure appropriate dosing recommendations for adult and paediatric patients who require combination therapy.

Keywords: epilepsy, pharmacokinetics, drug-drug interactions, modelling and simulations, personalised medicine

Table of Links

Ligands
carbamazepine
clobazam
clonazepam
lamotrigine
levetiracetam
oxcarbazepine
phenobarbital
phenytoin
topiramate
valproic acid
zonisamide

These Tables of Links list key ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in The Concise Guide to PHARMACOLOGY 2015/16 [2]

WHAT IS KNOWN ABOUT THIS SUBJECT

- First-line and alternative first line anti-epileptic drugs (AEDs) are often used in combination with second-line line drugs (i.e., add-on).
- Many AED combinations lead to pharmacokinetic (PK) drug-drug interactions (DDIs), which may result in large changes in drug exposure.
- The implications of such DDIs have not been characterised in existing clinical guidelines.

WHAT THIS STUDY ADDS

- We evaluate how demographic and clinical factors, including co-medications (polytherapy), affect systemic exposure to AEDs in the target patient population. In addition, we demonstrate that AED dosing regimens can be optimised to ensure drug concentrations are maintained within a reference therapeutic range.
- DDIs can lead to significant changes in AED exposure and potentially alter the efficacy and safety profile of AEDs in adult and paediatric patients.
- These results form the basis for a comprehensive review of clinical guidelines for the use of first and second line AEDs, including novel algorithms for dose adjustment.

INTRODUCTION

Epilepsy is a collection of syndromes characterised by the occurrence of paroxysmal seizures. Many patients require prolonged and often life-long treatment with anti-epileptic drugs (AEDs), which are developed and approved based primarily on the evidence of efficacy in specific seizure types. From a clinical perspective, this has led to treatment choices based on a classification system that discriminates AEDs into first and second-line treatment. A first-line treatment is tried first and usually used on its own. If first-line treatment does not work, then another drug (i.e., an alternative first-line treatment) may be tried on its own. First-line treatment drugs may also be used as combinations (i.e., add-on treatment) if seizure control is not achieved or a given regimen is not tolerated [3].

At the moment approximately 20 AEDs are available including first and second line treatment options. Different guidelines have been proposed to guide health care professionals and prescribing physicians on the use of AEDs, with special focus on the criteria for selection of newer drugs. In addition to providing recommendations for the treatment of specific populations such as women and HIV patients, attention is also given to the importance of dose titration and tapering procedures. Nevertheless, it has been shown that 10-20% of the patients whose target dose has been achieved, still show unresolved seizures and can benefit from dose-adjustments [4,5]. Despite evidence on the role of pharmacoresistance and progression of the underlying pathological processes, the lack of response can be partly explained by inter-individual variability in the pharmacokinetics (PK) [6]. The impact of such variability is particularly important in the paediatric population, where maturation processes and developmental growth are known to affect drug disposition [7–9]. In addition, children who do not adequately respond to first-line

treatment are given multiple AEDs in combination, which can incur PK (and pharmacodynamic (PD)) drug-drug interactions (DDIs).

Population PK modelling has been widely used across many therapeutic areas to describe drug exposure and identify sources of variability, which are then incorporated into models as covariate factors [10,11]. Consequently, differences in drug exposure due to explanatory factors such as DDIs or demographic and clinical parameters can be predicted before treatment is initiated. The availability of such models also allows us to perform clinical trial simulations (CTS) and not-in-trial simulations (NITS) and explore the potential implication of covariate effects on individual patients or subgroups of the target patient population [5,12]. When performed in a systematic manner, the use of simulation scenarios becomes a powerful tool for the evaluation of the impact of multiple, concurrent factors on drug exposure, providing the rationale for dose adjustment purposes [13,14]. Here, we show how clinical trial simulations can be used to characterise pharmacokinetic DDIs for the most widely used AEDs at clinically relevant doses and regimens. Scenarios are evaluated which reflect the impact of titration steps, different maintenance doses and add-on treatments. Bearing in mind current clinical practice, we aim to assess the impact of DDIs on the exposure to AEDs and establish the need for further dose adjustment. We anticipate that our analysis will assist the review of clinical guidelines, taking into account the role of covariate factors in future dosing recommendations. Most importantly, it will provide clinicians further insight into the role of PK variability in the overall efficacy and safety profile of AEDs.

METHODS

Pharmacokinetic models and virtual patient demographics

Models describing the PK of carbamazepine (CBZ) [15], clobazam (CLBZ) [16], clonazepam (CLNZ) [17], lamotrigine (LMT) [18,19], levetiracetam (LVT) [20], oxcarbazepine (OXC) [21], phenobarbital (PHB) [22], phenytoin (PHT) [23], topiramate (TPM) [24], valproic acid (VPA) [25,26], and zonisamide (ZNS) [27] were collected from the published literature. Given the primary objective of our analysis, models were selected if covariate effects were identified for one or more AEDs and study population included > 50 patients. In addition, whenever possible, preference was given to models based on PK data from both adult and paediatric patients. Furthermore, parameterisation of the covariate effect (i.e., DDI) should be based on changes in clearance to allow easier differentiation between treatment conditions, i.e., the presence of the co-medication. An overview of the model structure, including details on the parameterisation of the covariate effects for each AED is presented in tables 1A and 1B. Further information on the clinical protocols used to develop the pharmacokinetic models and identify the covariate effects is provided in the **online supplemental material**. As modelling codes were not available in the original publications, models were transcribed manually into standard control-stream file format in NONMEM v7.2 [28]. For the sake of accuracy and quality, model transcription was assessed one by one before the implementation of the simulation scenarios by comparing model-predicted concentrations for the original patient population to the reported results in the corresponding publications (see **online supplemental material**). If no deviations were observed during this initial quality check, the PK model code was subsequently transcribed into the appropriate format for simulation purposes in R v3.1.1 [29]. Simulation scenarios, comprising treatment conditions at different dose levels and DDIs were selected for both adult and paediatric patients. For each scenario, a population of 1000 virtual patients was simulated using the demographic baseline characteristics listed in table 2. It was anticipated that spurious correlations

between covariates would be negligible using random sampling for such a large number of patients. One exception was the correlation (colinearity) between weight and age in children, which is highly relevant for the characterisation of pharmacokinetics in this population. This was particularly important for TPM, which had both weight and age as covariate factors in the model. In addition to demographic factors, other influential covariate factors such as genetic polymorphisms were also simulated if included in the original publication. To ensure accurate characterization of the covariate effects, demographic and other relevant clinical variables were sampled according to a uniform distribution.

