

Effect of age-related factors on the pharmacokinetics of lamotrigine and potential implications for maintenance dose optimisation in future clinical trials.

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Running head: Population pharmacokinetics of lamotrigine

Keywords: allometric scaling, population pharmacokinetics, extrapolations, lamotrigine, paediatrics, maturation, epilepsy

According to the GlaxoSmithKline's Clinical Trial Register, the data from GSK studies LAM100034 and LEP103944, corresponding to clinicaltrials.gov numbers NCT00113165 and NCT00264615 used in this work have been used in previous publications:

D. K. Naritoku, C. R. Warnock, J. A. Messenheimer, R. Borgohain, S. Evers, A. B. Guekht, V. A. Karlov, B. I. Lee and L. Ríos Pohl: Lamotrigine extended-release as adjunctive therapy for partial seizures. *Neurology* 2007;69;1610-1618

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Word count: ~4054

Numbers of tables: 5

Number of figures: 7

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 - 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 (0.2-2.2 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 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 by +76.5%, +129%, and -47.4%, respectively. Allometric principles allowed accurate extrapolation to older adults and children older than 4 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. 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 clinical trials.

Key points

- An integrated pharmacokinetic model shows that age and 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
- 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 (LMT) is a widely used anti-epileptic drug (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 [1–5]. 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 (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. 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 [9–13], children [14–20], and elderly patients [21–25].

Despite the availability of pharmacokinetic (PK) data in both healthy subjects and patients, a comprehensive 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 [9–31]. However, these investigations have not explored the implications of age-related differences in a systematic manner, except for a 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 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 adjustment and 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 established, but a clinically relevant target range for plasma concentrations has been considered between 3–14 mg/L [33]. Moreover, assessment of the effect of demographic characteristics on drug disposition parameters 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 previously in randomised clinical trials [34]. 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 [35].

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. 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 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 population (adolescents and adults aged 14-88), 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, 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 65-91 years, children 4-13 years, and children <2.2 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 each subset can be found in the online supplement (Table 1S), demographics of the total patient pool are listed in Table 1.

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) [36]. The analysis workflow was performed within a platform including PsN v4.2.0 [37] and Piraña v2.90 [38,39]. R v3.1.1 was used for data processing, and statistical and graphical analysis [40]. 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 j^{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 .

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

$$Y_{ij,obs} = Y_{ij,pred} * (1 + \epsilon_1) + \epsilon_2 \quad (2)$$

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 co-medications 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.

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

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

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 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) (equations 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 (K_a) were estimated to account for differences between immediate release (IR) and extended release (XR) formulations (equation 7).

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

If necessary, a maturation function was included (equation 8) to describe the change in CL in infants and 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).

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

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 LMT. An iterative approach was taken in which an initial model, built on adult PK data (data set A) was evaluated using an internal and external validation data set (data sets B and C, respectively). Based on pre-defined model performance criteria, the model was then used for extrapolation purposes, i.e., to characterise LMT exposure in older adults (>65 years, data set D), children (4-11 years, data set E), and finally in infants and toddlers (<2.2 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 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 summarised in figure 2.

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%.

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

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

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 predictive check (VPC) stratified for age (strata: 0.2-2.2 years, 4-14 years, 14-65 years, 65-91 years) and a 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

The patient population pool aged 0.2-91 years was subdivided into 4 groups, for each of which body weights were derived according to the WHO growth charts [41] and Luscombe *et al.* [42] (table 2). Using the predicted clearance values obtained from the final PK model, LMT steady state concentrations (Css, equation 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 LMT doses and dosing regimens was used for each population with the objective of optimising steady state concentrations within a previously suggested target reference range [43].

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

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

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, inter-individual variability was identified in all PK parameters. Correlations between model parameters were tested and several were found significant. However, inclusion of these correlations resulted in unacceptable (>40%) increase in uncertainty on parameter values and therefore not incorporated into the final model. 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 inter-individual variability across the overall population. No bias is seen in the CWRES *versus* PRED or time after dose. On the other hand, it is worth mentioning that peak concentrations were slightly overpredicted. An overview of the final model performance is summarised by the visual predictive check in Figure 4, which shows the 95% prediction intervals along

with the observed data. Nonparametric bootstrap confirmed the parameter estimates obtained with the final model (table 3). Overall model performance was also corroborated by the results from the numerical predictive checks and normalised prediction distribution error (NPDE) (results not shown).

3.2. Extrapolation across populations

Whilst our aim was to identify a suitable parameterisation to describe the pharmacokinetics of LMT across the whole patient population, the approach 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 2.2 years of age (figure 5). This discrepancy seems to reflect the contribution of maturation processes, which account for changes in clearance in infants and toddlers (equation 8) (figure 6). Furthermore, a separate term was included to describe the decrease of 14.8% in CL in patients older than 65 years of age.

Equation 12 summarises the different factors which were identified as a covariate on clearance:

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

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 the term describing the effect of age in elderly patients, which takes a value of 0.852 in case of a patient's age >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 pre-defined target range during the maintenance phase of treatment. The first scenario explored was the use of a single dose regimen for each population. Based on the patient population characteristics included in the simulation scenarios, a dose of 350 mg/day was found to be the most suitable regimen in adults, as to maximise the proportion of patients with C_{ss} within the target range. Using 350mg/day 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 on a weight-banded dosing regimens, 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. When dose adjusting for the effect of age and weight, variation in LMT exposure (as assessed by the coefficient of variation, CV%) could not be reduced by much (roughly 60% in both scenarios). This is partly explained by the fact that the effect of co-medication was not included in these evaluations (Figure 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 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 > 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 as PMA-related changes lead to

significantly higher clearance values, as compared to children and adults. By contrast, a clearance reduction of roughly 15 % was observed in elderly patients, which correlated with known decrease in hepatic and renal function in this population.

