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

Dijkman, S.C. van

CHAPTER 6

IMPACT OF AGE-RELATED FACTORS ON THE PHARMACOKINETICS OF LAMOTRIGINE AND IMPLICATIONS FOR DOSING IN EPILEPSY PATIENTS

Impact of age-related factors on the pharmacokinetics of lamotrigine and implications for dosing in epilepsy patients

Sven C. van Dijkman, Nico C.B. de Jager, Willem M. Rauwé, Meindert Danhof, Oscar Della Pasqua

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SUMMARY

Background and Aims: In this study we evaluate 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 - 91 years of age. **Methods:** An allometrically scaled pharmacokinetic model was developed using adolescent and adult data, taking into account the effect of co-medications. Model parameters were then used to extrapolate lamotrigine pharmacokinetics to older adults (>65 years), children (4-13 years) and young children (0.2-2.6 years). In addition, simulations were performed to identify the implication of different doses and dosing regimens for each population, as to ensure steady-state concentrations within a predefined therapeutic window. **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 by +76.5%, +129%, and -47.4%, respectively. Allometric principles allowed accurate extrapolation to older adults and children older than 3 years of age. A maturation function was required to describe changes in exposure in younger patients. A child of 1.7 years has a 31.5% higher clearance compared to adults, after correcting for body weight. Patients > 65 years showed a decrease in clearance of approximately 15%. **Conclusion:** Population pharmacokinetic models are usually limited to a subgroup of patients, which may mask the identification of factors contributing to inter-individual variability. Availability of a single model, describing the population pharmacokinetics in the whole patient population provides insight into the dose rationale taking into account age-related changes in the disposition of lamotrigine.

Highlights

- Our study shows that lamotrigine pharmacokinetics can be described by allometric principles in patients older than 3 years of age, whereas a maturation function is required for younger patients.
- An integrated pharmacokinetic model shows that body weight along with the effect of co-medications (i.e., drug-drug interactions) are the primary factors affecting systemic exposure in patients of different ethnic backgrounds, aged 0.2-91 years, receiving immediate or extended release lamotrigine.
- Whereas the pharmacokinetic data obtained in children younger than 2 years of age are from historical clinical trials in which blood samples have been collected, our 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 (LMT) is a widely used AED, which has been approved for the treatment of patients with partial-onset seizures, primary generalized tonic-clonic (PGTC) seizures, and Lennox-Gastaut syndrome who are aged 2 years and older [1–4]. The pharmacokinetics of LMT is 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 to 350 mg twice daily. Mean apparent volume of distribution (Vd/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. LMT metabolism is predominantly hepatic via conjugation (UDP-glucuronosyltransferase 1–4, and UDP-glucuronosyltransferase 1–3). Following repeated dosing, LMT is known to induce its own metabolism, and oral clearance averages 0.35–0.59 mL/min.

These estimates result in plasma half-life ranging from 24 to 37 h [5-8]. In addition, considerable efforts have been made to characterise LMT exposure in special populations, such as pregnant women, children and elderly patients [9-11].

Despite the availability of pharmacokinetic (PK) data in both healthy subjects and patients, a model-based analysis of potential clinical and demographic covariates that affect the disposition of lamotrigine is still missing. In fact, population PK modelling has been used to describe the pharmacokinetics of lamotrigine in different patient groups and after administration of different dosage forms [12–21]. However, these investigations have not explored the implications of age-related differences in a systematic manner. From a methodological perspective, another factor needs to be considered, 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 [22], while changes in drug disposition in children younger than 2 years 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 co-medications and other intrinsic or extrinsic factors.