Simulation scenarios

One and two compartment models were implemented in R according to equations 1 and 2.1-2.5, as described in the PFIM optimal design tool documentation [31]. The concentration *versus* time profiles of each AED were simulated at steady state for the typical adult and paediatric populations (table 2), following the administration of a range of clinically relevant doses (table 3). Given the objectives of the current investigation, we have decided not apply bridging and extrapolation concepts to scale pharmacokinetic parameters from adults to children as basis for the paediatric dose selection [32]. Instead, paediatric doses were scaled by body weight on a mg/kg basis, as typically done by prescribing physicians in clinical practice. Secondary PK parameters were then derived, including average steady-state (C_{ss}), peak (C_{max}) and trough (C_{min}) concentrations.

A key premise for the evaluation of the different simulation scenarios is the set of assumptions used, which include the following points:

1. Attainment and maintenance of AED exposure within a target range is desirable for optimal treatment response, irrespective of drug use as a single agent (monotherapy) or as combinations. The reference target concentration ranges published by Patsalos et al [33] were considered as relevant for the adult and paediatric populations.

2. In addition, it was assumed that interindividual variability in pharmacodynamics, i.e., different individual sensitivity to individual drug effects are captured by the proposed target range, whereas resistance to treatment would impose exposure to higher drug concentrations, which are likely to be associated with poor tolerability.

3. Model misspecification was deemed to be minimal and parameter distributions to be precise and accurate to a sufficiently high degree to allow realistic simulations.

4. Covariate effects are reasonably well captured by the models, despite the limited number of patients included for the development of the models (table 1).

5. Bias in the estimates of the covariate effects is minimal even if DDIs are treated as discrete covariates in the model. It is acknowledged, however, that discrete covariate effects may impair one's ability to adjust the dose, as variability in exposure or the use of different dose levels of the add-on drug may alter the magnitude of the interaction. This is particularly important in the case of multiple DDIs.

6. Whereas discrete parameterisation of DDIs may not fully capture the range of conditions or variation in clinical practice, it does provide a stronger basis for the dose rationale, as compared to scenarios where DDIs are completely overlooked.

Simulations were performed in two steps. First, we aimed to identify the dose or dose levels that maximised the fraction of virtual patients whose C_{ss} values remained within the target exposure range for each drug. Subsequently, the impact of DDIs on the systemic exposure of

the first-line or alternative first-line AED was simulated (table 3). In total 76 scenarios were considered, taking into account the most clinically relevant dosing regimens and combinations. This resulted in a total of 33 scenarios for monotherapy and 43 scenarios for different AED combination. As scenario included 1000 virtual patients, our analysis comprises a population of 76000 patients.

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

$$\alpha = \frac{\frac{Q}{V_2}\cdot\frac{CL}{V_1}}{\beta} \quad (2.1)$$

$$\beta = \frac{1}{2}\left(\frac{Q}{V_1} + \frac{Q}{V_2} + \frac{CL}{V_1} - \sqrt{(\frac{Q}{V_1} + \frac{Q}{V_2} + \frac{CL}{V_1})^2 - 4\frac{Q}{V_2}\frac{CL}{V_1}}\right) \quad (2.2)$$

$$A = \frac{k_a}{V_1}\frac{\frac{Q}{V_2} - \alpha}{(k_a - \alpha)(\beta - \alpha)} \quad (2.3)$$

$$B = \frac{k_a}{V_1}\frac{\frac{Q}{V_2} - \beta}{(k_a - \beta)(\alpha - \beta)} \quad (2.4)$$

$$C_t = D\left(\frac{Ae^{-\alpha(t-t_D)}}{1-e^{-\alpha\tau}} + \frac{Be^{-\beta(t-t_D)}}{1-e^{-\beta\tau}} - \frac{(A+B)e^{-k_a(t-t_D)}}{1-e^{-k_a\tau}}\right) \quad (2.5)$$

$$C_{ss} = \frac{1}{24}\frac{DD}{CL} \quad (3)$$

Equations 1-3. C_t: concentration at time t. τ: dosing interval. D: Dose of dose interval τ. DD: Daily dose. V or V_1: central volume of distribution. k_a: absorption rate constant. CL: clearance. t: time. t_D: time of dose. Q: inter-compartmental clearance. V_2: peripheral volume of distribution. As none of the models included intravenous data, bioavailability estimates were not available; clearance and volume values used in the analysis were therefore based on apparent estimates.

Assessment of the impact of covariate effects on drug exposure

The target C_{ss} value used for optimisation purposes was set to the drug concentration half-way between the minimum and maximum values of the therapeutic window for each AED (table 3). Details of the rationale for this approach are described in a previous publication by our group, where different dosing algorithms have been assessed for personalisation of AED therapy [5]. In brief, the ratio between predicted C_{ss} and target C_{ss} was calculated (ratio=predicted/target) and results were subsequently summarised in tabular and graphical format. Whisker-box plots were generated separately for adults and children to describe the dispersion in drug exposure across the population, including the median and 95% prediction interval for each dose and DDI scenario. To facilitate the interpretation of the findings and visualise the impact of dosing titration and/or optimisation procedures, the percentage of the population with concentrations outside the therapeutic range was also summarised numerically along with the whisker-box plots. In addition, the percentage adjustment needed to bring the median C_{ss} values back to the target concentration was calculated and provided for each AED.

RESULTS

A preliminary analysis of the pharmacokinetic models showed acceptable performance for the purposes of our investigation. Different dose and dosing regimens were simulated for each AED according to the scenarios shown in table 3. For the sake completeness, an overview of the concentration vs. time profiles for each AED in adult and paediatric patients is presented in the **online supplemental material**. These results are complemented by a summary of the procedures used for evaluation of model performance, including the results relative to the secondary PK parameters (Cmax, Cmin).

