Clin Pharmacokinet (2018) 57:1039–1053
https://doi.org/10.1007/s40262-017-0614-5

ORIGINAL RESEARCH ARTICLE

Effect of Age-Related Factors on the Pharmacokinetics of Lamotrigine and Potential Implications for Maintenance Dose Optimisation in Future Clinical Trials

Sven C. van Dijkman[1] · Nico C. B. de Jager[1] · Willem M. Rauwé[1] · Meindert Danhof[1] · Oscar Della Pasqua[1,2,3]

For the Tucuxi drug file, drop everything that concerns maturation of clearance in children <4 years, and absorption of the extended release (XR) formulation, not available in Switzerland

Published online: 23 January 2018

Abstract

Background and Aims In this study, we evaluate the performance of allometric concepts to predict the implications of age and size on the pharmacokinetics of lamotrigine, and assess the dose rationale across different age groups from 0.2 to 91 years.

Methods An allometrically scaled pharmacokinetic model was developed using adolescent and adult data, taking into account the effect of comedications. Model parameters were then used to extrapolate lamotrigine pharmacokinetics to older adults (>65 years), children (4–12 years) and infants and toddlers (0.2–2.0 years). In addition, simulations were performed to identify the implication of different doses and dosing regimens for each population, so as to ensure steady-state concentrations within a predefined reference range.

Results The pharmacokinetics of lamotrigine was best described using a one-compartment model with first-order absorption and elimination. Carbamazepine, phenytoin, and valproic acid changed systemic clearance (CL) by +76.5, +129, and −47.4%, respectively. Allometric principles allowed accurate extrapolation of disposition parameters to older adults and children older than 4 years of age. A maturation function was required to describe changes in exposure in younger patients. Compared with adults, a child aged 1.7 years has a 31.5% higher CL, after correcting for body weight. Patients >65 years of age showed a decrease in CL of approximately 15%.

Conclusion Population pharmacokinetic models are usually limited to a subgroup of patients, which may mask the identification of factors contributing to interindividual variability. The availability of an integrated model including the whole patient population provides insight into the role of age-related changes in the disposition of lamotrigine, and potential implications for maintenance dose optimisation in any future trials.

Trial Registration According to GlaxoSmithKline's Clinical Trial Register, data from the GlaxoSmithKline studies LAM100034 and LEP103944, corresponding to ClinicalTrials.gov identifiers NCT00113165 and NCT00264615, used in this work, have been used in previous publications (doi: https://doi.org/10.1212/01.wnl.0000277698.33743.8b, https://doi.org/10.1111/j.1528-1167.2007.01274.x).

The original version of this article was revised as per the corrections listed in the following: https://doi.org/10.1007/s40262-018-0660-7.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40262-017-0614-5) contains supplementary material, which is available to authorized users.

✉ Oscar Della Pasqua
oscar.e.della-pasqua@gsk.com

[1] Division of Pharmacology, Leiden Academic Centre for Drug Research, Einsteinweg 55, 2333CC Leiden, The Netherlands

[2] Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, Uxbridge UB11 1BT, UK

[3] Clinical Pharmacology and Therapeutics Group, University College London, BMA House (North Entrance), Tavistock Square, London WC1H 9JP, UK

Key Points

An integrated pharmacokinetic model shows that age and body weight, along with the effect of comedications (i.e. drug–drug interactions), are the primary factors affecting systemic exposure in patients of different ethnic backgrounds, aged 0.2–91 years, and receiving immediate- or extended-release lamotrigine.

Our study also shows that the effect of body weight on the disposition of lamotrigine can be described by allometric principles in patients older than 4 years of age, whereas a maturation function is required for younger patients.

Whereas the pharmacokinetic data obtained in children younger than 2 years of age are from historical clinical trials, the current analysis suggests that different dosing regimens may be required in future studies in this population to ensure systemic exposure comparable to adults.

1 Introduction

Lamotrigine is a widely used antiepileptic drug (AED) that has been approved for the treatment of patients with partial-onset seizures, primary generalised tonic–clonic (PGTC) seizures, and Lennox–Gastaut syndrome who are aged 2 years and older [1–5]. The pharmacokinetics of lamotrigine are characterised by rapid absorption after oral administration, with negligible first-pass metabolism (absolute bioavailability is 98%). Dose proportionality was observed in systemic exposure, both in healthy subjects and patients over the dose range of 50–350 mg twice daily. Mean apparent volume of distribution (V_d/F: 0.9–1.3 L/kg) indicates distribution beyond total body water. Because lamotrigine is not highly bound to plasma proteins, clinically significant interactions with other drugs through competition for protein binding sites are unlikely. Lamotrigine metabolism is predominantly hepatic via conjugation (UDP-glucuronosyltransferase 1–4 and UDP-glucuronosyltransferase 1–3). Following repeated dosing, lamotrigine is known to induce its own metabolism, and oral clearance (CL) averages 0.35–0.59 mL/min. These estimates result in a plasma half-life ranging from 24 to 37 h [5–8]. In addition, considerable efforts have been made to characterise lamotrigine exposure in special populations, such as pregnant women [9–13], children [14–20], and elderly patients [21–25].

Despite the availability of pharmacokinetic data in both healthy subjects and patients, a comprehensive model-based analysis of clinical and demographic covariates known to affect the disposition of lamotrigine is still missing. In fact, population pharmacokinetic modelling has been used to describe the pharmacokinetics of lamotrigine in different patient groups and after administration of different dosage forms [9–31]; however, these investigations have not explored the implications of age-related differences in a systematic manner, except for the recent addition by Zhang et al. which resulted in the creation of separate models for each age category [20]. From a methodological perspective, another factor that needs to be considered are drug–drug interactions, as patients with epilepsy are usually exposed to polypharmacy. Hence, different approaches may be required to describe the impact of covariates across the overall population. For instance, appropriate scaling of pharmacokinetics to body weight (allometry) has been shown to allow the prediction of exposure in children older than 2 years of age [32], while changes in drug disposition in children younger than 2 years of age needs to be adjusted for by a separate maturation function. Yet, most investigations do not show how these factors can be disentangled from the effect of comedications and other intrinsic or extrinsic factors.

In this study, we attempt to develop an integrated population pharmacokinetic model to describe the pharmacokinetics of lamotrigine at steady state in patients from different ethnic backgrounds, aged 0.2–91 years, and receiving immediate-release (IR) or extended-release (XR) lamotrigine. Our analysis provides an opportunity to illustrate how population pharmacokinetic modelling and simulation can be used as a tool for dose adjustment and optimisation when patient population characteristics are likely to affect drug exposure [33]. In this regard, it should also be noted that a relationship between plasma concentration and clinical response and/or adverse effects has not been established for lamotrigine. Instead, plasma concentrations between 3 and 14 mg/L were considered as a clinically relevant target range [34]. Moreover, assessment of the effect of demographic characteristics on drug disposition parameters may provide insight into possible explanatory factors for the lack of efficacy of lamotrigine in patients aged 2 years and younger, which could not be demonstrated previously in randomised clinical trials [35]. These findings seem to contrast with the conclusions drawn by Pellock and collaborators regarding the possibility to extrapolate efficacy data in adults, which can be used to predict treatment response in partial onset seizures in children > 2 years of age. In fact, the authors declare that no attempt was made to quantitatively analyse the studies including lamotrigine due to the few trials eligible for their analysis [36].

Whereas multiple factors can contribute to the failure of a clinical trial, one cannot overlook the impact of differences in pharmacokinetics, especially when evidence suggests that young children show relatively higher CL [5], resulting in lower exposure levels even after correction for differences in body weight. Likewise, further attention needs to be given to the implications of reduced organ function and polypharmacy in older adults. Hence, our analysis aims to quantify the effect of changes in systemic exposure to lamotrigine due to developmental growth in younger patients (i.e. ontogeny, organ maturation), and reduced organ function and body mass in older adults. It can be anticipated that the availability of population parameter distributions, which account for the effect of covariate factors, will allow for the optimisation of future clinical trials, as well as the development of dosing algorithms for specific patient groups.

2 Methods

2.1 Data

All data used in the current investigation were obtained from GlaxoSmithKline's Clinical Trial Register. Pharmacokinetic data and patient characteristics were obtained from clinical pharmacology and efficacy studies with lamotrigine (ClinicalTrials.gov: NCT00043875, NCT00144872, NCT00113165, NCT00104416, NCT00516139, NCT00264615), all of which were performed in accordance with the rules and regulations of the respective countries where the studies were conducted. These studies contained both rich and sparse lamotrigine concentration data, patient demographics, and dosing information for a total of 492 patients receiving IR or XR formulations of lamotrigine for up to 45 weeks. As shown in Fig. 1, from this pooled data, six subsets were created for four age groups. Subsets A and B were created as 70 and 30% of the same population (adolescents and adults aged 14–88 years), including studies in which rich and sparse sampling were used (NCT00264615 and NCT00104416) for the purpose of model building and internal validation, respectively. Subset C was created for external validation (adolescents and adults aged 13–70 years), including a study in which sparse sampling was used (NCT00113165). Subsets D (NCT00516139), E (NCT00144872), and F (NCT00043875) were created for model extrapolations to adults aged 65–91 years, children aged 4–12 years, and infants and toddlers < 2.0 years, respectively. Except for study NCT00264615, all other studies included concentrations from samples taken at times when steady-state was expected to have been achieved. A detailed overview of the demographics of the patient population included in each subset can be found in electronic supplementary Table 1S; demographics of the total patient pool are listed in Table 1.

