Personalised pharmacotherapy in paediatric epilepsy : the path to rational drug and dose selection

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CHAPTER 5

INDIVIDUALISED DOSING ALGORITHMS AND THERAPEUTIC DRUG MONITORING FOR ANTIEPILEPTIC DRUGS

Individualised dosing algorithms and therapeutic monitoring for antiepileptic drugs

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SUMMARY

Pharmacokinetic (PK) models exist for most antiepileptic drugs (AEDs). Yet, their use in clinical practice to assess inter-individual differences and derive individualised doses has been limited. Here we show how model-based dosing algorithms can be used to ensure attainment of target exposure and improve treatment response in patients. Using simulations, different treatment scenarios were explored for 11 commonly used AEDs. For each drug, five scenarios were considered: i. all patients receive the same dose. ii. individual clearance (CL), as predicted by population PK models is used to personalize treatment. iii-v. individual CL, obtained by therapeutic drug monitoring (TDM) according to different sampling schemes is used to personalise treatment. Attainment of steady-state target exposure was used as performance criterion to rank each scenario. In contrast to current clinical guidelines, our results show that patient demographic and clinical characteristics should be used in conjunction with TDM to personalize the treatment of seizures.

Study Highlights

What is the current knowledge on the topic? Population pharmacokinetic models are available for many AEDs, most of which allow the characterisation of predictable (e.g. covariates) and random interindividual variability.

What question did this study address? Standard dosing recommendations and titration procedures have important limitations. A model-based algorithm is proposed for AED dose individualisation, which may be of great benefit for patients whom fail to respond to initial first-line therapy.

What this study adds to our knowledge AED dosing regimens based on typical population characteristics do not ensure attainment and maintenance of target exposure in patients. By contrast, model-based dosing algorithms result in significant reduction in the variability of AED levels at steady-state.

How this might change clinical pharmacology or translational science Our approach shows how dosing algorithms can be implemented in the clinic to deliver personalised and individualised treatments. It also shows the advantages of integrating TDM with model-based platforms.

1. Introduction

Epilepsy is a chronic neurological disease, manifesting as recurrent seizures. In spite of the efforts to identify novel, more effective antiepileptic drugs (AEDs), one-third of the patients are not responsive to the first treatment. Sadly, a considerable proportion of these patients eventually also fail after transition to alternative or second line treatment. Such inter-individual variability in the response to AEDs is a consequence of multiple interacting factors, including differences in the pathophysiology, pharmacokinetic, pharmacodynamic and genetic variation [1,2]. It is therefore acknowledged that rational prescribing of antiepileptic drugs (AEDs) requires not only an understanding of the seizure type and of the drugs' pharmacodynamic

properties, but also careful consideration of the factors known to affect drug disposition [3,4]. In fact, the impact of covariate factors on drug exposure and consequently on pharmacokinetic variability, efficacy and tolerability profile of AEDs has been highlighted in a recent publication by our group [5]. Our findings confirm the concerns raised by previous authors on the importance of accounting for covariate factors, particularly in patients at the extreme range of age, such as infants and elderly [6,7].

Given the impact of demographic, clinical and genetic covariate factors, one important question that remains unaddressed is whether the lack of response and subsequently switching to alternative first-line AEDs (or combination therapy) can be potentially avoided by a more robust dosing rationale. Many AEDs show large pharmacokinetic (PK) variability, especially when drug-drug interactions occur during combination therapy [5]. Nevertheless, despite the large number of investigations on the clinical pharmacokinetics of AEDs, limited attention has been given to the magnitude of such effects and their clinical implications. In most cases, covariate effects have been assessed as part of a population pharmacokinetic analysis, where the main objective is the characterization of the overall drug disposition properties and underlying sources of variability, rather than the optimisation of the therapeutic intervention in a wider patient population [8,9].

From a clinical point of view, the use of titration procedures, without taking into account the underlying inter- and intraindividual variability in pharmacokinetics, conflate PK variability with that of pharmacodynamics (PD) and disease progression. Usually, treatment is started at a low dose, followed by up-titration until adequate efficacy or unacceptable side effects are reached. Therapeutic drug monitoring (TDM) is eventually considered when side-effects are seen at a lower doses or inadequate efficacy is observed at a higher doses than expected. On the other hand, in some cases dosing regimens may be selected that aim at reaching steady state concentrations (C_{ss}) within a pre-defined therapeutic range [10,11].

Based on the aforementioned, it becomes clear that current guidelines for the selection and titration of AEDs overlook the impact of the underlying

variability in drug disposition. Even if only part of the variability in the PK of AEDs can be explained by demographic covariates such as weight and age, dose adjustments can provide a concrete opportunity for optimising therapy. Surprisingly, this contrasts with the fact that nomograms have had a place in the optimisation of AED therapy since the early 1970's, especially for phenytoin, which shows large variability due to its nonlinear pharmacokinetic properties. Nomograms have, however, important limitations. They allow for adjustment of only a few variables (see examples in Hudson *et al*. [12]) or otherwise can become convoluted (e.g. Lee *et al*. [13]). In contrast, the use of PK models allows dose adjustment to be made *a-priori* based on any number of covariates (i.e. personalisation). The availability of models also enable subsequent optimisation of the treatment based on clinical follow-up procedures such as TDM (i.e. individualisation) without the need for empirical calculations or drawing lines on graphs by hand. An additional advantage of PK models is the incorporation of statistical distributions to describe measurement error, which can theoretically lead to more accurate and/or precise parameter estimates depending on the error model; in turn this results in more accurate dosing recommendations. Moreover, PK models are one of the building blocks of clinical trial simulations, which can provide the basis for the evaluation of alternative dosing scenarios *in silico*.