Monotherapy: impact of standard dose regimens on systemic drug exposure

For most drugs the simulated average steady-state concentrations (C_{ss}) fall within the reference values for a large fraction of the adult and paediatric populations. Notable exceptions were PHT and VPA, where significant proportion of patients is at risk of achieving sub- or supra-therapeutic drug concentrations (figures 1 and 2). In fact, the deviations from the reference range are evident when considering the median estimates. Likewise, despite the use of dosing regimens in mg/kg, PHT concentrations in children fall outside the therapeutic window in at least 50% of the patients. For VPA the situation is somewhat more favourable, with roughly 20% of the simulated population falling outside the reference therapeutic range. In the case of PHT, the deviation in exposure is compounded by the known nonlinearity and large inter-individual variability in pharmacokinetics. There are important clinical implications for patients on PHT when plasma concentrations are > 20 mg/L. In reality, the evidence that a significant proportion of the population is exposed to drug concentrations above the therapeutic range may explain the incidence of adverse events.

Polytherapy: impact of DDIs on systemic drug exposure

The use of simulations reveals that DDIs can cause major changes to AED concentrations both in adults and children (figures 3 and 4). When more than one AED is added to the combination therapy, changes in the concentrations of the primary drug may be even larger. This contrasts with the results observed for monotherapy, where drug concentrations for the majority of the AEDs remained within the reference therapeutic range.

In many cases, AED interaction results in median C_{ss} values which lie outside the reference therapeutic window. On the other hand, in certain cases the interaction of multiple co-medications may partially or completely counteract each other, resulting in a 0% net change in the exposure to the first line drug. An example of the latter is the interaction of LMT with combination therapy including PHT and VPA. A preliminary evaluation of the effect of DDIs suggests that the doses of the first line and possibly second line drugs used as add-on treatment need to be adjusted, sometimes by even more than 200% (table 4).

DISCUSSION

Given the incidence of epileptic seizures across a wide age range in the patient population, rational prescribing of AEDs requires not only an understanding of the drugs' pharmacodynamic properties, but also careful consideration of the factors known to affect drug disposition [8]. Despite numerous publications in which demographic, clinical and genetic covariate factors have been identified, limited attention has been given to the magnitude and variability of such effects and their clinical implication. In most cases, covariate effects are assessed as part of a population PK analysis, where the main objective is the characterization of overall drug disposition properties, rather than the optimisation of therapeutic interventions in a wider patient population [34,35].

In a recent publication we have shown how model-based approaches can be used in conjunction with therapeutic drug monitoring to personalise AED therapy [5]. The current investigation was aimed at exploring the implications of covariate effects on systemic exposure, with special focus on drug-drug interactions (DDIs), i.e., when patients transition from monotherapy to combination treatment with alternative first line or second line therapy (polytherapy). We found that covariate effects on the disposition of levetiracetam,

phenytoin, and valproic acid leads to considerable variation in drug exposure and consequently to a large proportion of patients reaching average steady-state concentrations outside the therapeutic window (15%, 54%, and 21% respectively). The impact of covariate effects on the disposition of the other 8 drugs included in the analysis appears to be less strong, resulting in a smaller proportion of patients outside the therapeutic window. By contrast, when DDIs come into play, exposure to most AEDs deviates from the reference therapeutic window (up to 98% for valproic acid), most notably when more than one co-medication was added. Moreover, there was no clear correlation between the mechanism of interactions and their effect size [36].

Whilst the analysis and interpretation of the simulation results rely on a set of important assumptions regarding covariate effects, it is clear that the relevance of DDIs should not be overlooked in clinical practice, as first-line treatments are often accompanied by second-line drugs, which are combined as add-on therapy in patients who fail to show acceptable clinical response on monotherapy. We have assumed that the models described the DDIs to a sufficiently accurate degree to learn about their impact on exposure in the population. However, it should be highlighted that DDIs have been implemented as discrete covariates on clearance, i.e., clearance estimates change depending on whether a co-medication was given or not. We cannot exclude the possibility that despite steady-state concentrations the magnitude of such interactions may be dose-dependent [37]. To take into account the multiple inter-dependencies in the case of AED poly-therapy, the application of more physiology-based pharmacokinetic (PBPK) models may more accurately predict complex DDIs. On the other hand, if metabolic interactions (e.g., CYP enzymes) reflect high or maximum induction or inhibition when the co-medication exposure is at therapeutically relevant concentrations, further variation in dose or concentration may not affect the

magnitude of the interaction any more. In this light, the predicted dose changes of first line drugs in table 4 should be seen as typical values, based on commonly used dose levels of first-line and co-medication AEDs. These results do not exclude the fact that there may be additional variability, which is unaccounted for, depending on the dose of the co-medication(s).

Currently, clinical guidelines do not consider the need to assess in a quantitative manner the contribution of covariate factors on drug exposure and consequently on the rationale for dose selection or titration algorithms [5]. Whereas some product labels provide dosing recommendations for individuals with renal and hepatic impairment, no specific dose adjustment is proposed to account for other relevant factors. Often DDIs are mentioned but no formal dosing recommendation is provided, taking into account AED disposition and other relevant patient characteristics. This is particularly important in infants older than 2-3 months and children, in whom systemic clearance is higher than adults after normalization for differences in body weight. This general pattern has been shown for various AEDs [38,39]. At the other extreme of age, in the elderly, systemic clearance is generally reduced compared with younger adults because of less efficient metabolism, reduced renal function, or both [38]. Likewise, patient demographic characteristics, such as obesity, also lead differences in drug disposition, with significant changes in hepatic blood flow and/or metabolic activity (e.g. increased CYP enzyme expression), which have not been taken into account in our analysis, as weight range simulated did not include obese patients [40]. It should also be noted that despite known polymorphism in drug metabolism, there may be an interaction between genotype and degree of DDI that was not captured in the models that included CYP genotypes (table 4). We have assumed that such a CYP genotype – DDI interaction may have a limited role in the overall shift from the target exposure when

compared to the degree of DDI itself. Additional data from *in silico* systems, such as SIMCYP™ would be required to explore phenotypical and genotypical differences in a systematic manner [41]. Another potential factor leading to variability in systemic exposure, which has not been included in the current analysis, is plasma protein binding. In the presence of competing moieties, changes in unbound fraction may affect drug disposition and eventually treatment response, as has been described for VPA and PHT.