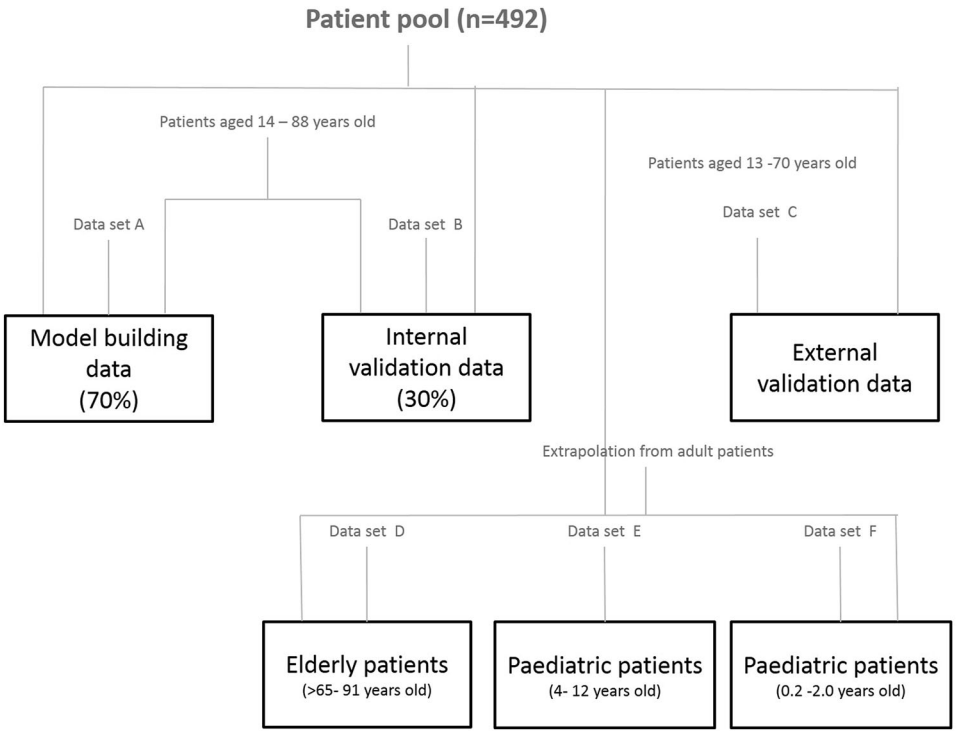

Fig. 1 Data sets and population characteristics for the development of a population pharmacokinetic model in adult, paediatric and elderly patients

Table 1 Demographics of the total modelling population. Carbamazepine–valproic acid: number of patients receiving the comedication and the range of doses

Demographic	Mean (SD)	Median (range)
No. of patients	494	–
Sex (M:F)	248:246	–
Age, years	45.3 (24.2)	29 (0.2–91)
Weight, kg	70.3 (27.5)	58 (3–151.9)
Lamotrigine dose, mg/day	255 (190)	200 (2–1200)
Comedication	**Frequency**	**Dose range**
Carbamazepine	62	300–1200 mg/day
Clobazam	11	2.5–40 μg/day
Clonazepam	22	0.25–175 μg/day
Gabapentin	13	100–3600 mg/day
Levetiracetam	67	125–4250 mg/day
Oxcarbazepine	25	150–1500 mg/day
Phenobarbital	33	24–400 mg/day
Phenytoin	81	40–780 mg/day
Topiramate	37	12.5–700 mg/day
Valproic acid	75	250–3000 mg/day

SD standard deviation, *M* male, *F* female

2.2 Population Pharmacokinetic Modelling

The population model describing the pharmacokinetics of lamotrigine was developed using a nonlinear mixed-effects modelling approach, as implemented in NONMEM version 7.3 (ICON Development Solutions, Hanover, MD, USA) [37]. The analysis workflow was performed within a platform including PsN v4.2.0 [38] and Piraña v2.90 [39, 40]. R v3.1.1 was used for data processing and statistical and graphical analysis [41]. One- and two-compartment models with first-order absorption and elimination were evaluated to fit the concentration versus time data. CL and volume of distribution (V_d) were estimated as apparent parameters (CL/F, V_d/F) as all concentration data were obtained after oral administration of lamotrigine. The first-order conditional estimation method with interaction (FOCE-I) was used to derive population (θ) pharmacokinetic parameters, their variability (η) and the residual variability between observed and predicted concentrations (ε). Interindividual variability in pharmacokinetic model parameters was described by an exponential model (Eq. 1), where P_{ij} is the estimate of the j^{th} parameter in individual i, θ_j is the typical value of the j^{th} parameter, and η_{ij} is a random variable for the i^{th} individual and the j^{th} parameter distributed with mean zero and variance ω^2. Residual variability was modelled using a combined proportional and additive error model (Eq. 2), where $Y_{ij,\text{obs}}$ and $Y_{ij,\text{pred}}$ are the observed and predicted concentrations of individual i at time j, respectively, and ε_1 and ε_2 are random variables with mean zero and variance σ^2.

$$P_{ij} = \theta_j \times e^{\eta_{ij}} \quad (1)$$

$$Y_{ij,\text{obs}} = Y_{ij,\text{pred}} \times (1 + \varepsilon_1) + \varepsilon_2. \quad (2)$$

2.2.1 Covariate Model

Age, body weight, formulation (IR or XR), and comedication were considered as factors to be included in the evaluation of covariate effects. Due to covariate identifiability limitations, only comedications taken by at least 10 individuals were considered for inclusion, i.e. carbamazepine, clobazam, clonazepam, gabapentin, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate and valproic acid. Evidence for potential covariate–parameter correlations was assessed graphically by plotting the random variability of the model parameter against the variable of interest. Potential continuous covariates were included into the model one-by-one and set in relation to the pharmacokinetic parameter (Eq. 3), where Cov_i is the value of the covariate for individual i and Cov_{med} is the median covariate value in the population (data set). The effect of binary covariates was described as shown in Eq. 4, where θ_{cov} represents the impact of the relevant covariate in question and Cov_i takes a value of 1 or 0.

$$Px = \theta_x \times \frac{\text{Cov}_i}{\text{Cov}_{\text{med}}} \quad (3)$$

$$Px = \theta_x \times (1 + \text{Cov}_i \times \theta_{\text{cov}}). \quad (4)$$

Next, all potential covariates were statistically tested based on the objective function value (OFV). During the forward inclusion steps of the analysis, covariates that showed statistically significant changes in OFV ($p < 0.05$) were included in the final model. To be included, a change in OFV > 3.84 (based on a Chi-squared distribution with 1 degree of freedom) was required. During backward covariate deletion, a change in OFV > 6.64 ($p < 0.01$) was used as threshold for evidence of the covariate effect. To determine the feasibility of extrapolating pharmacokinetics to other age groups, a priori allometric principles were applied to CL and V_d (Eqs. 5 and 6).

$$\text{CL} = \theta_{\text{CL}} \times \left(\frac{\text{WT}}{70}\right)^{0.75} \times e^{\eta_{\text{CL}}} \quad (5)$$

$$V_d = \theta_{V_d} \times \left(\frac{\text{WT}}{70}\right) * e^{\eta_{V_d}} \quad (6)$$

Different absorption rate constants (K_a) were estimated to account for differences between IR and XR formulations (Eq. 7).

$$K_{a_{IR}} = \theta_{K_{a_{IR}}} \times e^{\eta_{K_{a_{IR}}}} \text{ or } K_{a_{XR}} = \theta_{K_{a_{XR}}} \times e^{\eta_{K_{a_{XR}}}} \quad (7)$$

If necessary, a maturation function was included (Eq. 8) to describe the change in CL in infants and toddlers based on the individual's postmenstrual age (PMA). Maturation processes were parameterised using a sigmoidal function, including TM_{50}, a parameter describing the PMA at which CL values correspond to 50% of the maximum value when maturation is complete (A_{max}), and the slope of the curve (Hill).

$$E_{Mat} = 1 + \frac{A_{max} \times PMA^{Hill}}{PMA^{Hill} + TM_{50}^{Hill}} \quad (8)$$

2.2.2 Validation and Extrapolation

As described previously, different subsets were considered for the evaluation of the model and subsequent characterisation of the implications of age-related changes in the disposition of lamotrigine. An iterative approach was taken in which an initial model, built on adult pharmacokinetic data (data set A) was evaluated using an internal and external validation data set (data sets B and C, respectively). Based on predefined model performance criteria, the model was then used for extrapolation purposes, i.e. to characterise lamotrigine exposure in older adults (>65 years, data set D), children (4–12 years, data set E), and finally in infants and toddlers (<2.0 years, data set F). At each step, parameters were first fixed to the values obtained during the estimation procedure, including all previous data (models B–F), after which parameters were separately estimated using data from the patient population in question (models B*-F*), and in conjunction with all previous data (models B**–F**). These iterative steps are summarised in Fig. 2.

