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

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CHAPTER 7

ASSESSMENT OF LAMOTRIGINE EXPOSURE-RESPONSE:

DIFFERENTIAL EFFECTS IN PARTIAL ONSET VERSUS PRIMARY GENERALISED TONIC-CLONIC SEIZURES IN ADULTS

Assessment of lamotrigine exposure-response: differential effects in partial onset versus primary generalised tonic-clonic seizures in adults

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SUMMARY

Purpose: We aim to quantify the pharmacokinetic-pharmacodynamic relationships of lamotrigine (LMT) in partial onset (PO) and primary generalised tonic-clonic (PGTC) seizures in adult patients, taking into account the episodic nature of the disease. **Methods:** Adult clinical trial data of 235 PO and 146 PGTC patients receiving add-on lamotrigine therapy were analysed using a nonlinear mixed effects approach to describe seizure counts over time. The interaction of LMT with comedications and other covariates with regard to baseline seizure counts, placebo and treatment effect were also investigated. **Results:** The drug-disease model described the data well, and parameters were estimated with good accuracy.. Placebo effect led to a reduction in seizure activity of 13.8-21.9% in PO and 22.9-36.9% in PGTC. Typical maximum treatment effect was close to 100% both for PO and PGTC, but individual response showed large variability. No covariates were found to have a clinically relevant effect on parameters describing seizure counts or drug effect other than those identified for pharmacokinetics. **Conclusions:** The use of a Poisson model with extension for Markovian features, as well as the use of stochastic differential equations, provides suitable parameterisation of seizure activity in PO and PGTC patients, describing the time course of placebo and drug effects after treatment. Most importantly, it provides evidence of a unique exposure-response relationship for LMT in patients with PO and PGTC seizures. These models are able to describe interindividual differences in response and could be used for personalisation of therapy.

1. Introduction

Epilepsy is a serious neurological condition consisting of attacks of abnormal neuronal activity in the brain, or seizures. In the majority of patients, epileptic seizures originate from one hemisphere, called partial onset (PO) type epilepsy, which in some may then spread to other parts as secondary generalised seizures. Other patients exhibit seizures that directly affect both hemispheres, called primary generalised seizures, of which primary generalised tonic-clonic (PGTC) seizures are the most well-known. Treatment typically involves long-term, if not life-long pharmacotherapy. One of the most widely used anti-epileptic drugs (AEDs) is lamotrigine (LMT) [1]. It works as a sodium channel blocker, possibly with a secondary effect as a calcium channel blocker [2]. LMT has been approved, among others, for the adjunctive treatment of PO and PGTC seizures. The relationship between LMT exposure and response has not yet been characterised in strictly quantitative manner. In fact it remains unclear whether patients with different seizure types show different sensitivity to treatment and drug exposure.

The assessment of exposure-response relationships for AEDs is hindered by the episodic nature of the disease activity in terms of seizures or seizure counts. In drug development, this issue has been circumvented by instead analysing the efficacy of an AED through comparison of the mean seizure frequency between baseline and maintenance therapy, such as was performed in the majority of clinical trials, including those in which lamotrigine is used as adjunctive therapy for PO seizures [3]. Treatment success is then defined when seizure frequency reduction during the maintenance period is at least 50% relative to baseline. Due to the dichotomisation of efficacy (i.e. yes or no), the averaging across the population, and the reduction of the data to baseline and maintenance period, most of the information regarding the onset of treatment effect and variation is lost, resulting in difficulties in assessing exposure-response relationships. The randomness of seizures and subsequent difficulty in correlating exposure to effect in individual patients has led to a lack a stronger dose in clinical guidelines for AEDs. Pharmacokinetic (PK) and pharmacodynamic (PD) modelling has more recently allowed the

description of exposure-response relationships of some of the widely used AEDs based on several different types of clinical endpoints [4–8].