It should be highlighted that the lack of guidance regarding DDIs may be partly explained by the lack of consensus on the benefit of therapeutic drug monitoring, especially when performed in an empirical manner [9,42–43]. Another point to consider is that clinicians tend to focus on age as the explanatory factor influencing the PK profile of AEDs. However, systemic exposure at any age may depend on different covariate factors, such as body weight, genetics, co-morbidities, organ function and metabolic capacity. Clearly, in the presence of these multiple interacting factors, it may not be possible to disentangle the contribution of each one independently. Often unless quantitative clinical pharmacology methods are implemented, such a situation prevents us from proposing dosing adjustment algorithms that correctly account for the effect of DDIs. This concept has been illustrated by the integration of therapeutic drug monitoring with Bayesian algorithms to support dose adjustment for carbamazepine (CBZ) and/or valproate (VPA) [44], resulting in with increased seizure control, better safety profile and reduced treatment costs.

Our investigation does not focus on the advantages of any specific approach. Rather, it draws attention to the fact that the characterisation of covariate effects and variability in drug exposure is essential for dose optimisation [45–47]. However, we acknowledge that

not all clinically relevant DDIs have been evaluated or parameterised (e.g. the effect of VPA co-administration on PHT pharmacokinetics) [48,49].

We also recognise that even though many of the published models have been derived from limited clinical data and often lack a rigorous validation procedure in terms of parameter precision and predictive performance, some interesting lessons can be learnt from the simulation scenarios presented here. First, thanks to the identification of interindividual parameter variability, it is possible to select target (monotherapy) doses for most AEDs, which yield plasma concentrations that are within a reference therapeutic range, which is applicable to the majority of the population. This does not exclude the possibility that each patient may have an optimal target concentration and benefit from dose individualisation [5]. Second, DDIs can cause significant changes in the systemic exposure to first line drugs, and this also applies for many add-on drugs in a combination [50,51]. In theory, this implies that the observed treatment response, or lack thereof, when adding one or more drugs to the backbone first line AED cannot be directly attributed to the add-on drug. Instead, it may simply be the result of changes in exposure to the first drug in the combination. From a therapeutic perspective, one should envisage a scenario in which systemic concentrations of the primary drug are comparable when patients are switched from monotherapy to combinations. Such a scenario provides the appropriate basis for titration of the add-on drug.

In conclusion, we have explored the effects of DDIs on the systemic exposure to AEDs when used in combination therapy. Whereas numerous factors may contribute to lack of efficacy and poor tolerability, the effect of interindividual pharmacokinetic variability and covariate factors on drug disposition cannot be ignored in clinical practice. Our analysis offers a strong

basis for the review of clinical guidelines for the treatment of epileptic seizures with AEDs, taking into account the impact of DDIs on the dose rationale.

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Table 1a Overview of the population pharmacokinetic models used for the evaluation of drug-drug interactions for carbamazepine, clobazam, clonazepam, lamotrigine, levetiracetam, and oxcarbazepine

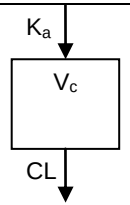
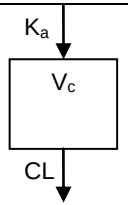
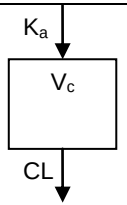
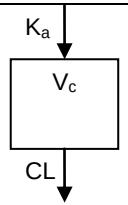
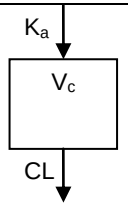
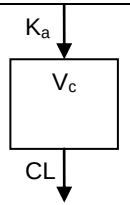
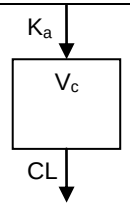
Model	Carbamazepine	Clobazam	Clonazepam	Lamotrigine Adults	Lamotrigine Children	Levetiracetam	Oxcarbazepine
First author	Jiao[15]	Saruwatari[16]	Yukawa[17]	Rivas[18]	He[19]	Toublanc[20]	Park[21]
Population	Chinese	Japanese	Japanese	German/Spanish	Chinese	Japanese (model building), US (validation)	Korean
Sample size (No.of patients)	585	85	137	284	600	259	199
Sample size (No.of patients)	687	128	259	404	1699	1833	254
Age (years)	1.2-85.1	1-52	0.3-32.6	26.8-51.3	0.5-17	4-55	3-80
Weight (kg)	5-115	8-102	5-90	61.8-85	6-98	14-107	10-95
Samples at	Trough	0-10 hours after dose	2-6 hours after dose	TDM	TDM	Random	TDM
Graphical representation							
Parameters	K_a, V_c ,CL	K_a, V_c ,CL	K_a, V_c ,CL	K_a, V_c ,CL	K_a, V_c ,CL	K_a, V_c ,CL	K_a, V_c ,CL
Between-subject variability	V_c, CL	K_a, V_c ,CL	V_c, CL	CL	CL	K_a, V_c ,CL	CL
Covariates CL	WT, Dose, PHB, PHT, VPA, Elderly (>65)	WT, PHB, PHT, ZNS, CYP2C19 & POR*28 genotypes	WT, CBZ, VPA	WT, CBZ, PHB, VPA	WT, CBZ, PHB, VPA	WT, Clearance Comedication (CBZ, PHB, PHT, VPA)	WT, EIAED (comedication CBZ/PHB/PHT)
Covariates V	WT	WT	WT	WT	WT	WT	WT

Table 1b Overview of the population pharmacokinetic models used for the evaluation of drug-drug interactions of phenobarbital, phenytoin, topiramate, valproate, and zonisamide.