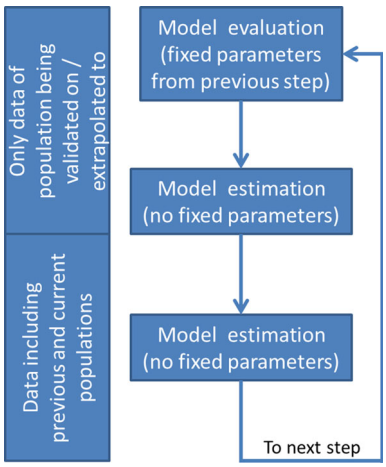

Fig. 2 Schematic overview of all validation and extrapolation steps

Model predictive performance was evaluated using goodness-of-fit (GOF) plots, including individual observed (DV) versus individual predicted (IPRED) lamotrigine concentrations, DV versus population predicted (PRED) lamotrigine concentrations, conditional weighted residuals (CWRES) versus PRED, and CWRES versus time after dose. Predicted parameter values from * models (x), estimated parameter values from ** models (tv), and the number of parameters (n) were used to calculate the relative error (RE) (Eq. 9) and normalised root mean square error (NRMSE) (Eq. 10), which reflect, respectively, the precision and accuracy of the predicted parameter estimates. Cut-off points for acceptable RE and NRMSE levels were set to 30%.

$$RE = 100 \times \left(\frac{x - tv}{tv}\right) \quad (9)$$

$$NRMSE = \frac{\sqrt{\sum \frac{(x-tv)^2}{n}}}{tv}. \quad (10)$$

The final model was subsequently evaluated by non-parametric bootstrapping using 1000 data subsets sampled from the original data with resampling. Bootstrap samples were stratified by age in the following manner: <1, 1–2, 2–4, 4–8, 8–16, 16–65 and >65 years. The ability of the final model to predict the overall data was examined using a visual predictive check (VPC) stratified for age (strata: 0.2–2.0, 4–12, 12–65 and 65–91 years) and a numerical predictive check (NPC) using 1000 samples. In addition, normalised prediction distribution errors (NPDEs) were calculated and summarised to assess the overall performance of the stochastic components of the model.

2.3 Dosing Recommendations

The patient population pool aged 0.2–91 years was subdivided into four groups, for each of which body weights were derived according to the WHO growth charts [42] and Luscombe and Owens [43] (Table 2). Using the predicted CL values obtained from the final pharmacokinetic model, lamotrigine steady-state concentrations (C_{ss}) (Eq. 11) were subsequently simulated. Given the observed variability in exposure and lack of a clear correlation between exposure and response, simulation scenarios were evaluated in which a range of lamotrigine doses and dosing regimens was used for each population with the objective of optimising C_{ss} within a previously suggested target reference range [44].

$$C_{ss} = \frac{D * F}{CL * \tau} \quad (11)$$

where D is dose, F is bioavailability, CL is clearance and τ is the dosing interval.

Table 2 Weight calculation formulas per age group, along with the CV % used in the simulations

Population	Age range	Weight mean	Weight CV %
Infants and toddlers	2–23 months	$9.35 \times (1 + 0.0587 \times \text{SEX}) \times \text{AGE}^{0.356}$	18
Children and adolescents	2 to < 18 years	3*AGE + 7	25
Adults	18–65 years	$65 + 10 \times \text{SEX}$	16
Older adults	65–91 years	$65 + 10 \times \text{SEX}$	16

CV % coefficient of variation

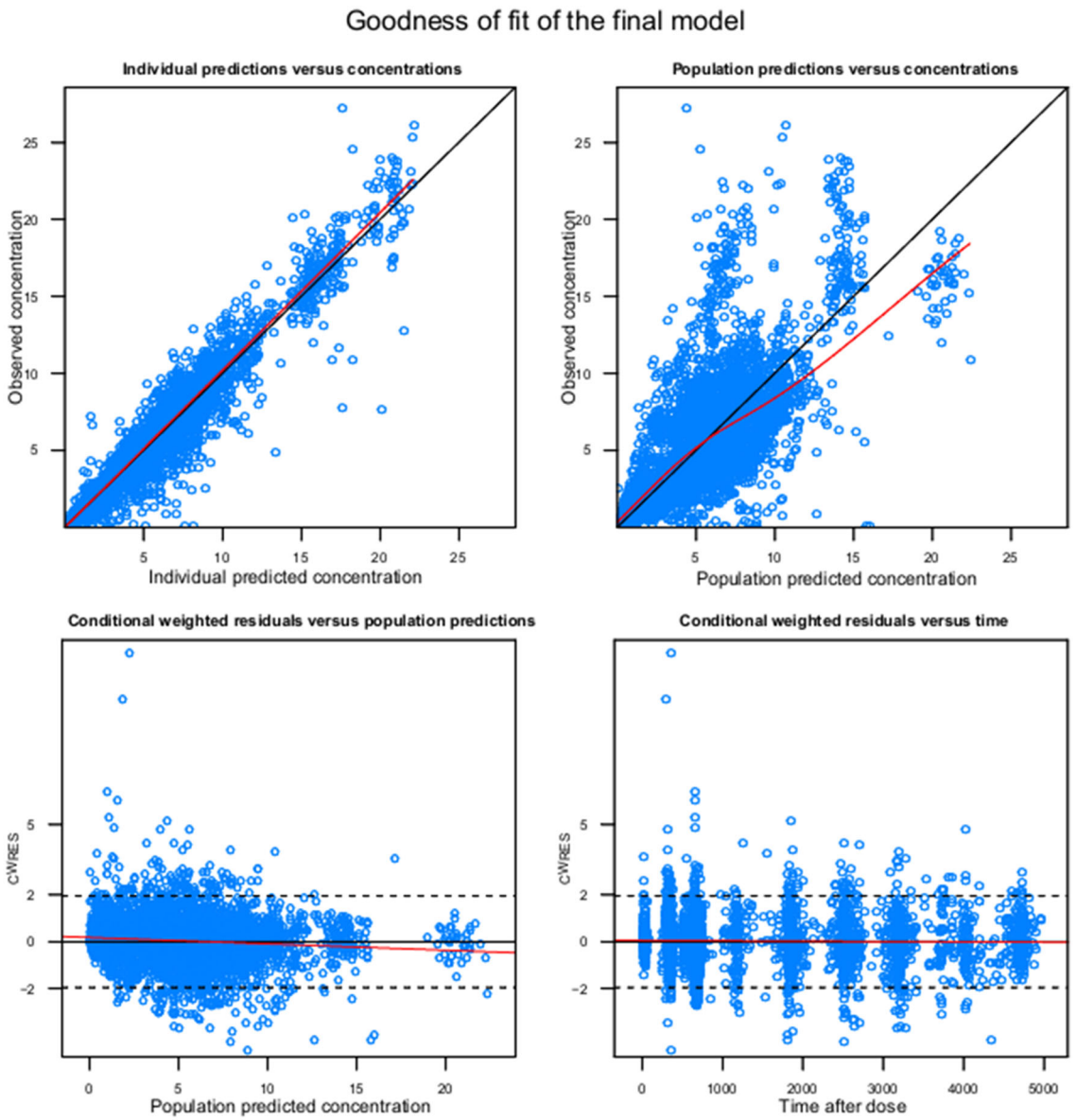

Fig. 3 Goodness-of-fit plots of the final model. Individual and population model predictions are compared with the observations. CWRES are compared with the population model predictions and time after dose. Black solid lines depict the identity line; red solid lines and blue circles indicate, respectively, the trend line and the individual data. Axes show lamotrigine concentrations in mg/L and time after first dose in hours. *CWRES* = conditional weighted residuals

3 Results

3.1 Model Development and Validation

The pharmacokinetics of lamotrigine was best described by a one-compartment model with first-order absorption and elimination. In addition, interindividual variability was identified in all pharmacokinetic parameters. Correlations between model parameters were tested and several were found significant; however, inclusion of these correlations resulted in an unacceptable (>40%) increase in the uncertainty in parameter values and were therefore not incorporated into the final model. In spite of the different comedications included in the data set, covariate analysis revealed a significant effect only for carbamazepine, phenytoin and valproic acid. Carbamazepine and phenytoin increased the CL of lamotrigine by 76.5 and 129%, respectively, whereas valproic acid reduced it by 47.4%. No correlation was found between the dose of the comedication and CL of lamotrigine. Given the objectives of our analysis, the effect of body weight on CL and V_d was parameterised using allometric principles, and kept in the model irrespective of the initial variation in OFV (see Table S2 in the electronic supplementary material). As depicted in Fig. 3, GOF plots show that the final model accurately describes interindividual variability across the overall population. No bias was seen in the CWRES versus PRED or time after dose. On the other hand, it is worth mentioning that peak concentrations were slightly over-predicted. An overview of the final model performance is summarised by the VPC in Fig. 4, which shows the 95% prediction intervals along with the observed data. Non-