The application of such models allows us to investigate whether the different seizure types, such as PO and PGTC seizures show different sensitivity to treatment and consequently whether the optimal therapeutic concentration range differs for each patient group. Furthermore, modelling also allows us to determine if any other demographic or clinical variables influence efficacy. Another important feature of drug-disease models is that they enable better integration of information from sparse data, which often is the case in paediatric medicine. The availability of a so-called drug-disease model ultimately provides an opportunity to identify dosing algorithms for specific groups of patients (personalised treatment) or eventually single patients (individualised treatment).

From a technical point of view, the application of PKPD modelling principles allows direct modelling of the seizure counts at all time points in each individual patient, thereby taking into account all available data [9,10]. Because of the apparent randomness of the occurrence of seizures, different methods have been suggested for its analysis. Some of the randomness can be described by Markov chains, i.e. a random process of transitions between disease states, where the probability of the next state depends solely on the current state. Seizure counts often show overdispersion, i.e. the variance is larger than the mean. The Poisson model has been extended to take into account overdispersion and Markovian features [10,11]. Conceptually, in this type of models treatment effect is handled as a covariate, i.e., treatment alters the parameter(s) describing the probability and rate of events. The aim our investigation is to determine the exposure-response of adjunctive lamotrigine in adult patients with PO and PGTC seizures, and to identify the contribution of any other demographic or clinical covariates that explain differences in response. Subsequently, our goal is to illustrate how the availability of such models may support the development of improved dosing algorithms as well as facilitate the extrapolation of efficacy across populations.

2. Methods

Data

Data from clinical trials of lamotrigine pharmacokinetics and efficacy in adults with partial onset seizures (LAM100034; clinicaltrials.gov number NCT00113165) and adults with primary generalised tonic-clonic seizures (LAM100036; clinicaltrials.gov number NCT00104416) were used in the following analysis. In either trial, subjects experienced an eight week baseline phase, seven week escalation (dose titration) phase, and 12 week maintenance phase. Dose titration was performed at dose levels of 50, 100, 200, and 300 mg per day. Dose levels of 50 and 100 mg per day were maintained for two weeks, while that of 200 mg per day was kept maintained for one week. Once the dose of 300 mg per day was reached, it was maintained for a maximum of two weeks. For patients with partial onset seizures, additional data of a 7 week blinded transition and 45 week open-label continuation phase was available. Both trials adhered to all required ethical regulations and received informed consent from all participating patients. Individual exposure levels, in terms of average daily concentration (Cavg), daily peak concentration (Cmax) and daily trough concentration (Cmin) were determined based on the doses and pharmacokinetic samples in the data in conjunction with a previously developed PK model (in-house data). Demographic information on the data can be found in table 1.

Table 1. Demographics. Weight, age and seizure frequency per day and trough, average and peak concentrations as mean (standard deviation). For each AED co-medication, number of patients receiving that AED is given with the dose range (mg/day) in brackets. Only co-medications received by at least 10 patients in the total data are listed.