Here we attempt to develop an integrated population PK model to describe the pharmacokinetics of lamotrigine at steady state in patients from different ethnic backgrounds, aged 0.2-91 years, receiving immediate or extended release lamotrigine. Our analysis provides an opportunity to illustrate how population PK modelling and simulation can be used as a tool for dose optimisation when patient population characteristics are likely to affect drug exposure. In this regard, it should also be noted that a relationship between plasma concentration and clinical response and/or adverse effects has not been stablished, but a clinically relevant target range for plasma concentrations has been considered between 3–14 mg/L [23]. Moreover, it allows us to investigate possible explanatory factors for the lack of efficacy of LMT in patients aged 2 years and younger, which could not be demonstrated in randomised clinical trials [24]. These findings

seem to contrast with the conclusions drawn by Pellock and collaborators regarding the evidence of efficacy data in adults, which can be used to predict treatment response in partial onset seizures in children > 2years of age. In fact, the authors declare that no attempt was made to quantitatively analyse the studies including LMT, due to the few trials eligible for their analysis [25].

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 clearance [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 on older adults. Hence, our analysis aims to quantify the effect of changes in systemic exposure to LMT due to developmental growth in younger patients (i.e. ontogeny, organ maturation) and reduced organ function and body mass in older adults. The availability of population parameter distributions, which account for the effect of covariate factors will allow for the optimisation of future clinical 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 LMT concentration data, patient demographics and dosing information for a total of 492 patients, receiving immediate- or extended release formulations of LMT for up to 45 weeks. As

shown in **Figure 1**, from this pooled data, 7 subsets were created for 4 age groups. Subsets A and B were created as 70% and 30% of the same data type (adolescents and adults aged 14-65, data from one rich and one sparse sampling study combined) for the purpose of model building and internal validation, respectively. Subset C was created for external validation (adolescents and adults aged 11-65, data from a different study, in which pharmacokinetics was evaluated based on sparse sampling). Subsets D, E, and F were created for model extrapolations to adults >65-91 years, children 4-10 years, and children <3 years respectively. A detailed overview of the demographics of each subset can be found in the supplement (**Table 1S**), demographics of the total patient pool are listed in **Table 1**.

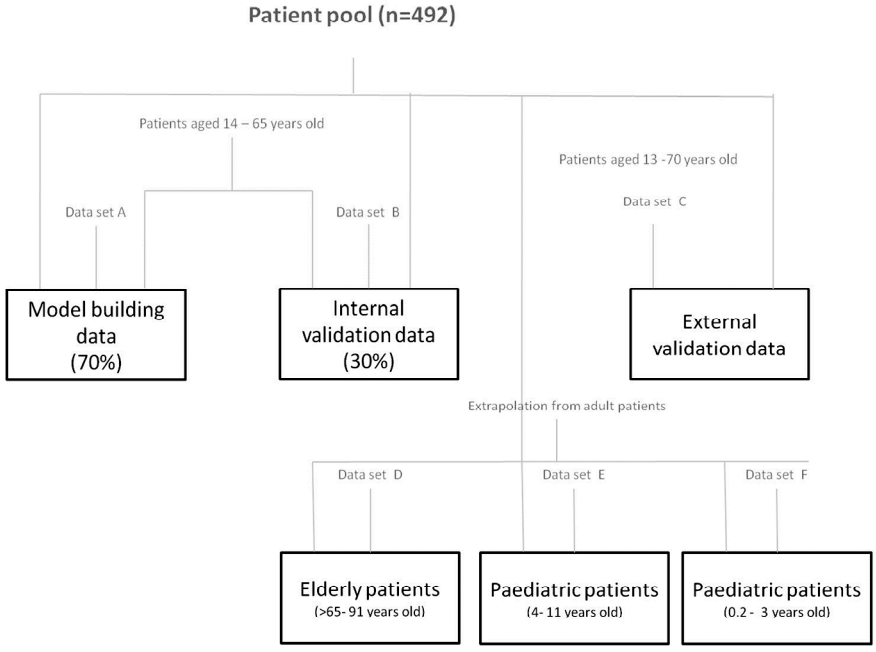

Figure 1. Data sets and population characteristics for the development of a population pharmacokinetic model in adult, paediatric and elderly patients.