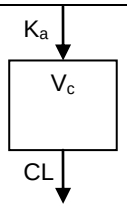
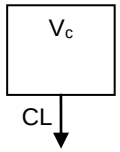
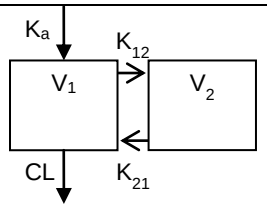
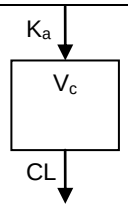
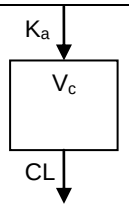
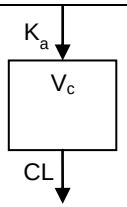
Model	Phenobarbital	Phenytoin	Topiramate	Valproate Adults	Valproate Children	Zonisamide
First author	Goto[22]	Odani[23]	Girgis[24]	Blanco-Serrano[25]	Blanco-Serrano[26]	Okada[27]
Population	Japanese	Japanese	NA (Caucasian presumably)	Spanish	Spanish	Japanese
Sample size (No.of patients)	79	116	1217	255	208	99
Sample size (No.of patients)	260	531	4640	770	534	282
Age	0.8-44	1-37	2-85	14-95	0.1-14	1.36-39.24
Weight	8-80	42.4±16.5	NA	4-74	27-100	10-117
Samples at	TDM	Peak/Trough	NA	TDM	TDM	4.3±2.8 hours after dose
Graphical representation						
Parameters	K_a, V_c ,CL	V_c ,CL (V_{max}, K_m)	K_a, V_{ss} (V_1 +V_2), K_{12}, K_{21}, CL	K_a, V_c ,CL	K_a, V_c ,CL	K_a, V_c ,CL
Between-subject variability	V_c, CL	V_c, V_{max}, K_m	K_a, V_c ,CL	CL	CL	CL
Covariates CL	WT, PHT, VPA	WT, Daily PHT Dose, ZNS	Age, WT, Inducers (CBZ/PHB/PHT), VPA, NEMD (ZNS)	WT, Dose, CBZ, PHT, PHB	WT, Dose, CBZ	WT, Dose, CYP2C19 genotype, CBZ, PHB, PHT
Covariates V	-	WT	WT	WT	WT	WT

Table 2 Patient baseline demographic characteristics used for the simulation scenarios, in which a virtual cohort of patients was treated with one or more AEDs.

Population	adults	children
Age (years)	18-65, uniformly distributed	4-14, uniformly distributed
Mean weight (kg)	75 (male) 65 (female)	(Age·3)+7†
Coefficient of variance on weight	16 %	10 %
Dose interval (hr)	12	12
Dose	mg/day	mg/kg/day
Number of simulated subjects per scenario	1000	1000

† Based on the weight-by-age formula proposed by Luscombe & Owens[30]

Table 3 Simulated doses, co-medications, and corresponding reference therapeutic range for each AED Reference AED concentration ranges were taken from Patsalos et al 2008 [33]. See main text for further details on the abbreviations and supporting references.

Drug	Doses adults (mg/day, * μg/day)	Doses children (mg/kg/day, * μg/kg/day)	Add-on medication simulated	Therapeutic window [33] (mg/L, * μg/L)
CBZ	400, 800, 1200	10, 15, 20	PHB ∨ PHT ∨ VPA	4-12
CLBZ	10, 20, 30 *	0.2, 0.3, 0.4 *	PHB ∨ PHT ∨ ZNS	30-300 *
CLNZ	2, 5, 8 *	0.05, 0.075, 0.1 *	VPA	20-70 *
LMT	200, 300, 400	4, 6, 8	((CBZ ⊕ PHB ⊕ PHT) ⊕ IND[a]) ∨ VPA	2.5-15
LVT	1000, 2000, 3000	20, 30, 40	Inducers[b]	12-46
OXC	600, 1200, 1800	15, 20, 25	CBZ ⊕ PHB ⊕ PHT	3-35
PHB	60, 150, 240	2, 4, 6	PHT ∨ VPA	10-40
PHT	200, 300, 400	5, 7.5, 10	ZNS	10-20
TPM	200, 300, 400	5, 7.5, 10	Inducers[c] ∨ VPA	5-20
VPA	400, 800, 1200	10, 20, 30	CBZ ∨ PHB ∨ PHT	50-100
ZNS	200, 300, 400	5, 7.5, 10	CBZ ∨ PHB ∨ PHT	10-40

∨ all combinations are possible, ⊕ only one combination is possible

[a] For LMT, if more than 1 of CBZ, PHB, or PHT is added, only the effect indicated by IND (and/or VPA) affects LMT clearance

[b] For LVT the original paper[19] mentions inducers "such as carbamazepine"

[c] For TPM, clearance is induced by adding any of the following: CBZ, PHB and PHT, no distinction is made between adding one or more of these

Table 4 Changes in dose (as %) of the backbone treatment (i.e., first-line or alternative first-line AED) which is required to ensure that drug concentrations remain within the reference therapeutic range when add-on treatment is initiated. (A) = adult patients; (P) = paediatric patients.