Seizure type	PO	PO	PGTC	PGTC	Both	Both	Total
Number of subjects	119	116	72	74	191	190	381
Gender	Male	Female	Male	Female	Male	Female	Both
Weight (kg)	74 (19)	69.9 (21.6)	64.3 (17.4)	59.6 (14)	72.2 (19.1)	68.1 (20.9)	68.3 (19.7)
Age (years)	34.2 (13.7)	39.3 (12.6)	30.4 (13.6)	27.1 (10)	33.5 (13.8)	37.1 (13.1)	33.8 (13.4)
Seizure frequency (/day)	0.328 (1.3)	0.333 (1.4)	0.139 (0.7)	0.167 (0.5)	0.293 (1.2)	0.304 (1.3)	0.299 (1.2)
Trough concentrations (Cmin) [a]	5.296 (2.7)	5.668 (3.6)	3.307 (4.6)	3.02 (4)	4.521 (3.7)	4.67 (3.9)	5.484 (3.2)
Average concentrations (Cavg) [a]	5.789 (2.7)	6.147 (3.6)	3.634 (4.8)	3.19 (4.1)	4.949 (3.8)	5.033 (4.1)	5.97 (3.2)
Peak concentrations (Cmax) [a]	6.078 (2.7)	6.413 (3.7)	3.834 (5)	3.282 (4.2)	5.204 (3.9)	5.233 (4.2)	6.248 (3.2)
Comedications[b]:							
Carbamazepine	55 (200-1800)	43 (200-2800)	21 (200-1600)	24 (10-1000)	76 (200-1800)	67 (10-2800)	143 (10-2800)
Clobazam	7 (10-40)	4 (5-20)	8 (10-40)	6 (5-20)	15 (10-40)	10 (5-20)	25 (5-40)
Clonazepam	1 (1-1)	5 (0-4)	5 (0-175)	5 (0-13)	6 (0-175)	10 (0-13)	16 (0-175)
Levotiracetam	13 (100-5000)	10 (500-4000)	1 (2000-2000)	2 (2000-3000)	14 (100-5000)	12 (500-4000)	26 (100-5000)
Oxcarbazepine	15 (300-3000)	20 (150-2400)	1 (600-600)	6 (450-1950)	16 (300-3000)	26 (150-2400)	42 (150-3000)
Phenobarbital	8 (15-468)	7 (60-600)	7 (60-400)	7 (100-200)	15 (15-468)	14 (60-600)	29 (15-600)
Phenytoin	16 (200-700)	20 (200-800)	32 (200-700)	14 (200-400)	48 (200-700)	34 (200-800)	82 (200-800)
Primidone	4 (125-1000)	1 (1500-1500)	2 (625-875)	4 (750-1125)	6 (125-1000)	5 (750-1500)	11 (125-1500)
Topiramate	18 (25-550)	21 (25-700)	4 (100-550)	10 (25-250)	22 (25-550)	31 (25-700)	53 (25-700)
Valproate	37 (400-2500)	30 (500-3000)	26 (500-3000)	42 (250-2100)	63 (400-3000)	72 (250-3000)	135 (250-3000)

[a]Trough, average, and peak concentrations based on individual parameters and doses during continuation phase of the studies, i.e. after dose titration. [b]Dose range for clobazam and clonazepam are listed in mcg/day, for all others dose ranges are in mg/day. POS: Partial-onset type seizures. PGTC: Primary generalised tonic-clonic seizures.

Model description and evaluation

All models were implemented in NONMEM© v7.2 [12], parameters were estimated using the SAEM algorithm, with NBURN set to 1000 and NITER set to 300. Model pre- and post-processing, and graphical and statistical analysis was done in a modelling environment consisting of Piraña 2.9.0 [13], PsN v3.5.3 [14], and R v3.1.1 [15]. Seizure counts were modelled as a Poisson distribution consisting of the parameter lambda (λ), which describes both the distribution mean and variance of event counts (i.e. seizures per day), with overdispersion (i.e. disparity between mean and variance of lambda) taken into account by an extra parameter (*OVDP*). If *n* is the number of events, the probability of observation *Y* in individual *i* at time *j* being count *n* is given by equation 1. The factorial *n!* is approximated using the Stirling approximation (equation 2), in the model transformed to the log-scale. Time-dependent changes in lambda were modelled using two different, but complementary methods. The first method estimates different lambdas based on whether the patient experienced seizures (PDV>0) or no seizures (PDV=0) on the directly preceding day [10]. Method two uses stochastic differential equations, as recently was proposed [16,17], to allow changes of lambda at each time point based on a random Brownian motion (equation 3). In all models, changes in lambda due to placebo effect and treatment effect were taken into account as defined in equation 4, with treatment effect modelled using the typical Emax model (equation 5) where Cmin, Cmax, and Cavg were tested for C_x and compared to a model using dose as the predictor of effect. EC_{50} is the concentration of lamotrigine at which 50% of the maximum effect (Emax) is reached. Variability of each parameter *x* was modelled in an additive manner on the log scale, corresponding to a log-normal distribution of parameters on the normal scale (equation 6).