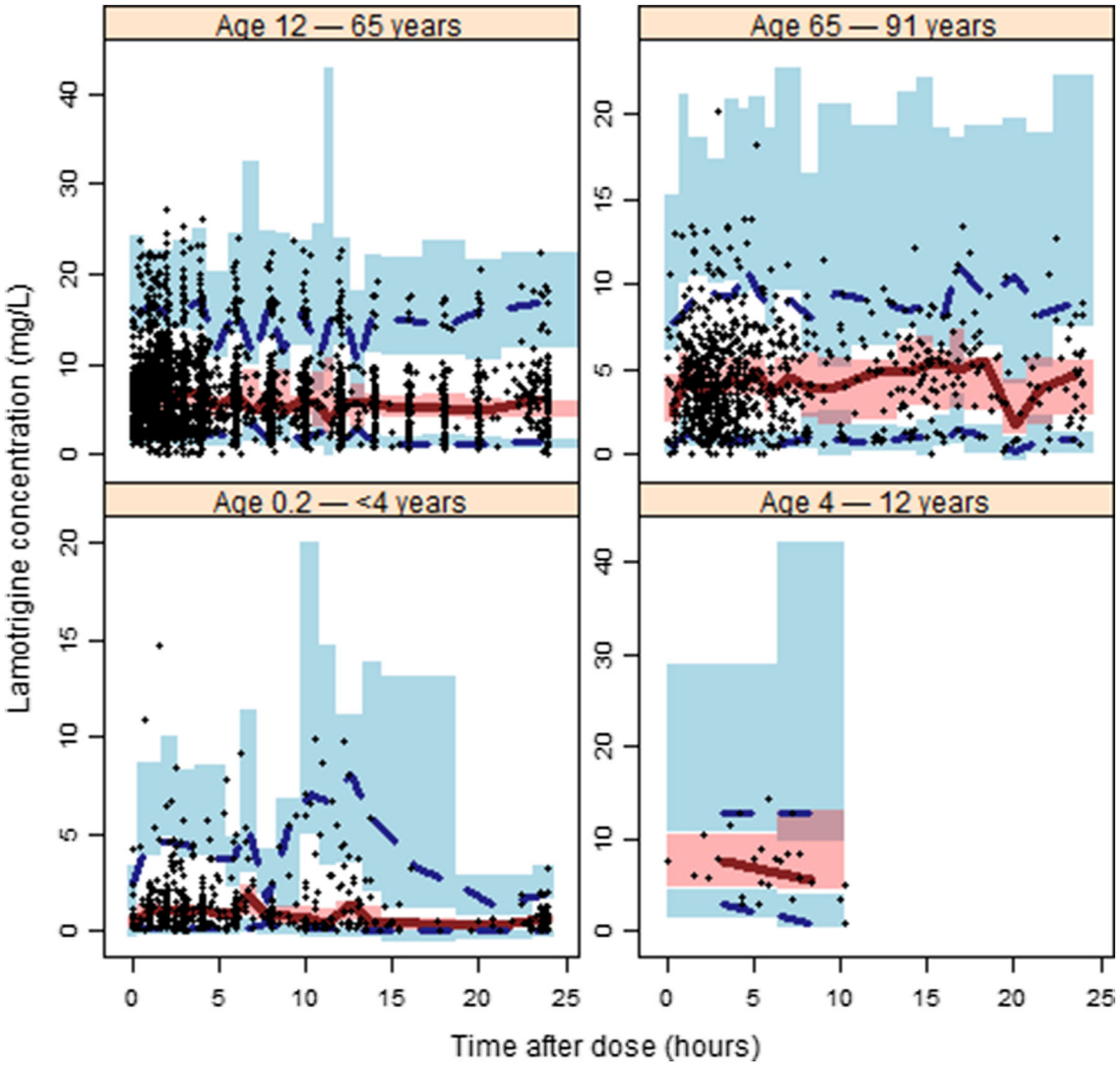

Fig. 4 Visual predictive check of the final model stratified by age. The median (red line) and 95% confidence interval (blue lines) of the observed data are plotted against the simulated data of 1000 subjects (shaded areas: median in red, 95% prediction intervals in blue). Individual observed concentrations are shown as black dots

Table 3 The final model parameter estimates along with the bootstrap results, including the 95% CIs

Parameter	Value (95% CI)	Bootstrap median (95% CI)
$\theta_{K_{a_{IR}}}$	2.43 (1.425–3.435)	2.56 (1.44–3.97)
$\theta_{K_{a_{XR}}}$	0.087 (0.073–0.101)	0.09 (0.07–0.11)
θ_{CL}	2.23 (1.985–2.475)	2.28 (2.01–2.53)
θ_{V_d}	1.97 (1.694–2.246)	1.92 (1.64–2.36)
θ_{CBZ}	0.765 (0.516–1.014)	0.75 (0.53–1.12)
θ_{PHT}	1.29 (1.041–1.539)	1.29 (1.02–1.55)
θ_{VPA}	− 0.474 (− 0.555 to − 0.393)	− 0.49 (− 0.57 to − 0.41)
θ_{TM50}	128.5 (76.9–333.3)	125 (100–250)
θ_{Hill}	− 5.66 (− 10.736 to − 0.584)	− 15.98 (− 152.94 to − 2.75)
$\theta_{A_{max}}$	0.629 (0.196–1.062)	0.60 (0.34–1.07)
θ_{Older}	0.148 (0.032–0.264)	0.16 (0.04–0.25)
$\omega^2_{K_{a_{IR}}}$	0.609 (− 0.536 to 1.754)	0.53 (0.0001–3.09)
$\omega^2_{K_{a_{XR}}}$	0.46 (− 0.442 to 0.715)	0.57 (0.27–1.18)
ω^2_{CL}	0.274 (− 0.263 to 0.811)	0.27 (0.22–0.32)
$\omega^2_{V_d}$	0.626 (0.3516–0.9004)	0.63 (0.31–1.09)
σ^2_{prop}	0.156 (0.103–0.209)	0.16 (0.11–0.20)
σ^2_{add}	0.236 (0.045–0.427)	0.23 (0.10–0.42)

CI confidence interval, θ population value, ω^2 variance of deviation (η) of individuals from population value θ, σ^2 variance of proportional (prop) and additive (add) residual errors (ε), *CBZ* carbamazepine, *CL* Clearance, *Hill* slope of the sigmoidal function describing CL maturation, $K_{a_{IR}}$ and $K_{a_{XR}}$ absorption rate constant for the IR and XR formulations, respectively, *PHT* phenytoin, TM_{50} post-menstrual age at which CL correspond to 50% of the maximum value when maturation is complete (A_{max}), *V* volume of distribution, *VPA* valproic acid

parametric bootstrap confirmed the parameter estimates obtained with the final model (Table 3). Overall model performance was also corroborated by the results from the NPCs and NPDE [results not shown].

3.2 Extrapolation Across Populations

While our aim was to identify a suitable parameterisation to describe the pharmacokinetics of lamotrigine across the whole patient population, the approach used during model building ensured identification and distinction between interacting factors, such as age and comedications. Accuracy (RE) and precision (NRMSE) of the predicted estimates for the Ka and V_d values were low, for which no improvement could be made using covariates other than the a priori allometry. The accuracy and precision of the predicted estimates for the parameter of interest (CL) were acceptable in all cases, except for extrapolation to children < 2.0 years of age (Fig. 5). This discrepancy seems to reflect the contribution of maturation processes, which account for changes in CL in infants and toddlers (Eq. 8, Fig. 6). Furthermore, a separate term was included to describe the decrease in CL of 14.8% in patients older than 65 years of age.

Equation 12 summarises the different factors that were identified as covariates on CL:

$$\mathrm{CL} = \theta_{\mathrm{CL}} * \left(\frac{WT}{70}\right)^{0.75} \times E_{\mathrm{Mat}} \times E_{\mathrm{ELD}} \times E_{\mathrm{CBZ}} \times E_{\mathrm{PHT}} \times E_{\mathrm{VPA}}, \quad (12)$$

where E_{CBZ}, E_{PHT} and E_{VPA} were, respectively 1.765, 2.29, and 0.536 if carbamazepine, phenytoin, and/or valproic acid were coadministered, or 1 otherwise. E_{ELD} is the term describing the effect of age in elderly patients, which takes a value of 0.852 in cases where a patient's age is >65 years.

3.3 Dose Optimisation in Future Clinical Trials

Our simulations identified algorithms for dose optimisation in future clinical trials, which could lead to a considerable increase in the proportion of patients attaining a predefined target range during the maintenance phase of treatment (Table 4). First, we explored the use of a single-dose regimen for each population. Based on the baseline population characteristics included in the simulation scenarios, a dose of 350 mg/day was found to be the most suitable regimen in adults, so as to maximise the proportion of patients with C_{ss} within the target range. Using 350 mg/day as reference regimen, our simulations show that lamotrigine doses need