Here we explore how clinical trial simulations and optimal design concepts can be used to identify suitable dosing algorithms and possibly personalise the treatment of seizures with the available AEDs. It can be anticipated that the implementation of model-based titration and dosing algorithms, as a criterion for dose adjustment and transition to alternative first-line or combination therapy, may prevent treatment failure in a considerable fraction of patients who currently do not respond to the first AED. Our approach may be of particular relevance for 10-20% of patients who still show unresolved seizures when their target dose has been achieved [3]. It may also allow the identification of individuals within the group of patients who would respond to optimised regimens, but currently remain refractory to treatment and are said to have drug-resistant epilepsy [4].

Finally, we aim to show how TDM procedures can be combined with inferential methods based on modelling and simulation to optimise doses and dosing regimens. These concepts have been increasingly applied to other therapeutic areas (e.g., anti-tumour, immunosuppressant and anti-infective drugs) where favourable treatment outcome depends on the attainment and maintenance of target drug exposure [14–18]. Such developments illustrate the effective introduction of individualised medicines to patients [19]. This diverges from current clinical practice in epilepsy, which relies on limited clinical evidence and somewhat randomly selected sparse pharmacokinetic sampling when TDM is used. In most cases, blood collection is performed without further understanding of the required number of samples or most appropriate time for collection to ensure accurate estimation of the clearance (CL), which is critical for subsequent dose individualisation. So far, no evidence exists on the optimality of such sampling strategies. Typically, optimal sampling is assumed to be at the end of the dosing interval (i.e. trough levels), but this is not always the case (e.g. sampling times between 2-6 hours post-dose in Yukawa *et al.* [20]). Moreover, there is often a large spread in sampling times in part due to factors such variable dosing time, patient availability, and blood withdrawal service opening times.

For the sake of clarity, here we refer to *personalisation* when treatment decisions, including dose adjustment are based on covariate factors, including demographic, clinical and pathophysiological data. Such a definition is required to account for the contribution and interaction between multiple factors, other than genotype and phenotype [21]. We also make use of the term *individualisation* to refer to dose adjustments based on therapeutic monitoring (TDM) and subsequent estimation of the individual patient's PK parameters (e.g., clearance). This distinction is important as in some cases treatment optimisation may be reached without the requirement for TDM. In fact, when used in conjunction with model-based approaches TDM may form the basis for the individualisation of therapy, in particular in special populations such as children and pregnancy [22–24].

2. Methods

Pharmacokinetic models and virtual patient demographics

Models describing the adult and paediatric PK of carbamazepine (CBZ) [37], clobazam (CLBZ) [38], clonazepam (CLNZ) [20], lamotrigine (LMT) [39,40], levetiracetam (LVT) [41], oxcarbazepine (OXC) [42], phenobarbital (PHB) [43], phenytoin (PHT) [44], topiramate (TPM) [30], valproic acid (VPA) [45,46], and zonisamide (ZNS) [47] were collected from the published literature. Models were transcribed into the appropriate format in R v3.1.1 [48], along with the parameter estimates and combined with analytical solutions of the mathematical equations describing the concentration over time profiles (equations 1 and 2.1-2.5 for one and two compartment models respectively) [12,49,50]. These equations were then implemented as scripts and used for all subsequent simulations. For each AED, separate adult and paediatric populations were evaluated (n=1000) using the baseline demographic characteristics described in table 1. Values of other influential factors, such as genetic polymorphisms were simulated according to their occurrence as in the original publication. Steady-state concentrations over 12 hour dose intervals and C_{ss} (equation 3) were simulated for typical adult and paediatric populations (table 1). Hypothetical dosing regiments were considered according to different dosing algorithms (table 2). Steady state concentrations (C_{ss}) were used as a surrogate marker for AED effect, with the therapeutic target C_{ss} (TC_{ss}) in each scenario set to the concentration half way between therapeutic minimum and maximum of the therapeutic window (table 3) [10].

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

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

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

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

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

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

$$C_{ss} = \frac{F*D*\tau}{CL} \quad (3)$$

$$D_i = \frac{1}{F} * CL_i * TC_{ss,i} * \tau_i \quad (4)$$

Equations 1-4. C_t: concentration at time t (mg/L or µg/L). D: Dose (mg or µg). V or V_1: central volume of distribution (L). k_a: absorption rate constant (h^{-1}). CL: clearance (L/h). t: time (h). t_D: time of dose (h). τ: dosing interval (h). Q: intercompartmental clearance (L/h). V2: peripheral volume of distribution (L). F: bioavailability (fraction of the dose that is absorbed). TC: target steady state concentration (mg/L or µg/L). i: individual *i*.

Table 1 Baseline characteristics of the patient population used across the different simulation scenarios

Demographic	**Adult values**	**Paediatric values**
Age range in years (uniformly distributed)	18-65	4-14
Mean, CV% of weight (kg) (normally distributed)	Male: 75, 16% Female: 65, 16%	3·Age+7 †, 10%
Gender	Male: 50% Female: 50%	Male: 50% Female: 50%

†Based on the weight-by-age formula created by Luscombe & Owens in Arch Dis Child 2007: a child's weight can be predicted by taking three times its age plus seven

Table 2 Model-based dosing algorithms tested in the different scenarios

Dosing algorithm name	Dose calculated using
Standard (Population)	Population CL
Personalised	Model-predicted CL, including covariate effects
Individualised (1)	individual CL prediction based on TDM with 1 sample at 12:00 post-dose
Individualised (2)	individual CL prediction based on TDM with 2 samples at 09:00 and 12:00 post-dose
Individualised (3)	individual CL prediction based on TDM with 3 samples at 06:00, 09:00, and 12:00 post-dose
D-optimised (1)	Individual CL prediction based on TDM with optimised sampling time (1 sample)
D-optimised (2)	Individual CL prediction based on TDM with optimised sampling times (2 samples)
D-optimised (3)	Individual CL prediction based on TDM with optimised sampling times (3 samples)

Table 3 Dose levels simulated for the initial dosing scenario, along with the corresponding therapeutic windows and target steady-state concentration for each drug.