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	-
Gender (M:F)	248:246	-
Age, years	45.3 (24.2)	29 (0.2-91)
Weight, kg	70.3 (27.5)	58 (3-151.9)
LMT dose	255 (190) mg/day	200 (2-1200) mg/day
Comedication	Frequency	Dose range
Carbamazepine	62	300-1200 mg/day
Clobazam	11	2.5-40 mcg/day
Clonazepam	22	0.25-175 mcg/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

2.2. Population PK 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) [26]. The analysis workflow was performed within a platform including Psn v4.2.0 [27] and Piraña v2.90 [28,29]. R v3.1.1 was used for data processing, and statistical and graphical analysis [30]. One and two-compartment models with first order absorption and elimination were evaluated to fit the concentration vs. time data. Clearance (CL) and volume of distribution (V) were estimated as apparent parameters (CL/F, V/F), as all concentration data were obtained after oral administration of LMT. The first-order conditional estimation method with interaction (FOCE-I) was used to derive population (θ) PK parameters, their variability (η) and the residual variability between observed and predicted concentrations (ε). Interindividual variability in PK model parameters was described by an

exponential model (equation 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 (equation 2), where $Y_{ij,obs}$ and $Y_{ij,pred}$ are respectively the observed and predicted concentrations of individual *i* at time *j*, and ε_1 and ε_2 are random variables with mean zero and variance σ^2.

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

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

2.2.1. Covariate modelling

Age, body weight (WT), formulation (immediate or extended release), and co-medication were considered as factors to be included in the evaluation of covariate effects. Due to covariate identifiability limitations, only those co-medication taken by at least 10 individuals were considered for inclusion; i.e. carbamazepine (CBZ), clobazam (CLBZ), clonazepam (CLNZ), gabapentin (GBA), levetiracetam (LVT), oxcarbazepine (OXC), phenobarbital (PHB), phenytoin (PHT), topiramate (TPM) and valproic acid (VPA). Evidence for potential covariate-parameter correlations was based on a graphical evaluation 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 PK parameter (equation 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 equation 4, where θ_{cov} represents the impact of the relevant covariate in question and Cov_i takes a value of 1 or 0.

$$Px = \theta_x * \frac{Cov_i}{Cov_{med}} \quad (3)$$

$$Px = \theta_x * (1 + \theta_{cov}{}^{Cov_i}) \quad (4)$$

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 of >3.84 (based on a χ^2 distribution with 1 degree of freedom) was required. During backward covariate deletion, a change in OFV of >6.64 (*p* <0.01) was used as threshold for evidence of the covariate effect. To determine the feasibility of allometric extrapolations to other age groups, *a priori* allometric principles were applied to clearance (CL) and volume of distribution (V) (equation 5 and 6).

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

$$V = \theta_V * \left(\frac{WT}{70}\right) * e^{\eta_V} \quad (6)$$

Different absorption rate constants (Ka) were estimated to account for differences between immediate release (IR) and extended release (XR) formulations (equation 7).

$$Ka_{IR} = \theta_{Ka_{IR}} * e^{\eta_{Ka_{IR}}} \text{ or } Ka_{XR} = \theta_{Ka_{XR}} * e^{\eta_{Ka_{XR}}} \quad (7)$$

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

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

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 LMT. An iterative approach was taken in which an initial model, built on adult PK data was firs evaluated using an index and an external validation data set (B+C). Based on pre-defined model performance criteria, the model was then used for extrapolation purposes to describe LMT exposure in older adults (>65 years, D), children (4-11 years, E), and finally in infants and toddlers children (<3 years, F). At each step, parameters were first fixed to the values obtained during the estimation step including all previous data (models B-F), after which parameters were estimated using data from the patient population in question separately (models B*-F*), and in conjunction with all previous data (models B**-F**). These iterative steps are illustrated in **Figure 2**.