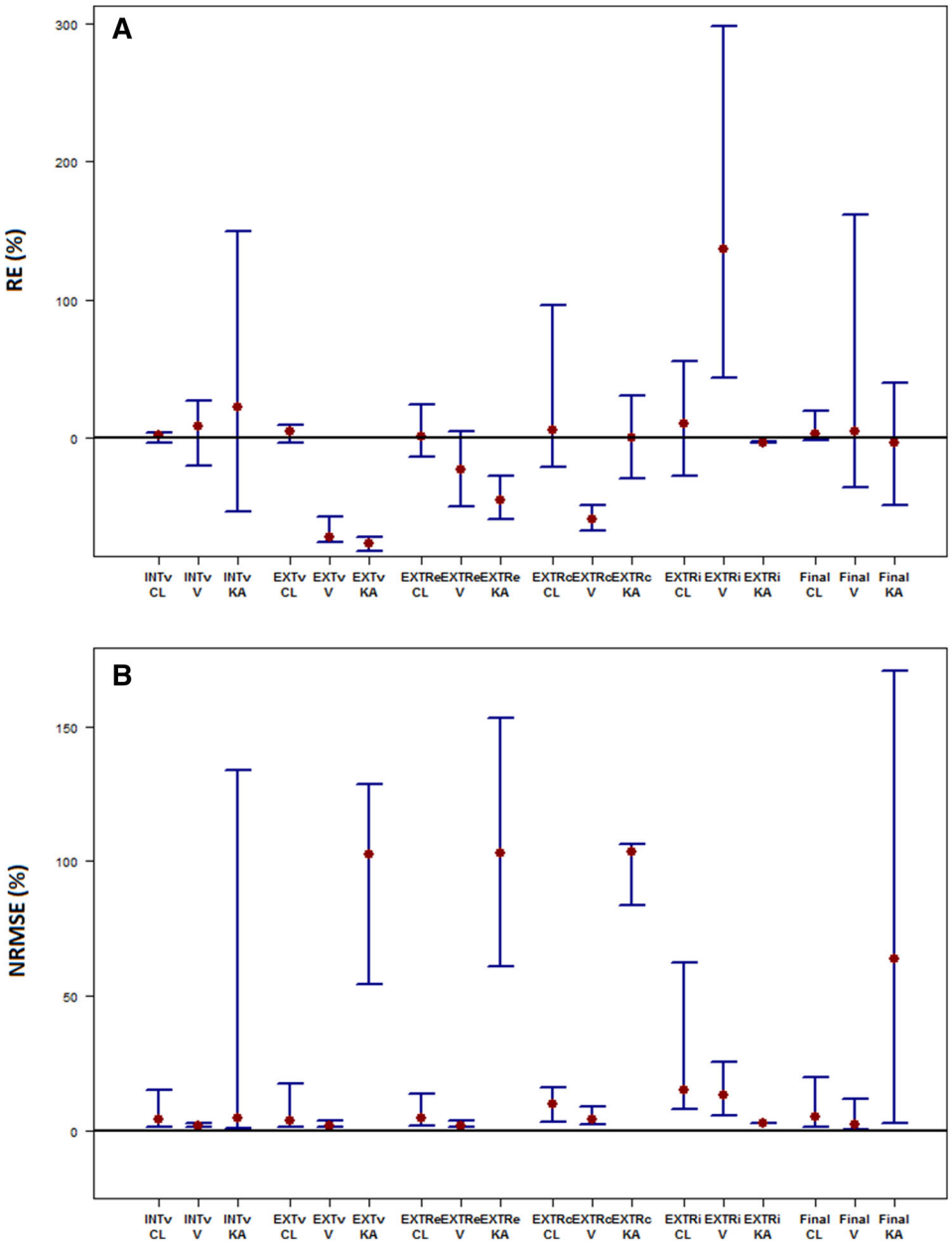

Fig. 5 Accuracy and precision of parameter estimates during the validation and extrapolation steps. The median (red dots) and 95% confidence intervals (bars) are shown for **a** REs and **b** NRMSEs. *INTv* internal validation, *EXTv* external validation, *EXTRe* extrapolation to adults aged 65–91 years, *EXTRc* extrapolation to children aged 4–12 years, *EXTRi* extrapolation to infants and toddlers aged < 2 years, *Final* final model with and without maturation function, *REs* relative errors, *NRMSEs* normalised root mean square errors

to be reduced to 300 mg/day in adults older than 65 years of age, whereas a 6 mg/kg/day dosing regimen, or values rounded to the closest number, would be desirable in children. Finally, it appears that children younger than 2 years of age would benefit from a weight-banded dosing regimen, with two weight bands. The optimum dose for infants between 2 and 4 months of age was predicted to be 70 mg/day, while infants and toddlers aged 4–23 months would require 100 mg/day. When dose adjusting for the effect of age and weight, variation in lamotrigine exposure (as assessed by the coefficient of variation, CV %) could not be reduced significantly (approximately 60% in both scenarios). This is partly explained by the fact that the effect of comedication was not included in these evaluations (Fig. 7).

4 Discussion

In this study, we aimed to develop a population pharmacokinetic model that takes into account age-related changes in the disposition of lamotrigine. In addition, we made use of a stepwise approach to explore whether the use of allometric principles suffices to characterise the differences across the extremes of age, i.e. in infants, toddlers, children and elderly. Our results show that despite the contribution

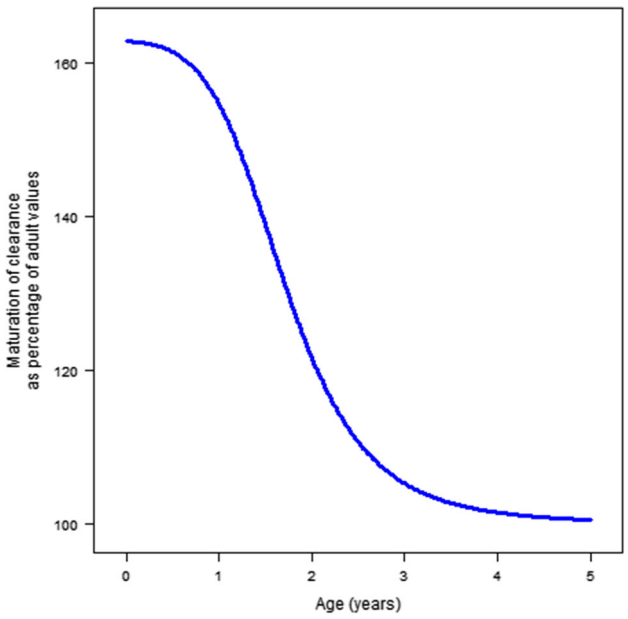

Fig. 6 Sigmoidal function describing changes in clearance associated with age and metabolic maturation processes

of other interacting factors, such as comedications, lamotrigine exposure can be accurately described across different population groups based on the inclusion of allometric principles in patients > 4 years of age. On the other hand, maturation processes appear to be a significant factor in the youngest group of patients (infants and toddlers), for whom PMA-related changes lead to significantly higher CL values, compared with children and adults. By contrast, a CL reduction of approximately 15% was observed in elderly patients, which correlated with known decreases in hepatic and renal function in this population.

Whereas our attempt to characterise age-related changes in the pharmacokinetics of lamotrigine does not include other factors known to be relevant in clinical practice, such as pregnancy, oral contraceptives, UGT enzyme polymorphisms or comorbidities, our analysis did provide further insight into the interaction between age, size and metabolic function. In general, pregnant patients or female patients taking oral contraceptives are not included in clinical studies during the early stages of clinical drug development. Furthermore, the study protocols did not include pharmacogenetic testing for polymorphisms in enzymes such as UGT. The lack of such data has prevented identification of additional explanatory factors for the observed differences in CL. The availability of these potential covariate factors might explain some of remaining interindividual variability [31, 45, 46].

Previous publications have reported the use of weight-based scaling to describe the pharmacokinetics of lamotrigine [14, 17, 18, 23, 27, 28, 47–51], but some authors have proposed a different approach [15, 16, 21, 26, 29–31]. Nevertheless, no publication has explored the effect of body weight in a standardised allometric manner across a wide population [52]. In fact, He and collaborators have used allometrically scaled CL [17], but their analysis included children only, and the allometric exponent was not set to the standard 3/4, which may explain why a maturation function was not required, despite the inclusion of patients below the age of 2 years.

From a methodological perspective, it should be noted that allometric scaling does not necessarily improve model fitting if patient characteristics do not comprise a wide range of the variable of interest, i.e. body weight. This may represent a limitation when analysing data from clinical trials, where inclusion and exclusion criteria restrict patients in terms of their age, weight and body mass index. Likewise, covariate identifiability may be affected when analysing data from patient subgroups. In fact, an assessment has been made of the impact of differences in patient population characteristics and covariate distribution on the predictive performance of pharmacokinetic models [53, 54]. Pharmacokinetic data from a different class of compounds, as well as from hypothetical drugs for which the type and magnitude of the covariate effect has been defined a priori, show that allometric or other correlations may not be identified during model development when subsets of the population are used or samples are too sparse to allow accurate characterisation of interindividual variability.

Table 4 Optimised maintenance dosing regimens and predicted steady-state concentration (Css) per age group in the simulated scenarios

Population	Age range	Dose	% $C_{ss} > 20$ mg/L	% $C_{ss} > 15$ mg/L	% $C_{ss} < 2.5$ mg/L
Infants	2–6 months	70 mg/day	0.49	1.9	10.6
Toddlers	6–23 months	100 mg/day	0.89	3.4	6.4
Children and adolescents	$\geq$ 2–18 years	6 mg/kg/day	1.9	6.1	3.7
Adults	18–65 years	350 mg/day	2.0	6.6	3.5
Older adults	65–91 years	300 mg/day	2.1	6.6	3.5

Each column summarises the proportion of patients in each group who are exposed above the toxicity level (20 mg/L), above the therapeutic maximum (15 mg/L), and below the therapeutic minimum (2.5 mg/L). These scenarios do not include the initiation dose or titration steps, which are required to reduce the risk of serious cutaneous adverse reactions and account for interindividual differences in pharmacodynamics and safety