Drug	Adult standard dose	Paediatric standard dose	Therapeutic concentration window [9]	Target Steady-state concentration
CBZ	700 mg/day	15 mg/kg/day	4-12 mg/L	8 mg/L
CLBZ	20 µg/day	0.4 µg/kg/day	30-300 µg/L	165 µg/L
CLNZ	5 µg/day	0.08 µg/kg/day	20-70 µg/L	45 µg/L
LMT	400 mg/day	7 mg/kg/day	2.5-15 mg/L	8.75 mg/L
LVT	2500 mg/day	50 mg/kg/day	12-46 mg/L	29 mg/L
OXC	1000 mg/day	20 mg/kg/day	3-35 mg/L	19 mg/L
PHB	150 mg/day	4 mg/kg/day	10-40 mg/L	25 mg/L
PHT	300 mg/day	10 mg/kg/day	10-20 mg/L	15 mg/L
TPM	300 mg/day	8 mg/kg/day	5-20 mg/L	12.5 mg/L
VPA	1200 mg/day	20 mg/kg/day	50-100 mg/L	75 mg/L
ZNS	300 mg/day	6 mg/kg/day	10-40 mg/L	25 mg/L

Personalised dosing algorithms

Two different dosing algorithm scenarios were simulated based on the population pharmacokinetic models alone. In an initial scenario, exploratory simulations (not shown) were performed to select one dose for the whole population that resulted in exposures which were the closest to the target exposure in the largest proportion of the population. This *population* scenario was selected as a *reference* scenario. For subsequent comparisons under the assumption that the selected doses reflect the titration procedures used in clinical practice. By contrast, in the *personalised* dosing scenario, individual clearance estimates were calculated for each patient *i* (CL_i) using the covariates included in the model. The difference between the initial *population* dose and *personalised* dosing scenarios represents the impact of inter-individual variability in clearance, which is explained by covariates. Finally, an additional dosing scenario was generated for PHT based on the nomogram of Ludden et al. [51]. This nomogram requires two samples at different steady-state doses. We have therefore used 300 and 200 mg/day for adults, and 10 and 6.7 mg/kg/day for children. Based on their nomogram, parameters Vmax and Km are calculated and an updated dose can be derived using the formula $Vmax*TC_{ss}/Km+TC_{ss}$. It should be noted that the nomogram will derive a negative Km when higher concentrations are observed for a lower dose as compared to that of the higher dose, in which case their median reported Km of 7.73 was used instead.

Individualised dosing algorithms

Given that the AEDs are titrated to steady-state conditions, the average plasma concentration at steady-state will vary according to the individual patient's clearance (CL). Empirical Bayesian estimation (EBE) procedures can be used to obtain accurate predictions of the individual parameter of interest. The EBE determines the deviation (η, eta) from the population value (θ, theta) of the parameters of interest (e.g. rate of absorption, volume of distribution, clearance, etc.), taking into account the residual variability (ε, epsilon) [52]. Thus, AED concentrations derived from TDM can be used in conjunction with EBE to individualise the dose [10,11,53]. In theory, such an approach allows one to account for the variability in

clearance and other individual pharmacokinetic parameters which are not described by the underlying covariate effects. To date, it is unclear to what degree such a dosing algorithm yields higher proportions of patients achieving target C_{ss} (TC_{ss}) when compared to conventional dose adjustment for AEDs based on TDM only.

Here we present three *individualised* dosing scenarios, in which EBEs were obtained for clearance (CL_i), under the assumption of blood sampling being performed according to empirical sampling schemes, including 1, 2, or 3 samples for each individual patient. When only one sample was collected, sampling was performed at the end of the dosing interval (12 h) to ensure information about the trough levels. When two samples were used, blood sampling was such that information was obtained about the elimination phase in addition to the trough sample at the end of the dosing interval, i.e., at 9 h and 12 h post dose. For three samples, data on the elimination phase was obtained at 6, 9 and 12 h post dose. EBEs of clearance were obtained by minimising the Bayesian objective function (equation 5):

$$OFV_i = \sum\left(\frac{\bar{Y}_{ij}-Y_{ij}}{\sigma^2}+\ln(\sigma^2)\right)+\sum\left(\frac{{\eta_{ik}}^2}{{\omega_k}^2}\right) \quad (5)$$

where $\bar{Y}_{ij}$ is the j^{th} concentration prediction for individual *I*, Y_{ij} is the j^{th} concentration observation for individual *I*, σ is the variance of the residual error, η_{ik} is the deviation (eta) from population parameter *k* in individual *I*, and ω is the variance of the k^{th} eta. Although EBEs were estimated for all etas, only those for clearance were subsequently used for dose optimisation using equation 4. The difference between *personalised* and *individualised dosing* scenarios reflects the contribution of the parameter distribution describing an additional fraction of the unexplained inter-individual variability in clearance.

Optimised blood sampling for TDM

D-optimality concepts have been used across different therapeutic areas as a tool to improve parameter precision. This represents an important advantage when sparse sampling is for the purpose of population pharmacokinetic modelling. Here three *D-optimised* scenarios were considered, in which 1, 2, or 3 time points were optimised for the estimation of individual CL. Data analysis was performed using

the PFIM software [49] to maximise the approximation of the Bayesian Fisher information matrix:

$$M_{BF}(\xi)^{\infty} = H^T F(\theta,\xi)^T \sum(\theta,\xi)^{-1} F(\theta,\xi) H + \Omega^{-1} \quad (6)$$

where $H = diag(\theta_1, \ldots, \theta_p)$, $F(\theta,\xi) = \frac{\partial f(\theta,\xi)}{\partial \theta^T}$, and ξ are sampling times $t_1, \ldots, t_n$ with the constraint that only sample times were allowed to be taken between 0.5 and 12 hours after dose, at discrete points each half hour, resulting in a total of 24 possible sampling time points. Samples obtained by D-optimality were then used in the simulation scenarios. EBEs of CL_i were derived as for the *individualised* dosing scenarios described previously. The difference between the *individualised* and *D-optimised* dosing scenarios reflects the impact of D-optimal design on the precision of individual clearance estimates.