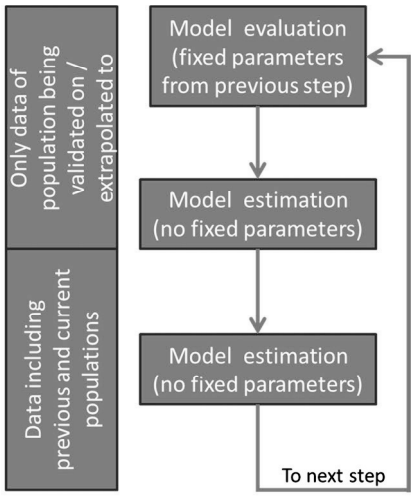

Figure 2. Schematic overview of validation and extrapolation steps.

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

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

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

The final model was 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 year, 1-2 years, 2-4 years, 4-8 years, 8-16 years, 16-65 years, and >65 years. The ability of the final model to predict the overall data was examined using a visual (VPC) and numerical predictive check (NPC) using 1000 samples. In addition, normalized prediction distribution errors (NPDE) were calculated and summarised to assess the overall performance of the stochastic components of the model.

2.3. Dosing recommendations

A virtual patient population of age 0.2-91 years was subdivided into 4 groups, for which the body weights were derived according to the WHO growth charts [31] and Luscombe *et al.* [32] (table 2). Using the predicted clearance values obtained from the final PK model, LMT steady state concentrations (Css, equation 10) 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 LMT doses and dosing regimens was used for each population with the objective of optimising steady state concentrations within a previously suggested target therapeutic range.

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

Table 2. Weight (WT) calculation functions per age group, and its coefficient of variance (CV%) used in the simulations.

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

3. Results

3.1. Model development and validation

The pharmacokinetics of LMT was best described by a one compartment model with first order absorption and elimination. In addition, interindividual variability was identified in all PK parameters. Covariate analysis revealed that CBZ and PHT increased the clearance of LMT by 76.5% and 129%, respectively, whereas VPA reduced it by 47.4%. No correlation was found between the dose of the co-medication and clearance of LMT. No other significant correlation was identified between the clearance of LMT and use of other AEDs. Given the objectives of our analysis, the effect of body weight on clearance and volume of distribution was parameterised using allometric principles and kept in the model irrespective of the initial variation in OFV (see **Table S2** in supplemental materials). As depicted in **Figure 3**, goodness-of-fit plots show that the final model accurately describes interindividual variability across the overall population. No bias is seen in the CWRES *versus* PRED or time after dose.

An overview of the final model performance is further summarised by the visual predictive check in **Figure 4**, which shows the 95% prediction intervals along with the observed data. It is worth mentioning the model accurately describes the data, with only minor overprediction of the peak concentrations. The results of the numerical predictive checks along with the normalized prediction distribution error (NPDE) provide further evidence of accurate model performance (results not shown). Nonparametric bootstrap results confirm the parameter estimates of the final model (**Table 3**).