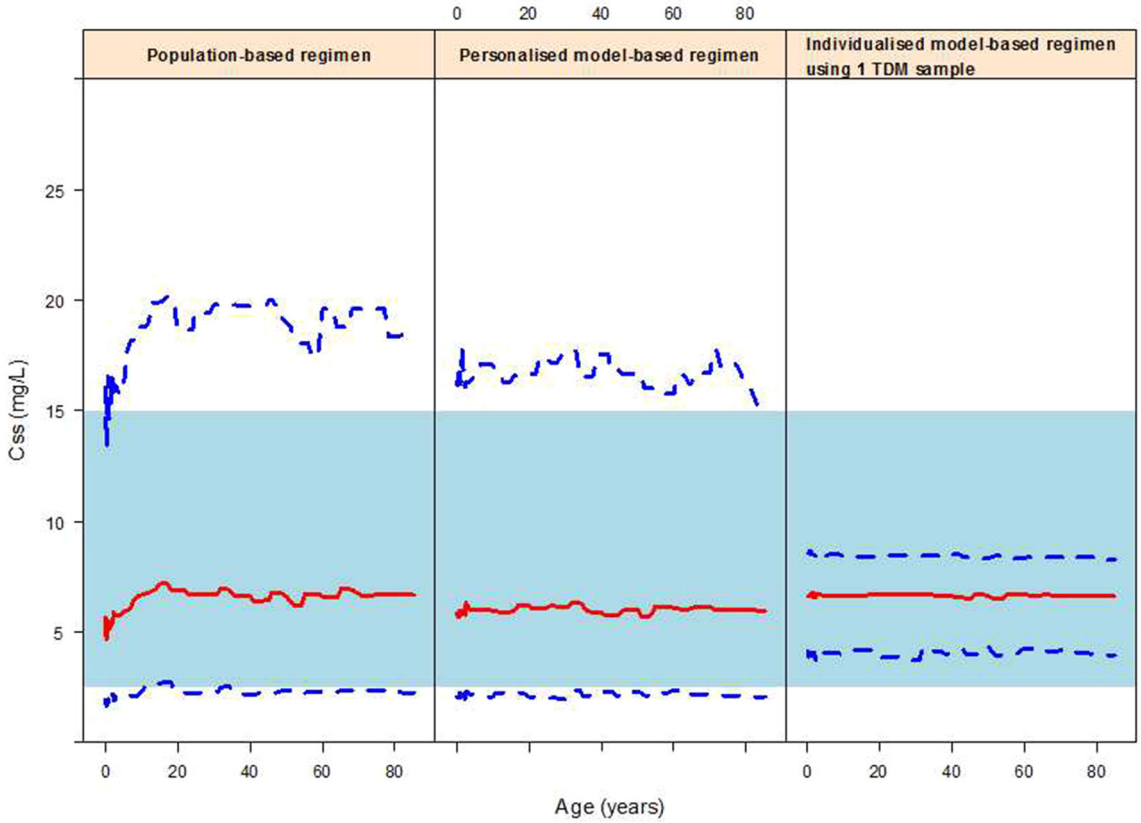

Fig. 7 C_{ss} ranges resulting from optimised dosing regimens over age, as listed in Table 4. Shown are the median (red line) and 95% prediction intervals (blue dashed lines) of the simulated C_{ss} values. The blue shaded area is the putative reference range. C_{ss} steady-state concentrations

By contrast, our analysis is not affected by such limitations. In addition, by using a stepwise approach to covariate identification, extrapolation from adults to children, and then to infants and toddlers, it became evident that allometry can only fully account for changes in CL and V_d in patients older than 2 years of age [32]. This is demonstrated by the estimation of CL, which showed RE and NRMSE values within the acceptable range during most extrapolation steps, except when extrapolating to children below 2 years of age. Given the current understanding of the metabolic processes associated with the biotransformation and elimination of lamotrigine, a sigmoidal maturation function was considered the most plausible descriptor of the changes in drug disposition in infants and toddlers, which has an asymptotic inflection point just before 3 years. On the other hand, it cannot be excluded that reduced absorption could lead to a higher apparent CL. As intravenous data are not available, it is not possible to distinguish the true cause of the differences in systemic exposure (i.e. changes in apparent or intrinsic CL).

Despite the large sample size, our analysis also faced a few limitations. Absorption parameters proved particularly difficult to estimate due to high variability in the data and lack of frequent samples during the absorption phase. Nevertheless, parameter estimates were in agreement with values previously reported in the published literature (Table 5), including the different absorption rate constants found for IR and XR formulations. Moreover, we have been able to estimate the effect of comedications, namely carbamazepine, phenytoin, and valproic acid, on the CL of lamotrigine. In addition, no discernible effect was observed for phenobarbital, which may be explained by the fact that < 10% of our population was co-treated with this AED. Given that blood sampling did not span over long treatment intervals within each patient, it was not possible to estimate time-dependent changes in CL. Overall, our results seem to reflect those previously reported in some publications [55–57], but differ from other reports [17, 21, 47, 50]. Another challenge was the lack of literature information regarding the maturation processes associated with the elimination of lamotrigine in infants and toddlers, which ultimately affects the rationale for maintenance doses in this age group [58]. As shown in Fig. 6, maturation processes lead to higher weight-adjusted CL in very young children, which slowly decreases to adult levels between the age of 2 and 3 years. This is an important observation given that lamotrigine is not approved for children younger

Table 5 Final model estimates, along with previously published pharmacokinetic data in each age group

Population	Parameter	Final model values	Literature values
Adults	$K_{a_{IR}}$ (/h)	2.43	0.38–3.19 [12, 16, 17, 20, 21, 34, 35, 45]
	$K_{a_{XR}}$ (/h)	0.087	0.0739 [45]
	V_d (L/kg)	1.97	0.9–1.9 [12, 16, 17, 19–21, 34–36]
	CL (L/h/kg)	0.0319	0.028–0.15 [12, 16, 17, 19–21, 34–36]
Older adults aged 65–91 years	$K_{a_{IR}}$ (/h)	2.43	2.98–3.5 [14, 45]
	$K_{a_{XR}}$ (/h)	0.087	0.0739 [45]
	V_d (L/kg)	1.97	1.3–1.42 [14, 45]
	CL (L/h/kg)	0.0271	0.033–0.039 [14, 45]
Children and adolescents aged 2–18 years	$K_{a_{IR}}$ (/h)	2.43	1–3.5 [13, 18, 21]
	$K_{a_{XR}}$ (/h)	0.087	–
	V_d (L/kg)	1.97	0.6–2.12 [13, 18, 21]
	CL (L/h/kg)	0.0374	0.036–0.09 [13, 18, 21]
Infants and toddlers	$K_{a_{IR}}$ (/h)	2.43	1 [18]
	$K_{a_{XR}}$ (/h)	–	–
	V_d (L/kg)	1.97	0.6 [18]
	CL (L/h/kg)	0.051–0.10	0.037 [18]

CL Clearance, $K_{a_{IR}}$ and $K_{a_{XR}}$ absorption rate constant for the IR and XR formulations, respectively, *V* volume of distribution

than 2 years of age. It should be highlighted that this phenomenon cannot be explained by changes in activity of its main metabolic pathway, UGT-1A4, which increases over time, or by β-glucuronidation, which decreases to adult levels at a much earlier age [59]. There may be a role for UGT-2B7 or reduced lamotrigine protein binding, although the data are so far inconclusive [31, 45, 46, 60, 61]. Given the evidence for reduced metabolic CL in newborn infants (0–1 month of age), the current findings cannot be extrapolated beyond the age range described here.

Having identified a common parameterisation to describe age-related changes across the target patient population, we have shown how clinical trial simulation concepts can be applied to evaluate whether maintenance doses can be optimised across different age groups to ensure comparable lamotrigine exposure within a predefined target range for most patients. Our results also reveal the complex interaction between multiple covariates, which need to be accounted for if one attempts to individualise a patient's dose and dosing regimen. Whereas additional factors need to be considered for the development of a dosing algorithm aimed at individualised therapy, interindividual variability in CL was found to be reasonably explained by the interacting terms in Eq. 12.

Irrespective of interindividual differences in the sensitivity to lamotrigine due to factors such as disease severity, seizure type and pharmacodynamic polymorphisms, the simulated regimens show that lamotrigine doses should be titrated at the onset of therapy and how subsequent dose adjustments can be made if therapeutic drug monitoring (TDM) is used during the maintenance phase. In fact, understanding of the role of covariate factors can aid investigators achieving a preset target steady-state concentration to a moderate degree, in proposed clinical trials. Integration of TDM with a model-based algorithm may lead to a significant reduction in interindividual variability in target C_{ss} (from 57% to approximately 17%) (Fig. 7). It can be anticipated that such a dosing algorithm may serve as a tool for investigators when developing their trial protocols. Once a target maintenance dose is reached, model-guided dose adjustments may be considered in conjunction with TDM sampling to further personalise therapy [62, 63]. However, given the concern with high peak concentrations, dose adjustments and treatment personalisation in young children may need to be implemented according to a twice-daily regimen.

5 Conclusions

An integrated population pharmacokinetic model was developed for lamotrigine, which describes the effect of comedications and age-related changes in drug disposition in patients aged from 0.2 to 91 years. This analysis confirms previous findings in which interindividual variability in the disposition of lamotrigine has been evaluated. Clearly, lamotrigine C_{ss} is affected by the interaction between multiple intrinsic (e.g. body weight, age) and extrinsic (e.g. comedication, formulation) factors. The use of allometric principles in conjunction with a maturation function provided insight into the contribution of intrinsic

factors to interindividual variability. Simulation scenarios have made evident that these covariates need to be considered before the start of dose titration as the magnitude of the covariate effect will depend on an individual patient's characteristics. Finally, it seems plausible that the lack of efficacy in previous clinical trials including infants and toddlers may have resulted from subtherapeutic exposure to lamotrigine, i.e. higher apparent CL than what may be expected from simple weight-based dose adjustment. The observed lamotrigine exposure was considerably lower than the drug levels observed in children and adolescents at comparable doses. These results should form the basis for the dose rationale in any future clinical trials in infants and toddlers. As the recommended low initiation dose, titration steps and interindividual differences in pharmacodynamics and safety were not evaluated here, they do not constitute recommendations for patients in clinical practice.

Acknowledgements The authors thank Khilit Shah for his assistance in retrieving the clinical study data, and Corine Visser for her editorial support.

Author Contributions Sven van Dijkman, Nico de Jager and Willem Rauwé performed the data analysis; Sven van Dijkman and Oscar Della Pasqua wrote the manuscript; and Meindert Danhof and Oscar Della Pasqua coordinated the investigations and reviewed the manuscript.