$$P(Y_{ij} = n) = \frac{\lambda^n}{n!} * e^{-\lambda} \quad (1)$$

$$n! \sim \sqrt{(2\pi n)} \cdot \left(\frac{n}{\mathrm{e}}\right)^n \quad (2)$$

$$d\lambda_{i,t} = f(\lambda_{i,t}, x_{i,t}, \psi_i)dt + \sigma_w dw_{i,t}, \quad w_{i,t} - w_{i,s} \in N(0, |t-s|I) \quad (3)$$

$$\lambda = e^{\lambda^{Baseline}+\lambda^{Placebo}+\lambda^{Lamotrigine}} \quad (4)$$

$$\lambda^{Lamotrigine} = \frac{E_{max}*{C_x}^{\gamma}}{{EC_{50}}^{\gamma}+{C_x}^{\gamma}} \quad (5)$$

$$\log(Parameter_{x,i}) = \theta_x + \eta_i \quad (6)$$

The statistical significance of model changes and introduction of covariates was determined by a chi-squared test of a reduction in the objective function value (OFV), with a decrease in OFV of 3.84 corresponding to a statistical significance of $p<0.05$. Model fits were evaluated by goodness of fit plots of difference between observed and predicted seizure counts (residuals), observed vs predicted cumulative seizure counts, and observed vs predicted overdispersion. Accuracy of parameter values were determined by the covariance step.

3. Results

Model development

Changes in OFV for all modelling steps, separately for patients with either PO or PGTC seizures are listed in table 2. The models with SDEs generally performed better than those without, at the cost of model run time, with a decrease in OFV for patients with PO, but not with PGTC seizures. The use of SDEs allowed the characterisation of the change in lambda over time, but did not reveal generalisable patterns. Not including a factor for overdispersion or Markovian features greatly worsened the OFV in all cases. Parameter values are shown on the log-scale in table 2. Parameter values for baseline seizure activity and overdispersion were very comparable between the non-SDE and SDE models, whereas those for placebo effect, maximum treatment effect (Emax), and the concentration at which 50% of Emax is reached (EC_{50}) differed significantly. Baseline seizure activity (lambda) as estimated by the non-SDE model was more than twice as high in patients with PO seizures (0.371 when PDV>0, 0.295 when PDV=0) compared to those with PGTC seizures (0.150 when PDV>0, or 0.125 when PDV=0), corresponding well with average seizure frequencies as reported in

table 1. The placebo and treatment effect differed largely depending on the use of SDEs. Without SDEs, the placebo effect resulted in a 21.9% (PO) or 36.9% (PGTC) decrease in lambda, while using SDEs gave a placebo effect of 13.8% (PO) or 22.9% (PGTC) decrease in lambda. The maximum treatment effect was high in all cases, with a mean 99.2% (PO) or 98.3% (PGTC) decrease in lambda (not using SDEs), and a 81.0% (PO) or 99.8% (PGTC) decrease (using SDEs) in lambda. Using different exposure measures (Cmax, Cavg, Cmin) had mixed results, but Cmin most consistantly outperformed the other measures. EC_{50} was found to be lower in patients with primary generalised tonic-clonic seizures (5.99 mg/L) compared to those with partial-onset type seizures (13.1 mg/L), when not using SDEs, whereas EC_{50} was higher for PGTC (18.9 mg/L) compared to PO (9.87 mg/L) when using SDEs. Due to better model stability and smaller shrinkage in etas, the model without SDE's was considered the better model for the purpose of our investigation. **Figure 1** shows the estimated correlations between lamotrigine effect (as a percentage of the maximum effect E_{max}) and concentration (in mg/L) in the upper panels, and the corresponding change in seizure frequency (lambda) in the lower panels. Due to the exponentiation in equation 4 for lambda, a lamotrigine concentration at EC_{50} does not result in a 50% reduction in lambda. Although the values for EC_{50} and Emax were estimated quite differently between the models without and with SDE, the impact on lambda is fairly similar for PGTC, while for PO a large difference can be observed. An attempt at estimating a mixture model to have a portion of the population not showing any efficacy ($\lambda^{lamotrigine}$=0) resulted in model instability and the inability to estimate any variability on placebo and treatment effect. The inclusion of a Hill factor (γ) to estimate the slope of the Emax equation resulted in a value close to 1 (i.e. no change in slope compared to the equation without the Hill factor) and was thus left out. An alternative, more flexible parameterisation of the drug effect as a percentage reduction in lambda on the normal scale did not lead to an improvement in OFV or goodness-of-fit and was thus abandoned. Only when not using SDEs, a slightly higher median EC_{50} was found in patients with PO seizures concurrently receiving valproic acid compared to those who did not (12.6 vs 10.9 mg/L respectively), but this difference was estimated with high imprecision (RSE of 131%), hence it was not included as