Graphical and statistical summaries of the simulated scenarios

The ratio RTC_{ss} = C_{ss}/TC_{ss} was used to describe how well the C_{ss} resulting from a dosing algorithm compared to the theoretical TC_{ss}. Consequently, values for RTC_{ss} below or above 1 represent underdosing or overdosing, respectively. The observed differences between dosing algorithms for each drug and simulation scenario were graphically analysed using whisker-box plots of the median and 95% prediction intervals. In addition, the range of PFIM-derived sampling times was used to assess differences in parameter information content for the scenarios involving sampling time optimisation. Furthermore, bias and precision of RTC_{ss} were determined by calculating the relative error (RE%) as (C_{ss} – TC_{ss}) * 100%, and coefficient of variance (CV%) as mean(RTC_{ss}) / sd(RTC_{ss}) * 100% respectively. The impact of dosing algorithms on ability to attain TC_{ss} was determined by taking the difference in CV % and RE% estimates between simulated scenarios.

3. Results

Implications of dosing algorithms for systemic exposure to AEDs

Although dose levels were found that resulted in concentrations that are within the therapeutic window for eight out of eleven AEDs in at least 95% of the adult population, large inter-individual differences in CL resulted in a wide spread of C_{ss} relative to the target concentration, i.e., RTC_{ss} in the population (**figures 1 & 2**). Personalisation improved the precision of RTC_{ss} (CV% of *population* – CV% of *personalised* scenario) in adults for PHT (36.0%) and ZNS (8.5%). No relevant changes (between -5 to +5%) were found for CBZ, CLBZ, CLNZ, LMT, LVT, OXC, PHB, TPM and VPA. In children, personalisation also improved the precision of TC_{ss} for PHT (32.9%) and ZNS (5.9%). No relevant differences were found for CBZ, CLBZ, CLNZ, LMT, OXC, PHB, TPM, and VPA. The CV% for the *personalisation* scenario was worse for LVT (-15.6%). *Personalisation* procedures resulted in a reduction of the bias in TC_{ss} (RE% of *population* – RE% of *personalised* scenario) for PHT (8.2%), TPM (7.9%) and ZNS (13.5%) in adults, and CLBZ (6.3%), CLNZ (9.4%), OXC (12.8%) and TPM (8.7%) in children. Some bias was observed by personalised dosing of LMT (-6.0%) in children. No relevant differences in bias were found for any of the other AEDs.

By contrast, the integration of model-based algorithms with EBE estimates from TDM using one sample showed that improvement in terms of target C_{ss} for nearly all AEDs. Reductions in CV% of TC_{ss} in adults varied between 6.6% for CBZ and 20.9% for CLBZ. The effect of these procedures was found to be negligible only for TPM (4.6%). In children, similar reductions were observed in CV% of TC_{ss}, with values varying between 6.0% for CLBZ to 19.9% for CLNZ. Further reductions in the variability in TC_{ss} could be achieved by evaluating two blood samples instead of one.

Such an improvement was observed for LVT (7.5%) in adults and CLBZ (8.4%) in children. Finally, bias in the TC_{ss} estimates (RE%) in children could be reduced using one TDM sample only for LMT (6.9%). No improvement in bias was found for any of the other AEDs, irrespective of the number of TDM samples.