Compliance with Ethical Standards

Conflict of Interest Sven van Dijkman had support from the Global Research in Paediatrics consortium (GRiP). In addition to his role in GRiP, Oscar Della Pasqua is also Senior Director, Clinical Pharmacology, at GlaxoSmithKline. Nico C. B. de Jager, Willem M. Rauwé and Meindert Danhof declare no conflicts of interest.

Ethical Approval The research presented in this paper was based on already existing data. The data used were derived from clinical trials performed by GlaxoSmithKline, which were all performed according to the Declaration of Helsinki and any additional ethical and practical standards applicable at the local trial sites.

Funding The research leading to these results has received funding from the European Union Seventh Framework Programme FP7/2007-2013 under Grant agreement no. 261060.

References

1. Steiner TJ, Dellaportas CI, Findley LJ, Gross M, Gibberd FB, Perkin GD, Park DM, Abbott R. Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin. Epilepsia. 1999;40(5):601–7.
2. Mullens EL. Clinical experience with lamotrigine monotherapy in adults with newly diagnosed epilepsy: a review of published randomised clinical trials. Clin Drug Investig. 1998;16(2):125–33.
3. Fitton A, Goa KL. Lamotrigine: An update of its pharmacology and therapeutic use in epilepsy. Drugs. 1995;50(4):691–713.
4. Brodie MJ, Richens A, Yuen A, UK, Lamotrigine/Carbamazepine Monotherapy Trial Group. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. Lancet. 1995;345(8948):476–9.
5. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. Clin Pharmacokinet. 2013;52(8):627–45.
6. Anderson GD, Saneto RP. Modified-release formulations of second-generation antiepileptic drugs: pharmacokinetic and clinical aspects. CNS Drugs. 2015;29(8):669–81.
7. Lovrić M, Božina N, Hajnšek S, Kuzman MR, Sporiš D, Lalić Z, et al. Association between lamotrigine concentrations and ABCB1 polymorphisms in patients with epilepsy. Ther Drug Monit. 2012;34(5):518–25.
8. Landmark CJ, Baftiu A, Tysse I, Valsø B, Larsson PG, Rytter E, Johannessen SI. Pharmacokinetic variability of four newer antiepileptic drugs, lamotrigine, levetiracetam, oxcarbazepine, and topiramate. Ther Drug Monit. 2012;34(4):1.
9. Ohman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. Epilepsia. 2000;41(6):709–13.
10. Pennell PB, Peng L, Newport DJ, Ritchie JC, Koganti A, Holley DK, et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. Neurology. 2008;70(22):2130–6.
11. Chen H, Yang K, Choi S, Fischer JH, Jeong H. Up-regulation of UDP-glucuronosyltransferase (UGT) 1A4 by 17beta-estradiol: a potential mechanism of increased lamotrigine elimination in pregnancy. Drug Metab Dispos. 2009;37(9):1841–7.
12. Fotopoulou C, Kretz R, Bauer S, Schefold JC, Schmitz B, Dudenhausen JW, et al. Prospectively assessed changes in lamotrigine-concentration in women with epilepsy during pregnancy, lactation and the neonatal period. Epilepsy Res. 2009;85(1):60–4.
13. Pirie DAJ, Al Wattar BH, Pirie AM, Houston V, Siddiqua A, Doug M, et al. Effects of monitoring strategies on seizures in pregnant women on lamotrigine: A meta-analysis. Eur J Obstet Gynecol Reprod Biol. 2014;172(1):26–31.
14. Chen C. Validation of a population pharmacokinetic model for adjunctive lamotrigine therapy in children. Br J Clin Pharmacol. 2000;50(2):135–45.
15. Gidal BE, Anderson GD, Rutecki PR, Shaw R, Lanning A. Lack of an effect of valproate concentration on lamotrigine pharmacokinetics in developmentally disabled patients with epilepsy. Epilepsy Res. 2000;42(1):23–31.
16. Reimers A, Skogvoll E, Sund JK, Spigset O. Lamotrigine in children and adolescents: the impact of age on its serum concentrations and on the extent of drug interactions. Eur J Clin Pharmacol. 2007;63(7):687–92.
17. He D, Wang L, Qin J, Zhang S, Lu W, Li L, et al. Population pharmacokinetics of lamotrigine in Chinese children with epilepsy. Acta Pharmacol Sin. 2012;33(11):1417–23.
18. Brzaković B, Vučićević K, Kovačević SV, Miljković B, Prostran M, Martinović Ž, et al. Pharmacokinetics of lamotrigine in paediatric and young adult epileptic patients–nonlinear mixed effects modelling approach. Eur J Clin Pharmacol. 2014;70(2):179–85.
19. Baldoni AO, Freitas-Lima P, de Santi Ferreira FI, Martinez EZ, Queiroz RHC, Sakamoto AC, et al. An investigation of the influence of patient-related factors and comedications on lamotrigine clearance in patients with epilepsy. Clin Exp Pharmacol Physiol. 2016;43(7):685–9.
20. Zhang Z, Ji S, Han Y, Zang L, Wang Y. Population pharmacokinetic models of lamotrigine in different age groups of Chinese children with epilepsy. Eur J Clin Pharmacol. 2017;73:445–53.
21. Reimers A, Skogvoll E, Sund JK, Spigset O. Drug interactions between lamotrigine and psychoactive drugs: evidence from a therapeutic drug monitoring service. J Clin Psychopharmacol. 2005;25:342–8.

22. Lott R. Lamotrigine: treatment of epilepsy in the elderly. Consult Pharm. 2003;18(11):979–92.
23. Punyawudho B, Ramsay RE, Macias FM, Rowan AJ, Collins JF, Brundage RC, et al. Population pharmacokinetics of lamotrigine in elderly patients. J Clin Pharmacol. 2008;48(4):455–63.
24. Polepally AR, Remmel RP, Brundage RC, Leppik IE, Rarick JO, Ramsay RE, et al. Steady-state pharmacokinetics and bioavailability of immediate-release and extended-release formulations of lamotrigine in elderly epilepsy patients: use of stable isotope methodology. J Clin Pharmacol. 2015;55(10):1101–8.
25. Tomson T. Gender aspects of pharmacokinetics of new and old AEDs: pregnancy and breast-feeding. Ther Drug Monit. 2005;27:718–21.
26. Wegner I, Wilhelm AJ, Lambrechts DAJE, Sander JW, Lindhout D. Effect of oral contraceptives on lamotrigine levels depends on comedication. Acta Neurol Scand. 2014;129(6):393–8.
27. Wegner I, Wilhelm AJ, Sander JW, Lindhout D. The impact of age on lamotrigine and oxcarbazepine kinetics: a historical cohort study. Epilepsy Behav. 2013;29(1):217–21.
28. Mallaysamy S, Johnson MG, Rao PGM, Rajakannan T, Bathala L, Arumugam K, et al. Population pharmacokinetics of lamotrigine in Indian epileptic patients. Eur J Clin Pharmacol. 2013;69(1):43–52.
29. Hussein Z, Posner J. Population pharmacokinetics of lamotrigine monotherapy in patients with epilepsy: retrospective analysis of routine monitoring data. Br J Clin Pharmacol. 1997;43(5):457–65.
30. Chan V, Morris RG, Ilett KF, Tett SE. Population pharmacokinetics of lamotrigine. Ther Drug Monit. 2001;23(6):630–5.
31. Singkham N, Towanabut S, Lertkachatarn S, Punyawudho B. Influence of the UGT2B7-161C-T polymorphism on the population pharmacokinetics of lamotrigine in Thai patients. Eur J Clin Pharmacol. 2013;69(6):1285–91.
32. Holford N, Heo Y, Anderson B. A pharmacokinetic standard for babies and adults. J Pharm Sci. 2013;102(9):2941–52.
33. van Dijkman SC, Alvarez-Jimenez R, Danhof M, Della Pasqua O. Pharmacotherapy in pediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go. Expert Opinion Drug Metab Toxicol. 2016;12(10):1143–56.
34. Wolf P. Lamotrigine: preliminary clinical observations on pharmacokinetics and interactions with traditional antiepileptic drugs. J Epilepsy. 1992;5(2):73–9.
35. Piña-Garza JE, Levisohn P, Gucuyener K, Mikati MA, Warnock CR, Conklin HS, et al. Adjunctive lamotrigine for partial seizures in patients aged 1 to 24 months. Neurology. 2008;70(22 Pt 2):2099–108.
36. Pellock JM, Carman WJ, Thyagarajan V, Daniels T, Morris DL, D'Cruz O. Efficacy of antiepileptic drugs in adults predicts efficacy in children: a systematic review. Neurology. 2012;79(14):1482–9.
37. Bauer RJ. NONMEM user guide introduction to NONMEM 7.3.0. Hanover: ICON Development Solutions; 2014.
38. Lindbom L, Pihlgren P, Jonsson N. PsN-Toolkit: a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed. 2005;79:241–57.
39. Keizer RJ, van Benten M, Beijnen JH, Schellens JHM, Huitema ADR. Piraña and PCluster: a modeling environment and cluster infrastructure for NONMEM. Comput Methods Programs Biomed. 2011;101(1):72–9.
40. Keizer RJ, Karlsson MO, Hooker A. Modeling and simulation workbench for NONMEM: tutorial on Pirana, PsN, and Xpose. CPT Pharmacomet Syst Pharmacol. 2013;2:e50.
41. R Development Core Team. R: a language and environment for statistical computing. Vienna: The R Foundation for Statistical Computing; 2011.
42. de Onis M, The WHO. Child growth standards. World Rev Nutr Diet. 2015;113:278–94.
43. Luscombe M, Owens B. Weight estimation in resuscitation: is the current formula still valid? Arch Dis Child. 2007;92(5):412–5.
44. Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs—best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring. ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49(7):1239–76.
45. Liu L, Zhao L, Wang Q, Qiu F, Wu X, Ma Y. Influence of valproic acid concentration and polymorphism of UGT1A4*3, UGT2B7 -161C > T and UGT2B7*2 on serum concentration of lamotrigine in Chinese epileptic children. Eur J Clin Pharmacol. 2015;71(11):1341–7.
46. Milosheska D, Lorber B, Vovk T, Kastelic M, Dolžan V, Grabnar I. Pharmacokinetics of lamotrigine and its metabolite N-2-glucuronide: influence of polymorphism of UDP-glucuronosyltransferases and drug transporters. Br J Clin Pharmacol. 2016;82:399–411.
47. Rivas N, Buelga DS, Elger CE, Santos-Borbujo J, Otero MJ, Domínguez-Gil A, et al. Population pharmacokinetics of lamotrigine with data from therapeutic drug monitoring in German and Spanish patients with epilepsy. Ther Drug Monit. 2008;30(4):483–9.
48. Almeida AM, Falcão AC, Sales F, Baldeiras I, Rocha MJ, Caramona MM. Lamotrigine pharmacokinetic evaluation in epileptic patients submitted to VEEG monitoring. Eur J Clin Pharmacol. 2006;62(9):737–42.
49. Lardizabal DV, Morris HH, Hovinga CA, Mar Del Carreño M. Tolerability and pharmacokinetics of oral loading with lamotrigine in epilepsy monitoring units. Epilepsia. 2003;44(4):536–9.
50. Grasela TH, Fiedler-Kelly J, Cox E, Womble GP, Risner ME, Chen C. Population pharmacokinetics of lamotrigine adjunctive therapy in adults with epilepsy. Pharmacokinet Pharmacodyn. 1999;39(4):373–84.
51. Ramsay RE, Pellock JM, Garnett WR, Sanchez RM, Valakas AM, Wargin WA, et al. Pharmacokinetics and safety of lamotrigine (Lamictal) in patients with epilepsy. Epilepsy Res. 1991;10:191–200.
52. Anderson BJ, Holford NHG. Mechanistic basis of using body size and maturation to predict clearance in humans. Drug Metab Pharmacokinet. 2009;24(1):25–36.
53. Cella M, Knibbe C, de Wildt SN, Van Gerven J, Danhof M, Della Pasqua O. Scaling of pharmacokinetics across paediatric populations: the lack of interpolative power of allometric models. Br J Clin Pharmacol. 2012;74(3):525–35.
54. Piana C, Danhof M, Della Pasqua O. Influence of covariate distribution on the predictive performance of pharmacokinetic models in paediatric research. Br J Clin Pharmacol. 2014;78(1):145–57.
55. Weintraub D, Buchsbaum R, Resor S, Hirsch L. Effect of antiepileptic drug comedication on lamotrigine clearance. Arch Neurol. 2005;62(9):1432–6.
56. Arif H, Svoronos A, Resor SR Jr, Buchsbaum R, Hirsch LJ. The effect of age and comedication on lamotrigine clearance, tolerability, and efficacy. Epilepsia. 2011;52(10):1905–13.
57. Kim H-J, Kim T-E, Joo EY, Seo D-W, Lee S-Y, Hong SB. Effect of comedication on lamotrigine clearance in Korean epilepsy patients. Clin Chim Acta. 2015;2014(438):269–73.
58. Lamotrigine (Rx). Lamictal, Lamictal XR, Lamictal ODT: Dosing and uses. http://reference.medscape.com/drug/lamictal-lamotrigine-343012. Accessed 25 Sept 2017.
59. Miyagi SJ, Collier AC. Pediatric development of glucuronidation: the ontogeny of hepatic UGT1A4. Drug Metab Dispos. 2007;35(9):1587–92.
60. Strassburg CP, Strassburg A, Kneip S, Barut A, Tukey RH, Rodeck B, et al. Developmental aspects of human hepatic drug glucuronidation in young children and adults. Gut. 2002;50:259–65.