		Primary AED												
		CBZ	CLBZ	CLNZ	LMT (A)	LMT (P)	LVT	OXC	PHB	PHT	TPM	VPA (A)	VPA (P)	ZNS
Add-on drug(s)	+CBZ	-	-	+22	+60	+138	+22	+31	-	-	+94	+36	+36	+24
	+PHB	+17	+66	-	+80	+88	-	+31	-	-	+94	+40	-	+29
	+PHT	+43	+93	-	+94	-	+22	+31	-15	-	+94	+54	-	+28
	+VPA	+21	-	+14	-51	-53	+22	-	-32	-	-31	-	-	-
	+ZNS	-	-52	-	-	-	-	-	-	+16	-37	-	-	-
	+CBZ&PHB	+17	+66	+22	+22	+349	+22	+31	-	-	+94	+90	+36	+60
	+CBZ&PHT	+45	+93	+22	+32	+138	+22	+31	-15	-	+94	+110	+36	+60
	+CBZ&VPA	+21	-	+39	-22	+12	+22	+31	-32	-	+33	+36	+36	+24
	+CBZ&ZNS	-	-52	+22	+60	+138	+22	+31	-	+16	+23	+36	+36	+24
	+PHB&PHT	+70	+220	-	+49	+99	+22	+31	-15	-	+94	+115	-	+65
	+PHB&VPA	+42	+66	+14	-12	-11	+22	+31	-32	-	+33	+40	-	+29
	+PHB&ZNS	+17	-20	+22	+22	+349	+22	+31	-	+16	+23	+90	+36	+60
	+PHT&VPA	+75	+93	+14	-5	-43	+22	+31	-42	-	+33	+54	-	+28
	+PHT&ZNS	+45	-7	-	+94	-	+22	+31	-15	+16	+23	+54	-	+28
	+VPA&ZNS	+21	-52	+14	-51	-43	+22	-	-32	+16	-56	-	-	-
	+CBZ&PHB&PHT	+70	+220	+22	+137	+349	+22	+31	-15	-	+94	+193	+36	+105
	+CBZ&PHB&VPA	+42	+66	+39	-40	+111	+22	+31	-32	-	+33	+90	+36	+60
	+CBZ&PHB&ZNS	+17	-20	+22	+22	+349	+22	+31	-	+16	+23	+90	+36	+60
	+CBZ&PHT&VPA	+75	+93	+39	-35	+12	+22	+31	-32	-	+33	+110	+36	+60
	+CBZ&PHT&ZNS	+45	-7	+22	+32	+139	+22	+31	-15	+16	+23	+110	+36	+60
	+CBZ&VPA&ZNS	+21	-52	+39	-22	+12	+22	+31	-32	+15	-15	+36	+36	+24
	+PHB&PHT&VPA	+105	+220	+14	-27	-11	+22	+31	-32	-	+33	+115	-	+65
	+PHB&PHT&ZNS	+70	+55	-	+49	+99	+22	+31	-15	+16	+23	+115	-	+65
	+PHB&VPA&ZNS	+41	-20	+14	-12	-11	+22	+31	-32	+16	-15	+40	-	+29
	+PHT&VPA&ZNS	+75	-7	+14	-5	-53	+22	+31	-42	+16	-15	+54	-	+28

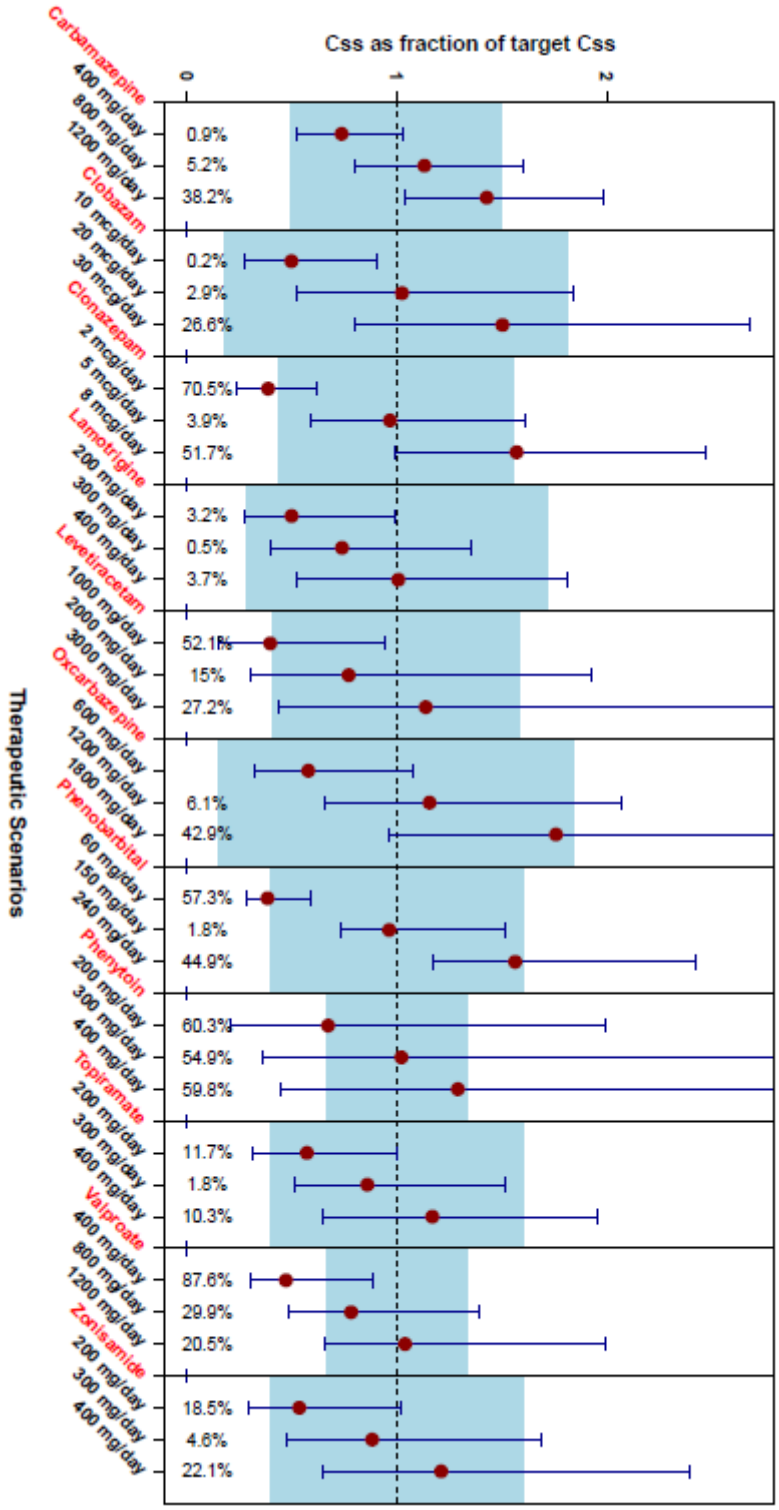


Figure 1 Median (circles) and 95% prediction interval (bars) for the steady-state concentrations (C_{ss}) achieved in adults for different AEDs and dosing scenarios. Shaded area represents the reference therapeutic range; numbers shown below each bar are percentages of the population with C_{ss} values outside the reference therapeutic range.