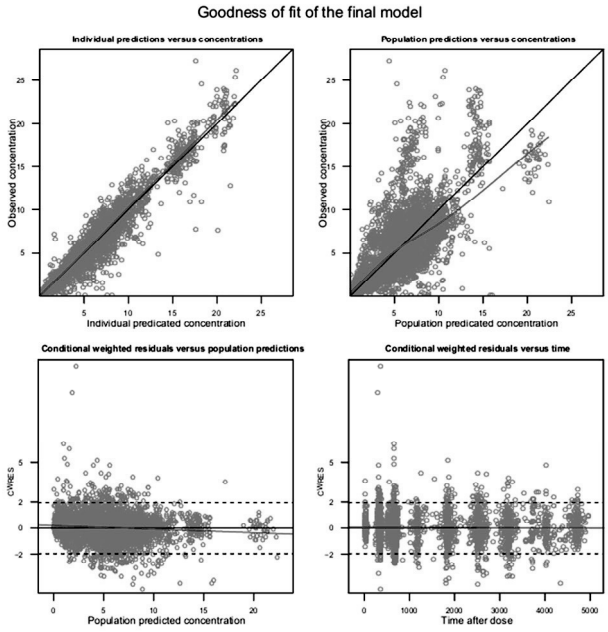

Figure 3. Goodness of fit plots of the final model. Individual- (IPRED) and population (PRED) model predictions are compared to the observations (DV). Conditional weighted residuals (CWRES), are compared to the PRED and time after dose. Black solid lines: identity line. Red solid lines: trend line. Blue circles: individual data.

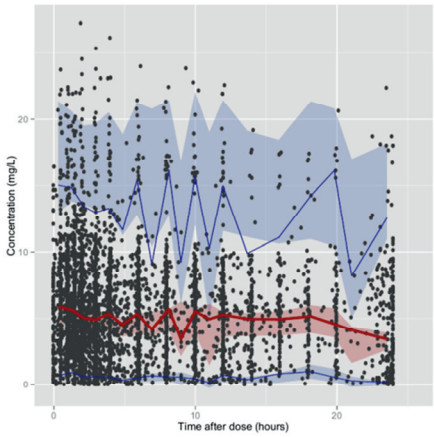

Figure 4. Visual predictive check (VPC) of the final model. The median (red line) and 95% CI (blue lines) of the observed data are plotted against the simulated data of 1000 subjects (highlighted areas; median in red, 95% prediction interval in blue). Individual observations in the data are shown as black dots.

Table 3. The final model parameter estimates and corresponding bootstrap results, including the 95% confidence intervals (CI). 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).

Parameter	Value (95% CI)	Bootstrap median (95% CI)
$\theta_{Ka\ IR}$	2.43 (1.425 – 3.435)	2.56 (1.44 – 3.97)
$\theta_{Ka\ XR}$	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}	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 – -0.393)	-0.49 (-0.57 – -0.41)
θ_{TM50}	128.5 (76.9-333.3)	125 (100-250)
θ_{Hill}	-5.66 (-10.736 – -0.584)	-15.98 (-152.94 – -2.75)
θ_{Amax}	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)
$\omega^2_{Ka\ IR}$	0.609 (-0.536 – 1.754)	0.53 (0.0001 – 3.09)
$\omega^2_{Ka\ XR}$	0.46 (-0.442 – 0.715)	0.57 (0.27 – 1.18)
ω^2_{CL}	0.274 (-0.263 – 0.811)	0.27 (0.22 – 0.32)
ω^2_{V}	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)

3.2. Extrapolation across populations

Whilst the objective of our analysis was to identify model parameterisation that allowed for the characterisation of the pharmacokinetics of LMT across the overall patient population, the set of steps used during model building ensured identification and distinction between interacting factors, such as age and co-medications. Accuracy (RE) and precision (NRMSE) of the predicted estimates for the absorption rate constant (Ka) and distribution volume (V) 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 (clearance) were acceptable in all cases except for the extrapolation to children below 2 to 3 years of age (**Figure 5**). This discrepancy reflects the need for additional parameterisation describing the underlying maturation processes, which account for changes in clearance in infants and toddlers (equation 11) (**Figure 6**). Furthermore, a separate term was included to describe 14.8% decrease in CL in patients older than 65 years of age. Equation 12 summarises the different factors which were identified as a covariate on clearance, where E_{CBZ}, E_{PHT} and E_{VPA} are 1.765, 2.29, and 0.536 if the co-medication carbamazepine, phenytoin, and/or valproic acid respectively were co-administered or 1 otherwise. E_{ELD} is 0.852 is the term describing the effect of age in elderly patients.