a covariate. Variability was large on all parameters, with high shrinkage observed on variabilities associated with effect parameters. While this would normally be sufficient reason to discard those variabilities, doing so resulted in a large increase in OFV and diminished goodness-of-fit of individual seizure counts. Plotting these eta's revealed heavy-tailed distributions, which may explain high shrinkage. Adjusting for the heavy tails by a semi-parametric approach [18] did not improve their description, nor the OFV. The distribution of eta's for overdispersion revealed a bi-modal distribution, attempts to describe this using mixture modelling of two separate distributions, resulted in the likelihood for one of the distributions approaching 1, and an increase in OFV, and was therefore not used in the final model. Using the placebo dose to describe the magnitude of placebo effect in the non-SDE model resulted in an improved OFV for PGTC, with an EPB50 at 50 mg/day, but this did not explain variability on the placebo effect and resulted in instability in the SDE model. This was therefore considered a spurious finding. Estimation for an interaction term between placebo and treatment effect for the period in which placebo and treatment overlapped in PO patients, revealed a very small, but statistically significant impact (up to 1% reduction in lambda). The clinical relevance of such an interaction term was deemed minimal and was therefore not included in the final model. **Figure 2** shows the goodness-of-fit plots for the model that included SDEs. Residuals of predicted and observed seizure counts showed no evident bias over time, but large differences remain between observed and predicted number of seizures due to randomness (lower and upper left panel). However, cumulative numbers of seizures were predicted well for most patients (upper right panel). Dispersion, or mismatch between mean and variance of seizure counts, was well described in all but a few patients, with no predictors for the outliers (lower right panel).

Table 2. Summary of the objective function values for the different model structures that have been evaluated. Statistically significant decreases in OFV (ΔOFV) are highlighted.

Model description	Non-SDE OFV (ΔOFV)		SDE (ΔOFV)	
	PO	PGTC	PO	PGTC
Base model	113095.8 (0)	19398.3 (0)	112588.3 (0)	19669.5 (0)
Without overdispersion factor	127412.7 (14316.9)	20075.6 (677.3)	126893.5 (14305.2)	20285.4 (615.9)
Without Markov factor				
Cmax for Cx	113056.3 (-39.5)	19594.6 (196.3)	112576.1 (-12.2)	19789.8 (120.3)
Cavg for Cx	113049.8 (-46)	19598.7 (200.4)	112525.5 (-62.8)	17690.7 (-1978.8)
Cmin for Cx	113039.8 (-56)	16685.6 (-2712.7)	112480.3 (-108)	19818.7 (149.2)
Interaction EPB & ETMT	113500.5 (404.7)	-	111802.2 (-786.1)	-
Mixture model ETMT	113079.5 (-16.3)	18905.2 (-493.1)	112061.6 (-526.7)	13921.6 (-5747.9)
EC50 VPA addition	113058.4 (-37.4)	19634.9 (236.6)	112946.8 (358.5)	-
Placebo dose EPB50	113994.4 (898.6)	18637.2 (-761.1)	113094.1 (505.8)	-
Mixture model OVDP	112758.3 (-337.5)	18740.3 (-658)	111771.3 (-817)	18121 (-1548.5)
T-distribution eta's	113307.4 (211.6)	19601.3 (203)	112737.2 (148.9)	19868.1 (198.6)
Covariance LBASE & ETMT	112890 (-205.8)	19499 (100.7)	112397.1 (-191.2)	19704.7 (35.2)

PO: Partial onset seizures; PGTC: Primary generalised tonic clonic seizures; SDE: models using stochastic differential equations; Non-SDE: models not using SDEs; Cmax: maximum daily concentrations; Cavg: average daily concentration(s); Cmin: minimum daily concentrations.