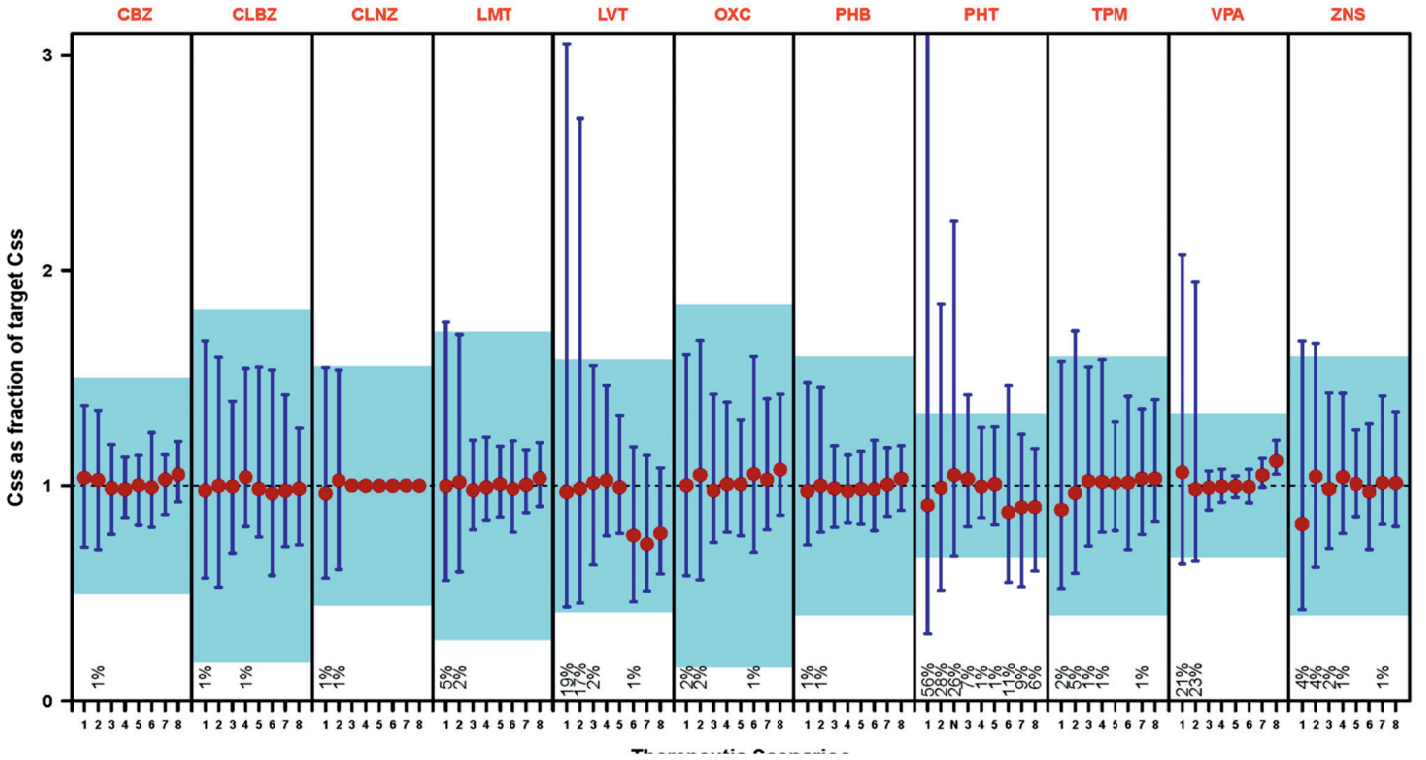

Figure 1 Overview of median (circles) and 95% prediction interval (bars) of drug exposures (C_{ss} as the fraction of target C_{ss}) in adults for different drugs and dosing scenarios, therapeutic window shown as a shaded area, numbers listed below the bars are percentages of the population with C_{ss} falling outside the therapeutic window, only values other than 0% are shown. The values of TRC_{ss} at the unity line in the case of clonazepam are probably due to the underlying model parameterisation, which does not include absorption and distribution processes.

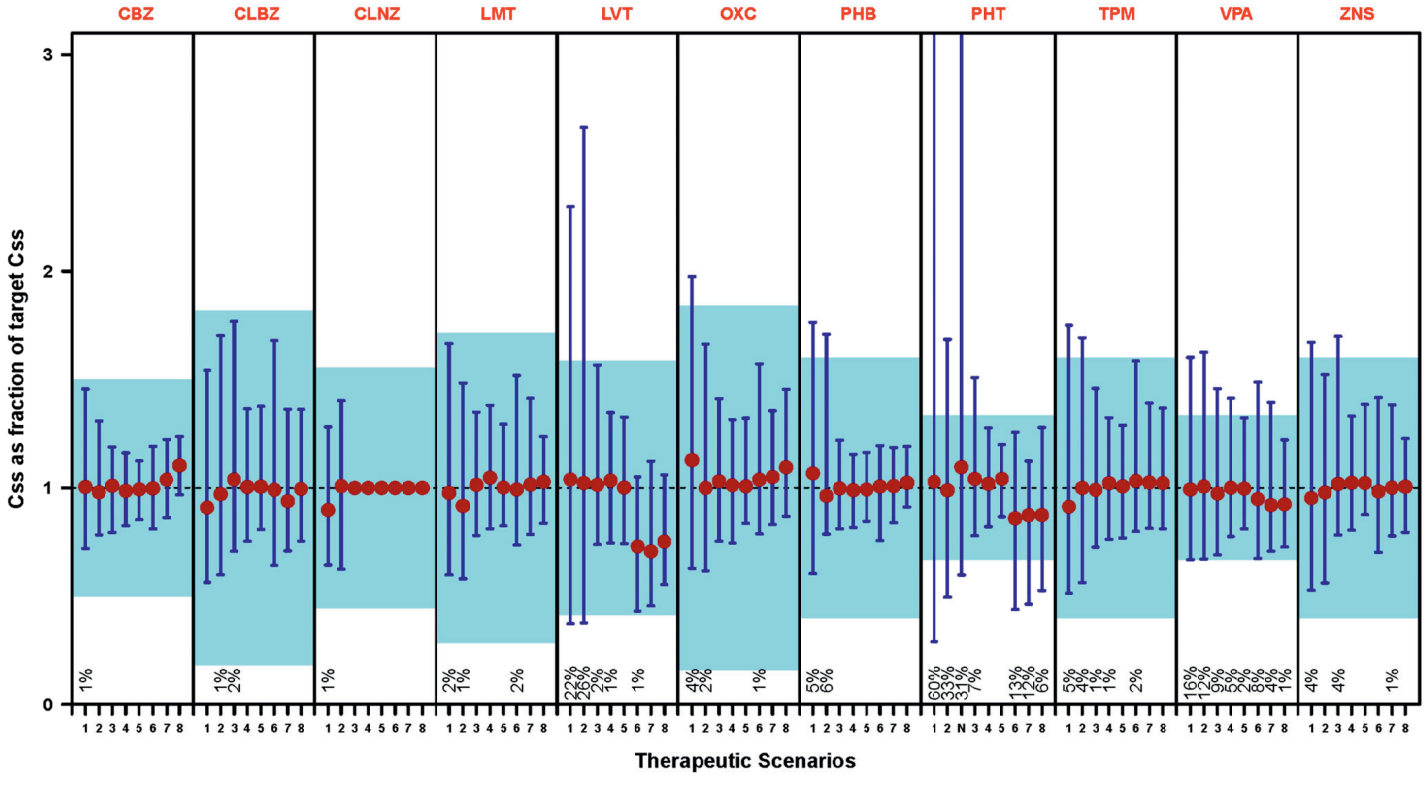

Figure 2 Overview of median (circles) and 95% prediction interval (bars) of drug exposures (C_{ss} as the fraction of target C_{ss}) in children for different drugs and dosing scenarios, therapeutic window shown as a shaded area, numbers listed below the bars are percentages of the population with C_{ss} falling outside the therapeutic window, only values other than 0% are shown. The values of TRC_{ss} at the unity line in the case of clonazepam are probably due to the underlying model parameterisation, which does not include absorption and distribution processes