Whereas our attempt to characterise age-related changes in the pharmacokinetics of LMT does not include other factors known to be relevant in clinical practice, such as pregnancy, oral contraceptives, UGT enzyme polymorphisms or co-morbidities, our analysis did provide further insight into the interaction between age, size and metabolic function. In general, pregnant patients or female patients on oral contraceptives are not included into clinical studies during the early stages of clinical drug development. Furthermore, the study protocols did not include pharmacogenetic testing for polymorphism in enzymes such as UGT. The lack of such data has prevented identification of additional explanatory factors for the observed differences in clearance. Availability of these potential covariate factors might explain some of remaining inter-individual variability [31,44,45].

Previous publications have reported the use of weight-based scaling to describe the pharmacokinetics of LMT [14,17,18,23,27,28,46–50], 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 the standardised allometric manner across a wide population [51]. In fact, He and collaborators have used allometrically scaled clearance [17], but this analysis include children only, and the allometric exponent was not set to the standard $\frac{3}{4}$, which may explain why a maturation function may not have been required, despite the inclusion of patients below the age of 2.

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 [52,53]. 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 inter-individual 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 [32]. 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. On the other hand, it cannot be excluded that reduced absorption could lead to a higher apparent clearance. As intravenous data is not available, it is not possible to distinguish the true cause of the differences in systemic exposure (i.e., changes in apparent or in intrinsic clearance).

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 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, which may be explained by the fact that less than 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 clearance. Overall, our results seem to reflect those previously reported in literature [54–56], but differ from other publications [17,21,46,49]. 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 [57]. As shown in figure 6, maturation processes lead to higher weight-adjusted CL in very young children, which slowly decrease to adult levels between the age of 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 by β -glucuronidation, which decreases to adult levels at a much earlier age [58]. There may be a role for UGT-2B7 or reduced LMT protein binding, although the data is so far inconclusive [31,44,45,59,60]. Given the evidence for reduced metabolic clearance in new-born 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 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, inter-individual variability in clearance was found to be reasonably explained by the interacting terms in equation 12.

Irrespective of inter-individual differences in the sensitivity to LMT due to factors such as disease severity, seizure type and pharmacodynamic polymorphisms, the simulated regimens show that LMT doses may be titrated at the onset of therapy and how subsequent dose adjustments can be made if TDM is used during the maintenance phase. In fact, understanding of the role of covariate factors can

aid investigators achieving a pre-set 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 steady-state concentrations (from 57% to about 17%, Figure 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.[61,62]. However, given the concern with high peak concentrations, dose adjustments in young children may need to be implemented according to a b.i.d. regimen.

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 inter-individual 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 inter-individual variability. Based on simulation scenarios, it has become evident that these covariates may need to be considered before the start of 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 have resulted from sub-therapeutic exposure to LMT, i.e., higher apparent clearance than what may be expected from simple weight-based dose adjustment. The observed LMT 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 for lamotrigine in prospective clinical trials in infants and toddlers. As the recommended low initiation dose, titration steps and interindividual differences in pharmacodynamics and safety were not considered here, they do not constitute recommendations for patients in clinical practice.

Acknowledgment

The authors thank Khilit Shah for his assistance in retrieving the data from the GSK database, and Corine Visser for her editorial support.

Author contributions:

SvD, NdJ and WR performed the investigations; SvD and ODP wrote the manuscript; MD and ODP coordinated the investigations and reviewed the manuscript.

Conflict of interest

SvD had support from the Global Research in Paediatrics consortium (GRiP). In addition to his role in GRiP, ODP is also Senior Director Clinical Pharmacology at GlaxoSmithKline. The authors declare no conflict of interest.

Compliance with ethical standards

The research presented in this paper was based on already existing data. The data used was 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.

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1 **Figures and tables legends:**

2

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

5

6 Figure 2: Schematic overview of all validation and extrapolation steps.

7

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

12

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

17

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

24

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

27

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

31

32 Table 1: Demographics of the total modelling population. Carbamazepine-Valproic acid: number of
33 patients receiving the comedication and the range of doses.

34

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

37

38 Table 3: The final model parameter estimates and corresponding bootstrap results, including the 95%
39 confidence intervals (CI). θ : population value; ω^2 : variance of deviation (η) of individuals from
40 population value θ ; σ^2 : variance of proportional (prop) and additive (add) residual errors (ϵ).

41

42 Table 4: Optimised maintenance dosing regimens and predicted C_{ss} per age group in the
43 simulated scenarios. Each column summarises the proportion of patients in each group who are
44 exposed above the absolute toxicity level of 20 mg/L, above the therapeutic maximum of 15 mg/L, and
45 below the therapeutic minimum of 2.5 mg/L. These scenarios do not include the initiation dose

46 or titration steps, which are required to reduce the risk of serious cutaneous adverse
47 reactions and account for interindividual differences in pharmacodynamics and safety.

48

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

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