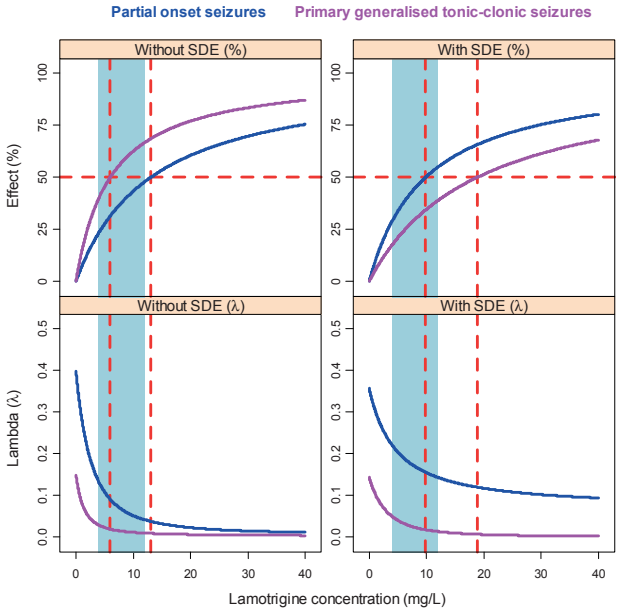

Figure 1. Effect as a percentage of maximum effect (upper panels) and change in lambda (lower panels) versus lamotrigine concentration (in mg/L) for patients with partial onset seizures (blue lines) and primary generalised tonic-clonic seizures (magenta lines) based on the estimates of baseline lambda (when the previous day seizure count>0), Emax and EC_{50} using the model without (left panels) and with (right panels) stochastic differential equations (SDE). The therapeutic window is shown in a blue shaded area.

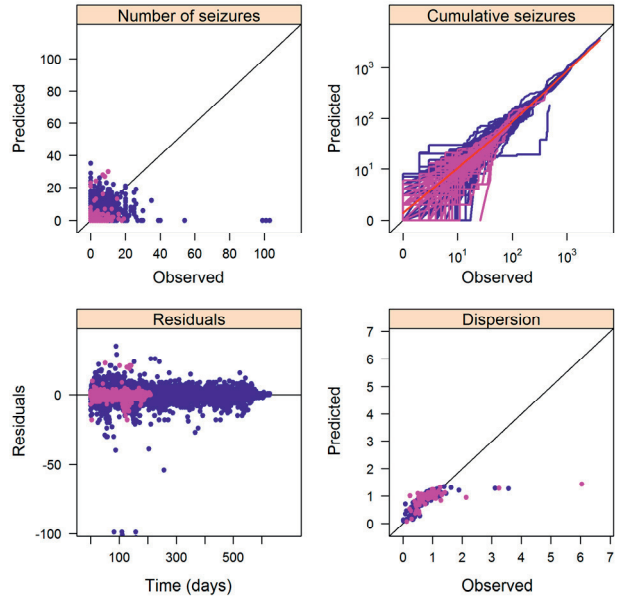

Figure 2. Goodness-of-fit plots for the final model not using stochastic differential equations for patients with PO (blue) and PGTC (magenta) seizure types. The red line in the upper right panel shows a loess fit of the cumulative observed versus predicted seizures.

Table 3. Parameter values for the models with and without stochastic differential equations (SDE). SGW and RV are SDE-specific parameters relating to the degree of intra-individual variability in lambda (equation 3). All parameter values are on the log-scale as they were defined in the model.