Implications of optimised sampling times for TDM

The sampling times for characterisation of clearance (trough levels) in adults could be optimised for 6 out of 11 AEDs, whereas for two other compounds, sampling times optimisation was achieved by including data relative to the upswing portion of the concentration vs. time curve (**figures 3 & 4**). Of note is the fact that optimisation procedures show a counterintuitive behaviour. When more frequent sampling is required or feasible, one should collect additional samples at time points close to the reference sampling times. The spreading of blood samples at wider intervals such as at 6, 9 and 12 hours after dose for once-daily regimens is often less informative than when the additional samples are collected at the end of the dosing interval.

Despite the possibility of introducing optimised times for blood sampling and obtaining increased precision for individual clearance estimates, our findings reveal that such efforts do not warrant improved target attainment. In fact, comparison of CV% of TC_{ss} between the *D-optimised* and *individualised* scenarios (i.e. one vs. one, two vs. two and three vs. three samples) reveals no reductions larger than 5%. By contrast, a worsening was found for PHT in adults (-7.4, -8.5 and -5.1%) and children (-5.4, -6.7 and -9.0%), and LMT (-5.3% for one sample) in children. In addition, bias was not reduced by taking samples at *D-optimised* sampling times. Surprisingly, D-optimised schemes introduced bias for LVT (-21.7, -24.7, and -21.4%), PHT (-9.2, -9.7, and -9.2%), and VPA (-11.4 when taking three samples) in adults, and for LVT (-25.7, -25.9, and -24.6%), PHT (-9.8, -10.7, and -8.3%), and VPA (-7.9, and -7.3% for two and three samples respectively).

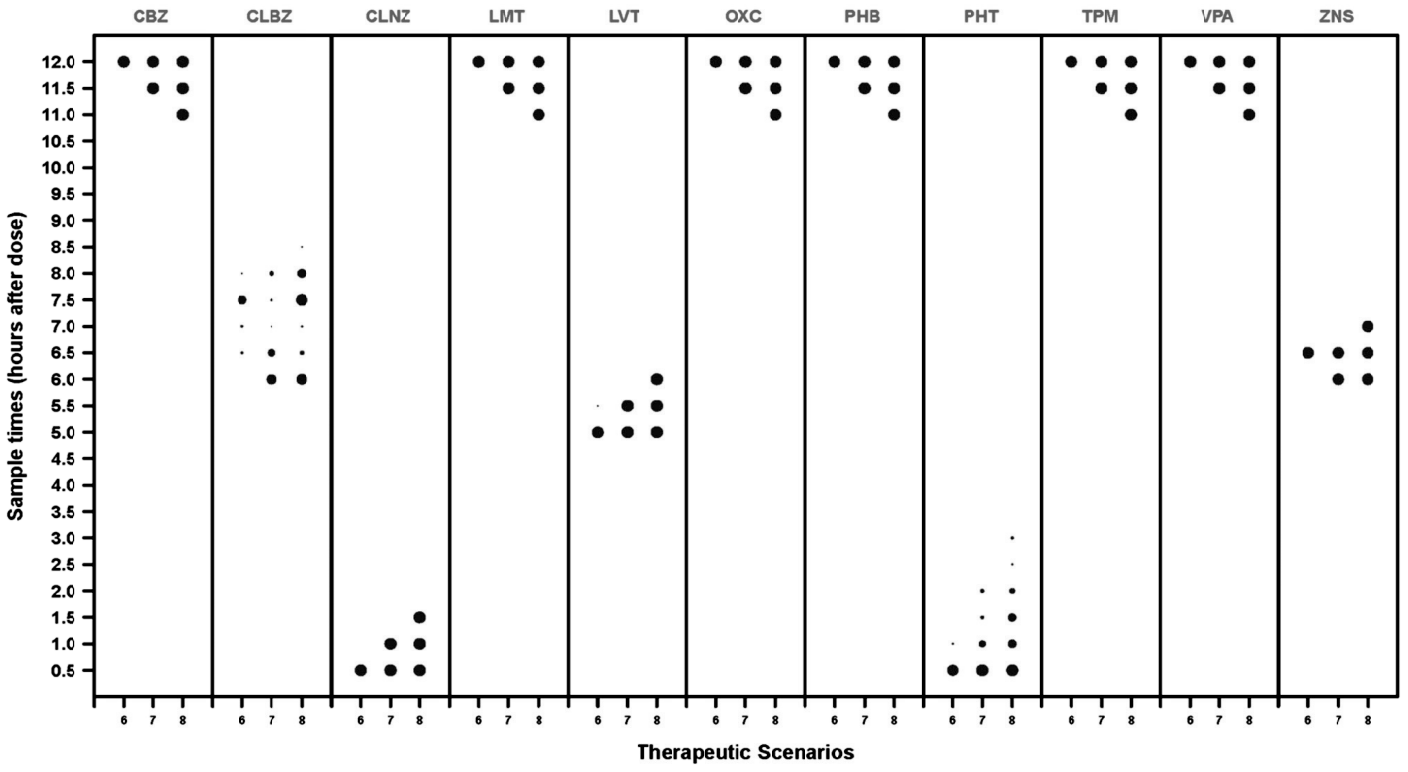

Figure 3 Overview of optimised samples in hours after dose (circles) for each drug and number of samples per individual. The relative size of the circle represents the relative frequency of sampling at each specific time point, i.e. if more patients were sampled at the time point, a larger circle is depicted.