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

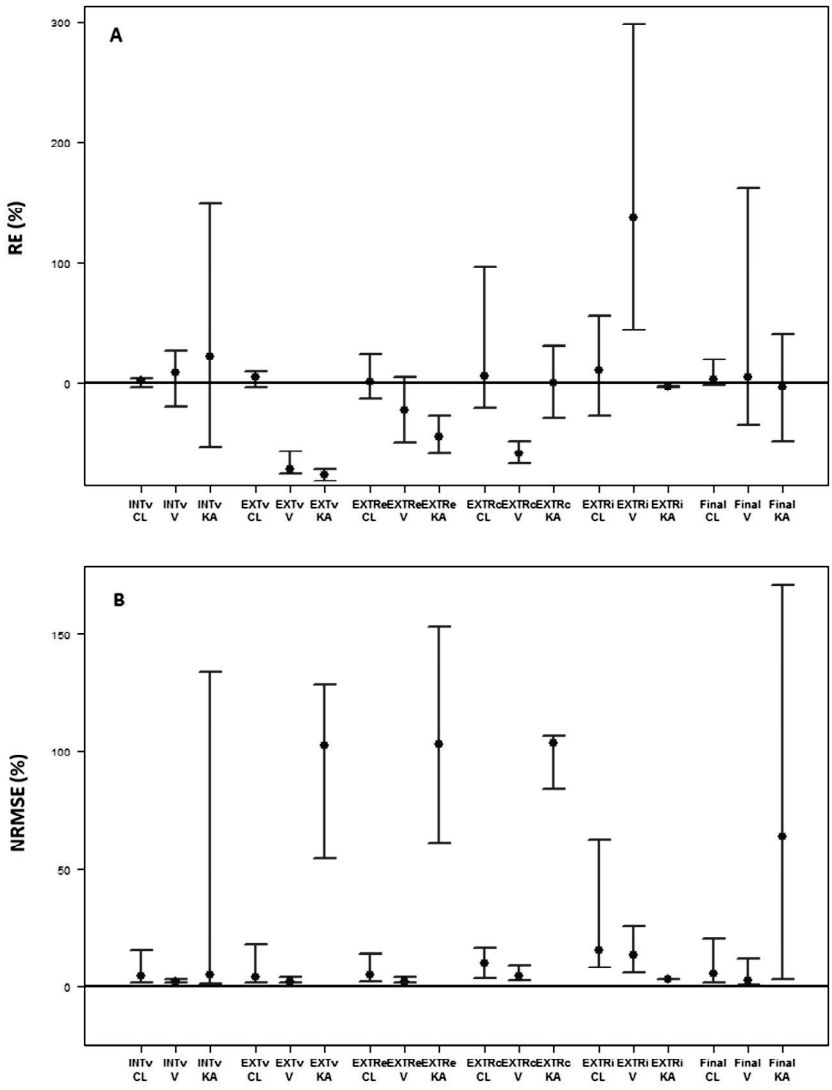

Figure 5. Evaluation of parameter predictions during validation and extrapolation steps; internal validation (INTv), external validation (EXTv), extrapolation to adults 65-91 years (EXTRe), extrapolation to children 4-11 years (EXTRc), extrapolation to infants and toddlers <2 years (EXTRi), evaluation of final model with and without maturation function (Final). The median (red dots) and 95% confidence interval (bars) are shown of relative errors (RE, panel A) and normalised root mean square errors (NRMSE, panel B).

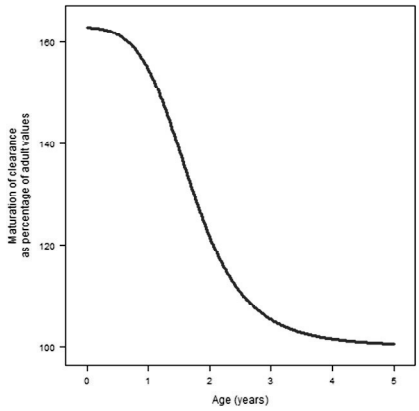

Figure 6. Sigmoidal function describing changes in clearance associated with age and metabolic maturation processes.