61. Krekels EHJ, Johnson TN, den Hoedt SM, Rostami-Hodjegan A, Danhof M, Tibboel D, et al. From pediatric covariate model to semiphysiological function for maturation: part II—sensitivity to physiological and physicochemical properties. CPT Pharmacomet Syst Pharmacol. 2012;1(10):e10.
62. van Dijkman SC, Rauwé WM, Danhof M, Della Pasqua O. Pharmacokinetic interactions and dosing rationale for antiepileptic drugs in adults and children. Br J Clin Pharmacol. 2017;. https://doi.org/10.1111/bcp.13400 **(Epub 16 Aug 2017)**.
63. van Dijkman SC, Wicha SG, Danhof M, Della Pasqua OE. Individualized dosing algorithms and therapeutic monitoring for antiepileptic drugs. Clin Pharmacol Ther. 2017;. https://doi.org/10.1002/cpt.777 **(Epub 27 Jun 2017)**.

Table 1S: Demographics of subpopulations A-F, derived from the total data pool G. Weight and age given as mean (SD), gender as (female:male), lamotrigine dose as range in mg/day, number of patients receiving co-medication with an anti-epileptic drug (AED) given with (dosing range); only shown here are the AEDs given to at least 10 individuals in the total dataset (carbamazepine, clobazam, clonazepam, gabapentin, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate and valproic acid).

	Populations						
Demographic	A	B	C	D	E	F	Total (G)
Weight (kg)	70.1 (21.3)	67.8 (18.9)	69.2 (20)	76.3 (17.5)	35.7 (15.7)	9.6 (2.4)	52.1 (36.6)
Age (years)	33.2 (14.1)	33.9 (14.4)	35:3 (12.8)	72.5 (5.5)	7.8 (2.7)	1.2 (0.5)	32.8 (28.1)
Gender (M:F)	41:39	14:18	51:45	58:58	18:6	64:80	246:246
# of patients	80	32	96	116	24	144	492
Formulations	IR and XR	IR and XR	XR	XR	XR	IR	IR and XR
LMT dose	12.5-1200	12.5-800	12.5-600	12.5-500	5-634	2-87	2-1200
Comedication frequency (dose range in mg/day)							
CBZ	20 (300-1200)	4 (600-1200)	24 (400-1200)	12 (300-1200)	0	2 (300-300)	62 (300-1200)
CLBZ (mcg)	4 (10-40)	2 (10-20)	3 (15-20)	0	0	2 (2.5-5)	11 (2.5-40)
CLNZ (mcg)	7 (0.5-175)	2 (1-2)	3 (0.5-3)	1 (0.5-0.5)	0	9 (0.25-2)	22 (0.25-175)
GBP	1 (400-400)	0	1 (2400-2400)	11 (100-3600)	0	0	13 (100-3600)
LVT	6 (1000-4250)	3 (500-3000)	10 (1000-4000)	46 (125-3500)	0	2 (125-500)	67 (125-4250)
OXC	3 (450-1200)	2 (600-1200)	9 (600-1500)	7 (150-1500)	0	4 (270-420)	25 (150-1500)
PHB	3 (60-400)	1 (120-120)	2 (120-120)	3 (60-120)	0	24 (24-120)	33 (24-400)
PHT	20 (200-780)	10 (200-400)	12 (200-400)	36 (200-400)	0	3 (40-40)	81 (40-780)
TPM	9 (25-400)	1 (100-100)	13 (100-700)	5 (25-200)	0	9 (12.5-400)	37 (12.5-700)
VPA	30 (250-3000)	12 (600-2100)	19 (600-3000)	11 (250-2000)	0	3 (250-600)	75 (250-3000)

Table 2S: Overview of the steps in model development and corresponding objective function value (OFV), starting from the base model (including population pharmacokinetic (PK) parameters accounting for the extended- (Ka XR) and immediate absorption rates (Ka IR), clearance (CL) and volume of distribution (V)), used to create the final lamotrigine model.

Model	Population(s)	Used model	OFV	p(dOFV)
A1	Pop. A	Base	9089.129	-
A2	“	A1 + η_{CL}	3284.756	<0.05
A3	“	A2 + η_{V}	3050.895	<0.05
A4	“	A3 + $\eta_{Ka\ XR}$	2809.051	<0.05
A5	“	A4 + $\eta_{Ka\ IR}$	2785.005	<0.05
A6	“	A5 + Allometry V and CL	2798.125	>0.05
A7	“	A6 + CBZ on CL	2787.155	<0.05
A8	“	A7 + PHT on CL	2749.179	<0.05
A	“	A8 + VPA on CL	2710.545	<0.05
B	Pop. B	Model A	1097.47	-
B*	“	Model B	982.732	<0.05
B**	Pop. A+B	Model B*	3657.37	-
C	Pop. C	Model B**	1289.906	-
C*	“	Model C	1041.63	<0.05
C**	Pop. A-C	Model C*	4890.933	-
D	Pop. D	Model C**	1507.48	-
D*	“	Model D	1235.55	<0.05
D**	Pop. A-D	Model D*	6236.311	-
E	Pop. E	Model D**	111.707	-
E*	“	Model E	86.707	<0.05
E**	Pop. A-E	Model E*	6347.644	-
F	Pop. F	Model E**	85.641	-
F*	“	Model F	-595.285	<0.05
F1*	“	Model F* + Maturation	-598.044	>0.05
F**	Pop. A-F	Model F*	6361.691	-
Final	“	Model F** + Maturation	6301.631	<0.05