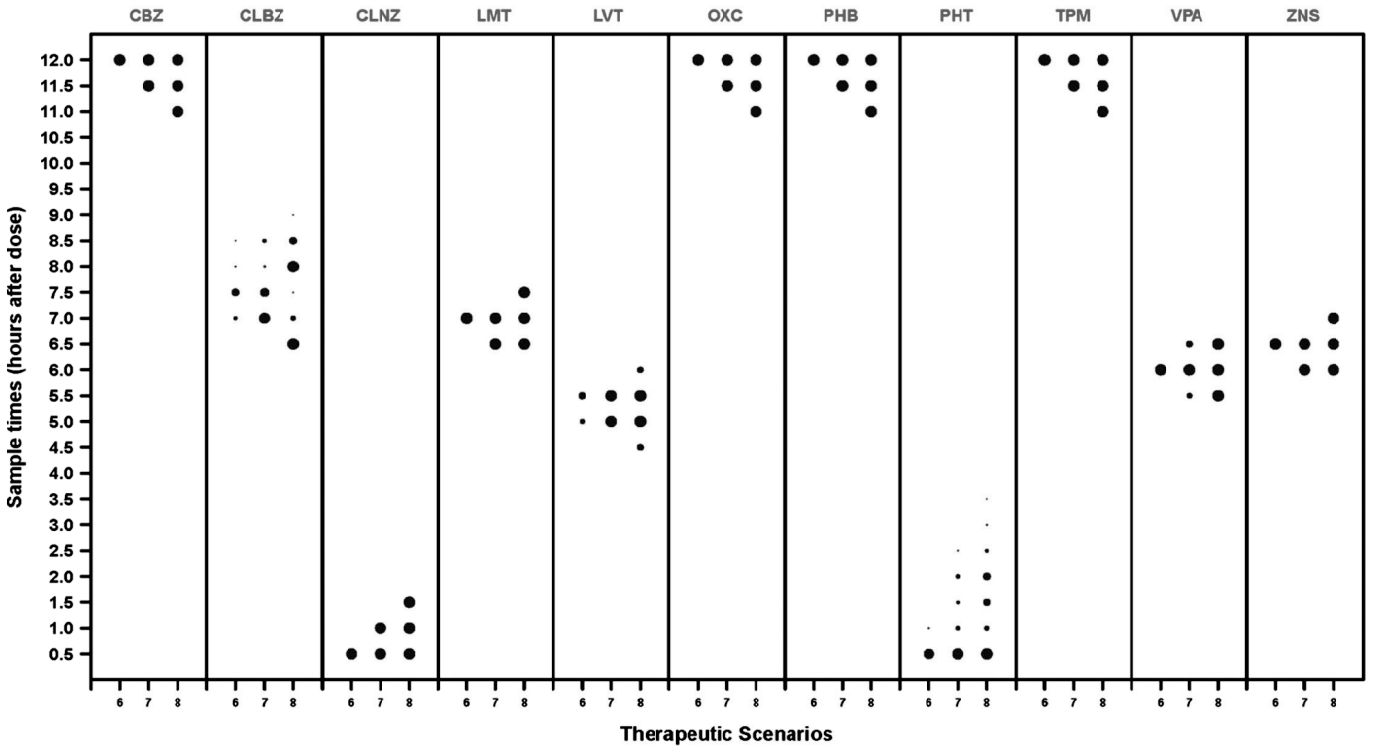

Figure 4 Overview of optimised samples in hours after dose (circles) for each drug, and number of samples per individual. The relative size of the circle represents the relative frequency of sampling at each specific time point, i.e. if more patients were sampled at the time point, a larger circle is depicted.

4. Discussion

The treatment of epileptic seizures with AEDs is based on the clinical classification of overt seizure type [20,21]. Whereas heterogeneity in disease is well known and treatment response varies considerably between patients, there has been a long debate about to what extent treatment should be complemented by therapeutic drug monitoring, which is aimed at establishing whether patients reach and maintain a predefined concentration or concentration range.

Our results show that despite the limited attention given to the impact of covariate factors on drug disposition, model-based dosing algorithms can be developed in conjunction with TDM to individualise treatment. The use of such an integrated approach allows a significant reduction in the variability in drug exposure, which is observed after administration of standard doses, even when titration steps are used at the start of treatment [22,23]. In addition, our investigation shows that individualisation based on a single TDM sample at the end of the dosing interval resulted in large improvements in target attainment. Further improvements could be achieved with one or two additional TDM samples, but differences were not marked.

Contrary to what one would expect, optimisation of sampling times by D-optimality did not improve precision or bias, and paradoxically resulted in worsening for some AEDs. Based on our optimisation results, sampling time optimisation seems unnecessary and may in some cases even introduce bias. It may still be of use in situations where the accurate information on the parameter of interest (here: clearance) cannot be as easily derived, e.g. in the case of multiple, variable dosing regimens, or polytherapy with drug-drug interactions.

Our investigation also shows that implementation of TDM without further integration with model-based techniques does not warrant effective individualisation of the dose. In this regard, the lack of consensus about the clinical relevance and performance of TDM may be partly explained by its use as a diagnostic tool, i.e., TDM results are treated similarly to any other clinical laboratory data. Instead, TDM should be seen as the input variable

for a dosing algorithm, in which inferences from individual drug levels are used to establish the contribution of multiple interacting factors [10,14,16,25]. While some evidence exist for the lack of significant impact of AED TDM on treatment outcome, such investigations did not include model-based dosing algorithms. More clinical evidence is required to build a stronger case for the advantages of parametric methods to obtain accurate estimates of interindividual variability in drug disposition, as expressed by (pharmacokinetic) model parameters. Irrespective of the limitations which some of the pharmacokinetic models present, our approach clearly illustrates how therapeutic platforms can be implemented to support personalised and individualised treatment. It also shows how clinical decision criteria and therapeutic guidelines can benefit from quantitative clinical pharmacology methods. We anticipate that as the relationships between AED exposure and efficacy become elucidated [26–30], this approach may be further refined by targeting individualized plasma concentrations to account for variability in pharmacodynamics. In any case, the assumption that standard doses and dosing regimens, whether or not corrected empirically by body weight or other covariate factor is no longer defendable for AEDs.