3.3. Dosing optimisation in future clinical trials

Our exploratory simulations identified a dosing algorithm for dosing optimisation in future clinical trials, which leads to a considerable increase in the proportion of patients attaining a pre-defined target therapeutic range during the maintenance phase of treatment (**Table 4, Figure 7**). Based on the patient population characteristics included in the simulation scenarios, a dose of 350 mg/day in adults was found to best result in C_{ss} within the target therapeutic range. Based on this dose as reference, our simulations show that LMT doses need to be reduced to 300 mg/day in adults older than 65 years, 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 dosing regimens based on a weight banded regimen, with two weight bands. The optimum dose for infants between 2-4 months was predicted to be 80 mg/day, whilst infants and toddlers aged 4-23 months would require 100 mg/day. As shown in **Figure 7**, the proposed doses and dosing regimens would allow for a considerable increase in the proportion of patients within the target steady state concentrations. However, given the concern with high peak concentrations in young children, a twice daily regimen should be carefully considered.

Table 4. Optimised dosing levels and predicted steady state concentrations (Css) per age group. Each column summarises the proportion of patients in each group who are exposed above the absolute toxicity level of 20 mg/L, above the therapeutic maximum of 15 mg/L, and below the therapeutic minimum of 2.5 mg/L.

Population	Age range	Dose	% Css > 20*	% Css > 15*	% Css < 2.5*
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	≥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

*mg/L

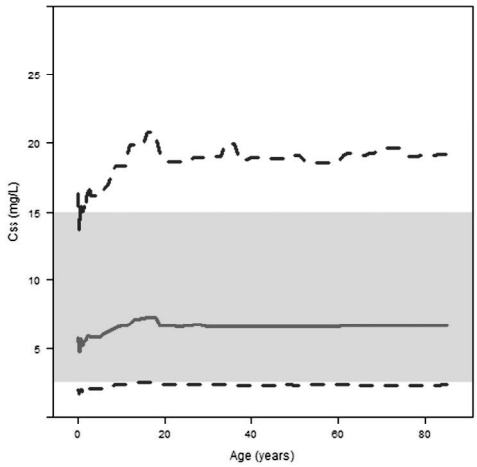

Figure 7. C_{ss} ranges resulting from optimised dosing regimens over age, as listed in table 5. Shown are the median (red line) and 95% prediction interval (blue dashed lines) of the simulated C_{ss} values. The blue shaded area is the putative target therapeutic range.

Table 5. Final model estimates along with previously published pharmacokinetic data in each population.

Population	Parameter	Final model values	Literature values
Adults	Ka IR (h^{-1})	2.43	0.38-3.19 [12,16,17,20,21,33,34,44]
	KA XR (h^{-1})	0.087	0.0739 [44]
	V (L/kg)	1.97	0.9-1.9 [12,16,17,19–21,33–35]
	CL (L/h/kg)	0.0319	0.028-0.15 [12,16,17,19–21,33–35]
Older adults 65-91 years	Ka IR (h^{-1})	2.43	2.98-3.5 [14,44]
	KA XR (h^{-1})	0.087	0.0739 [44]
	V (L/kg)	1.97	1.3-1.42 [14,44]
	CL (L/h/kg)	0.0271	0.033-0.039 [14,44]
Children and adolescents 2-18 years	Ka IR (h^{-1})	2.43	1-3.5 [13,18,21]
	KA XR (h^{-1})	0.087	-
	V (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	Ka IR (h^{-1})	2.43	1 [18]
	KA XR (h^{-1})	-	-
	V (L/kg)	1.97	0.6 [18]
	CL (L/h/kg)	0.051-0.10	0.037 [18]

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 have 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 of other interacting factors, such as co-medications, LMT exposure can be accurately described across different population groups based on the inclusion of allometric principles in patients > 2 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 as PMA-related changes lead to significantly higher clearance values, as compared to children and adults.