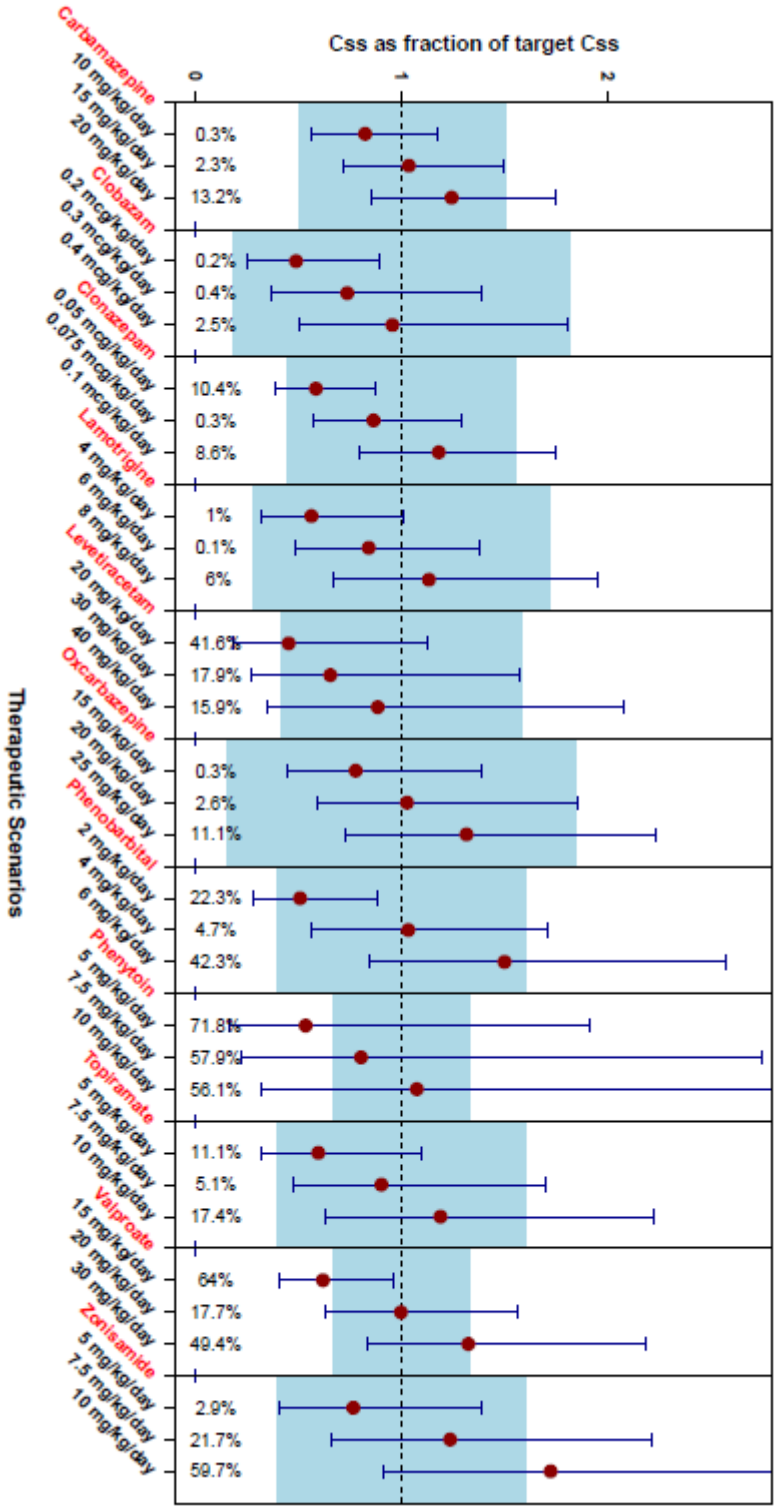


Figure 2 Median (circles) and 95% prediction interval (bars) for the steady-state concentrations (C_{ss}) achieved in children for different AEDs and dosing scenarios. Shaded area represents the reference therapeutic range; numbers shown below the bars are percentages of the population with C_{ss} values outside the reference therapeutic range.