Potential limitations

Given that models were retrieved from the published literature, one cannot exclude possible limitations when using them for simulation purposes. First, it should be noted that some of these models were based on sparse data. This may have resulted in an inflated variability in clearance, as often variability in absorption or distribution volume was not included. Consequently, these models may have indirectly produce results in favour of the *individualised* and *D-optimised* dosing algorithms, as these approaches take into account these other sources of variability. Clearly, given some of the simplifications, some models may not adequately describe the relevant physiological processes when applied other conditions or scenarios, such as dosing during non-steady state conditions. By contrast, other models may be considered overparameterised. For instance, the models for CLBZ and ZNS incorporate information on genetic polymorphisms for the prediction of clearance, which requires DNA sequencing, a procedure which is not yet commonly used in current clinical

practice and may therefore be of limited clinical value. Another example of such limitations is the case of CLNZ, for which the relative target attainment approached unity for the *individualised* and *D-optimised* dosing algorithms; the population pharmacokinetic model for this drug does include interindividual differences in absorption or distribution processes. In real life, some variation would be detected even after integration of the TDM with population pharmacokinetic concepts.

The discrepancies that were found in terms of precision and bias between dose individualisation using typical and optimised sampling times may also be due to model limitations, as in the case of LVT and PHT, for which information regarding the underlying correlation between clearance and volume of distribution and variability in the absorption kinetics was missing. A major difference between sampling time optimisation in adults and children was seen for drugs LMT and VPA. These differences are most probably caused by the fact that the pharmacokinetic models have been originally developed separately for adults and children. From a statistical perspective, the main difference between the two pharmacokinetic models was the use of additive (adults) and proportional (children) residual errors. When residual error is large and parameterised as proportional-only simulations will behave differently from combined error models.

Lastly, we have not limited the dose adjustments to the approved dose ranges or available dosage strengths, as the scope our investigation was to establish the relevance of model-based principles for the personalisation of treatment with AEDs. Nevertheless, we do not anticipate any major differences in the conclusions drawn so far. The predicted doses were within the approved dose ranges even if doses were not adjusted for available strengths.

The implementation of model-based dosing algorithms for individualisation of treatment in the clinic is subject to practical, technical and theoretical challenges, such as the characterisation of interindividual differences. As a consequence, historically AED dose adjustments have been restricted to the typical population parameter values, without taking into account the contribution of predefined covariate effects. In fact, exceptions are

illustrated by the requirements for dose adjustment in patients with varying degrees of renal and hepatic impairment. Treatment Individualisation or precision medicine has become goal of the clinical research community in other therapeutic areas such as oncology, but its wider acceptance seems to be hindered by limited evidence of its large-scale utility and impact [31]. Furthermore, the lack of user friendly software programs over the past decades has imposed the need for technical skills to access and use quantitative technologies. This situation has changed in recent times; advances in computing performance and continuous development of dedicated software packages, such as R and Shiny have allowed the development of dosing tools with user friendly graphical user interfaces [32]. For example, the use of TDM is popular in antibiotic treatment, and the application TDMx has been created to make use of the available PK models for TDM-based dosing adjustments [33]. Currently, no such software applications exist with the required functionality to integrate bioanalytical results from TDM with a population pharmacokinetic model and patient demographic, clinical and genetic information to derive individualised dose recommendations for AEDs. Given the availability of dosing algorithms in other fields of medicine, it appears that the lack of such applications for AEDs reflects the entrenched culture in clinical decision making, rather than a technical hurdle. Taking into account the possibility of performing TDM based on dried blood spot or saliva, it can be anticipated that the implementation of integrated platforms will not represent an increased burden to patient care in epilepsy [34,35]. A final obstacle for the uptake of TDM-based dosing individualisation applications is the validation of such a platform. This would constitute validation of the generic modelling framework into programming code (e.g. equations 1-5) and validation of predictions of models and parameters for specific drugs and situations (e.g. the AED models used here). Whereas the former may be simply validated by comparison of predictions for hypothetical scenarios with industry standards such as NONMEM© [36], validation of the latter may require external datasets, or clinical trials in which such applications are used to predict concentrations or optimal dosing in clinically relevant scenarios. At the moment, no clear guidelines exist for such validations, leading to a case-by-case evaluation of these applications and unnecessary

uncertainties for companies or institutes developing these tools. Standardisation of validation efforts may create a more secure environment for these applications to thrive in.

In summary, some important recommendations arise from our investigation. First, that the use of wide blood sampling intervals for TDM has limited impact on the characterisation of individual pharmacokinetic parameters. Second, AED target exposure levels are unlikely to be attained without the use of dosing algorithms and individualised dosing recommendations. Third, available pharmacokinetic models have limitations which highlight the need for standardisation and validation procedures. Simplified models can lead to under- or over-appreciation of variability and thereby imprecise dosing. On the other hand, models that are too complex may lead to identifiability issues. In essence, a balance needs to be struck between complexity and usability. The work presented here adds to the increasing evidence that individualised therapy provides an opportunity to prevent failure of treatment with first line and alternative first-line AEDs, disentangling truly drug resistant patients from those who are labelled as non-responders, i.e., whose phenotype is a consequence of sub-optimal exposure.

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