Whereas our attempt to characterise age-related changes in the pharmacokinetics of LMT does not include some factors known to be relevant in clinical practice, such as pregnancy or co-morbidities, our analysis provides further insight into the interaction between age, size and metabolic function. Based on previous publications, it appears that weight-based scaling has often been used to describe the pharmacokinetics of LMT [13–16,18,21,33–37], but a different approach has been used in many other cases [12,17,19,20,38–39]. Most interestingly, none of the publications has explored the effect of body weight in the standardised allometric manner across a wide population [40]. In fact, He and collaborators have used allometrically scaled clearance [18], but this analysis include children only, and the allometric exponent was not set to the standard ¾, which may explain why a maturation functions may not have been required, despite the inclusion of patients below the age of 2.

From a methodological perspective, it should be noted that the inclusion of allometric scaling does not necessarily improve model fitting if patient characteristics do not include 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 [41, 42]. 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.

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 reveal that allometry can only fully account for changes in clearance and volume of distribution in patients older than 2 years [22]. Of particular interest is the estimation of clearance which showed RE and NRMSE values within the acceptable range during most extrapolation steps, except when extrapolating to children below 2 years. Given 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 (post-menstrual age).

In spite of the large sample size, our analysis has also faced a few limitations. Due to high variability, absorption proved particularly difficult to estimate, which may pose problems as peak concentrations could not be well characterised. Nevertheless, parameter estimates were in agreement with values previously reported in the published literature (table 6), including the different absorption rates found for immediate and extended release formulations. Moreover, we have been able to estimate the effect of co-medications, namely carbamazepine, phenytoin, and valproic acid, on the clearance of LMT. In addition, no discernible effect was observed for phenobarbital. Overall, our results seem to reflect those previously reported in literature [38–40], but differ from other publications [18,30,33,36]. Another challenge was the lack of literature information regarding the maturation processes associated with the elimination of LMT in infants and toddlers, which ultimately affects the rationale for maintenance doses in this age group [43-45]. As shown in figure 6, maturation processes lead to higher weight-adjusted CL in very young children, which slowly decrease to adult levels between age 2 -3 years. This is an important observation, given that LMT is not approved for children younger 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 β-glucuronidation, which decreases to adult levels at a much earlier age [46]. There may be a role for UGT-2B7 or reduced LMT protein binding, although the data is so far inconclusive

[47–50]. Given the evidence for reduced metabolic clearance 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 as to ensure comparable LMT exposure within a pre-defined target range for the majority of patients. Irrespective of inter-individual differences in the sensitivity to LMT, the simulated dosing regimens provide further insight into how doses may 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. 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 clearance is reasonably explained by the interacting terms in equation 12. It can be anticipated that such a dosing algorithm may serve as a tool for clinicians at the start of treatment with LMT. Once target maintenance dose is reached, model-guided dose adjustments can be made in conjunction with TDM sampling [51].

In conclusion, an integrated population pharmacokinetic model was developed for LMT that describes age-related changes in patients from 0.2 to 91 years of age. This analysis confirms previous findings in which interindividual variability in the disposition of LMT has been evaluated. Clearly, LMT steady state concentrations are affected by the interaction between multiple intrinsic (e.g., body weight, age) and extrinsic (e.g., co-medication, formulation) factors. The use of allometric principles in conjunction with a maturation function provided insight into the contribution of intrinsic factors to interindividual variability. Based on simulation scenarios, it has become evident that these covariates may need to be considered before starting dose titration, as the magnitude of the effect of covariates will depend on an individual patient's characteristics.

Finally, it seems plausible that lack of efficacy in previous clinical trials including infants and toddlers may result from sub-therapeutic exposure to LMT. The observed increase in systemic clearance leads to considerably lower LMT exposure as compared to the drug levels observed in children and adolescents. These results should form the basis for the dose rationale for lamotrigine in prospective clinical trials in infants and toddlers.

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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