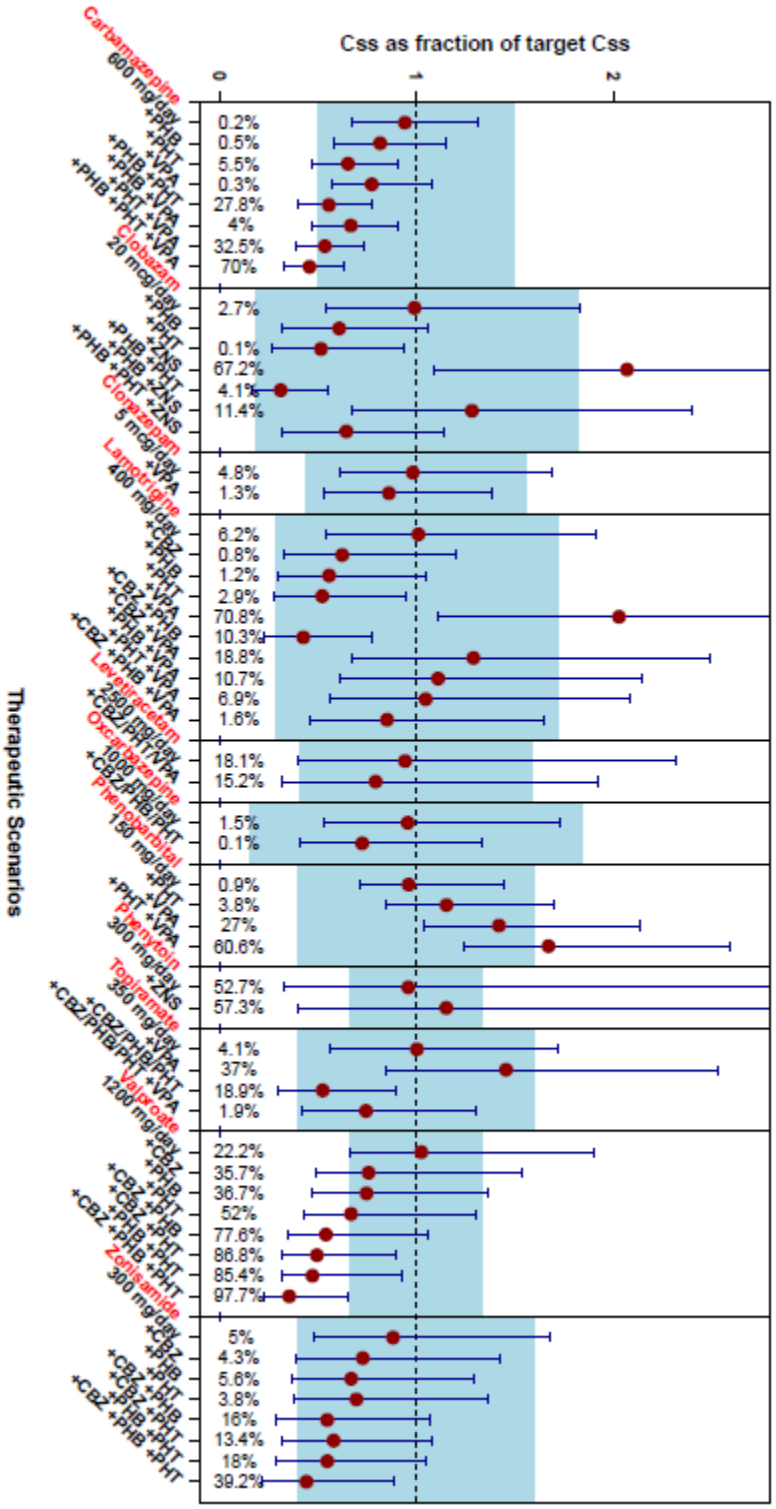


Figure 3 Median (circles) and 95% prediction interval (bars) for the steady-state concentrations (C_{ss}) achieved in adults for different AEDs and DDI scenarios. Shaded area represents the reference therapeutic range; numbers shown below the bars are percentages of the population with C_{ss} values outside the reference therapeutic range.

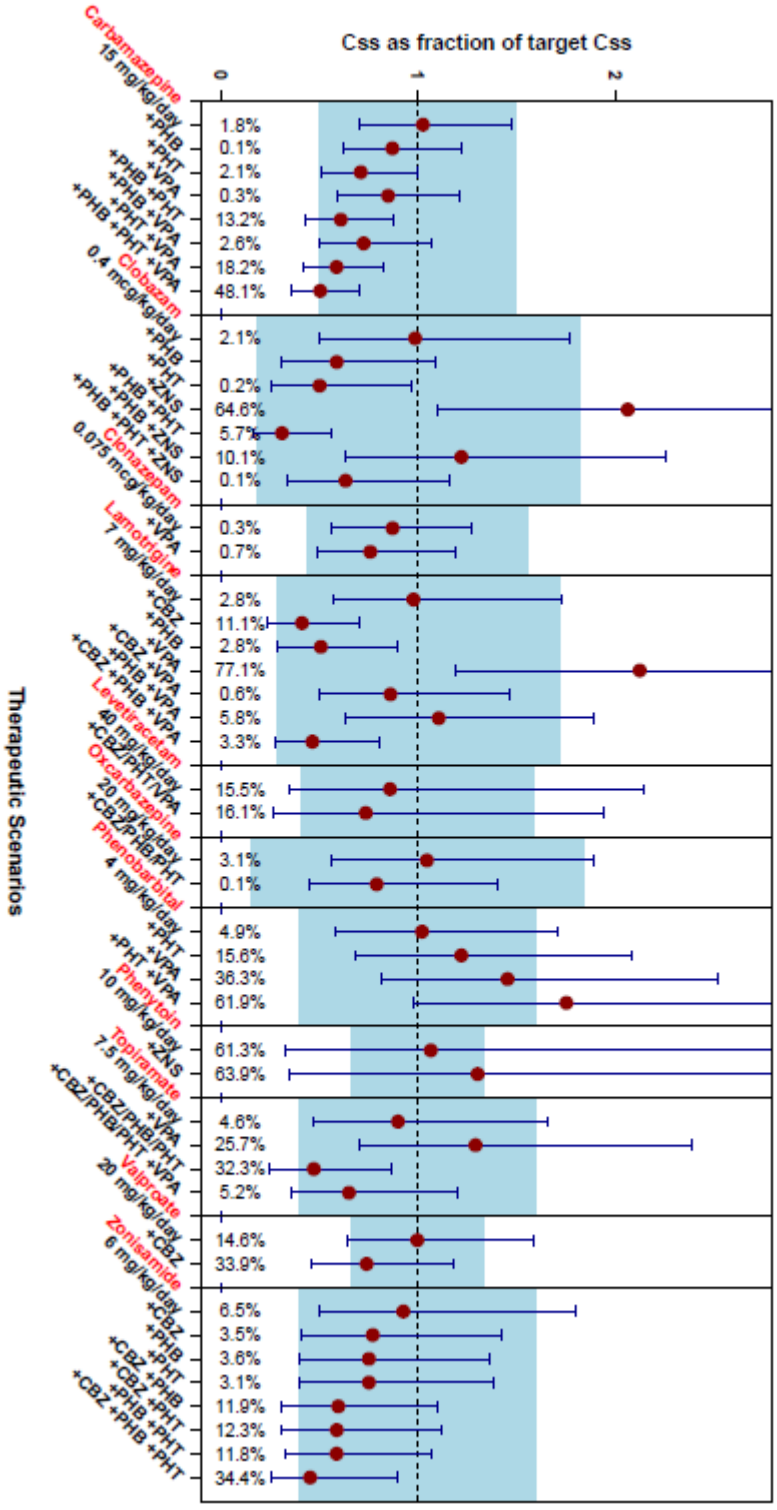


Figure 4 Median (circles) and 95% prediction interval (bars) for the steady-state concentrations (C_{ss}) achieved in children for different AEDs and DDI scenarios. Shaded area represents the reference therapeutic range; numbers shown below the bars are percentages of the population with C_{ss} values outside the reference therapeutic range.