	Without SDE		With SDE	
Population parameter	PO [%RSE]	PGTC [%RSE]	PO [%RSE]	PGTC [%RSE]
Lambda (PDV>0)	-0.992 [8]	-1.90 [8]	-1.03 [13]	-1.94 [9]
Lambda (PDV=0)	-1.22 [5]	-2.08 [5]	-1.21 [8]	-2.00 [4]
SGW	-	-	-0.00370 [2]	-0.00330 [10]
RV	-	-	1† [-]	1† [-]
OVDP	-1.26 [14]	-2.28 [21]	-1.07 [21]	-1.78 [28]
EPB	-0.247 [19]	-0.460 [21]	-0.149 [32]	-0.260 [48]
Emax	-4.70 [7]	-4.08 [23]	-1.66 [17]	-6.05 [41]
EC50	2.57 [6]	1.79 [29]	2.29 [17]	2.94 [28]
Variance as Ω^2 (% shrinkage)				
Lambda (PDV>0)	1.31 [7] (10)	1.26 [10] (24)	1.23 [8] (11)	1.32 [13] (27)
Lambda (PDV=0)	0.613 [6] (7)	0.533 [10] (12)	0.623 [7] (9)	0.438 [11] (18)
OVDP	7.70 [8] (15)	11.7 [21] (31)	7.25 [9] (14)	10.3 [21] (30)
EPB	0.0912 [13] (53)	0.218 [15] (49)	0.0621 [16] (60)	0.259 [19] (55)
Emax	11.8 [10] (29)	5.84 [25] (56)	2.08 [14] (43)	7.28 [72] (82)
EC50	1.58 [11] (34)	2.36 [26] (53)	3.59 [19] (49)	5.94 [34] (52)

† Fixed to a value of 1, due to unidentifiability, see also Deng et al [17]. All parameters are on the log-scale.

4. Discussion

Our aim was to use novel PD modelling approaches that can handle count data and determine if the exposure-response of adjunctive lamotrigine therapy in adult patients differs between partial onset and primary generalised tonic-clonic seizures. The data was well-described with a Poisson model with overdispersion, Markov, and stochastic differential equation (SDE) extensions. Despite the relatively short duration of the studies available for our analysis, the use of SDEs allowed us to directly observe changes in the underlying parameter lambda over time, making it possible to visually inspect time-varying treatment response, and the delay in effect. While variability in baseline disease activity and placebo effect seems to reflect common biological variation, our analysis suggests that variability in maximum efficacy is very large. As a consequence, individual prediction of response in the clinic may not be possible before start of treatment. However, it may be feasible to estimate an individual's lamotrigine potency (EC_{50}) and maximum effect during the titration phase, allowing the prediction of an optimal individual exposure level for maintenance therapy, thereby possibly shortening titration times. Estimates of lambda were similar to those directly calculated. Overdispersion of seizures in patients with PGTC was higher than that in PO, which could also be observed from the larger variance of seizures in the data. Placebo effect was estimated to be a clinically relevant factor and was found to be more than twice as high in PGTC patients compared to PO patients. However, it was still was much lower than half the maximum treatment effect. The EC_{50} of PGTC changed drastically by the use of SDEs, suggesting that part of the observed treatment effect could be explained by an improvement in the disease instead of a treatment effect.

Our models included factors for overdispersion and Markov features, which improved the description of the data. An alternative method, which reportedly handles overdispersion without the need for extensions, is the hidden Markov (Poisson) model (HMM), which separates observed seizure counts from hidden transitions between disease activity states [8]. Such an

HMM has theoretical promise in terms of mapping underlying disease states to observed seizures, but when briefly explored, it did not offer advantages in terms of predictive properties compared to the Poisson model with overdispersion, Markov features and SDEs, and was thus not further investigated. The lack of improvement seen when applying a HMM may be explained by a lack of mismatch between observed seizures and underlying disease state switches in our data, or other features in our data were more well-described using our model. The integration of a HMM with SDEs may allow to investigate such hypotheses, but was considered beyond the current scope.

Our models could be used for clinical trial simulations (CTS) to investigate new clinical trial protocols involving lamotrigine, for example in patient populations or settings in which the lamotrigine exposure-response is yet to be determined (e.g. patients younger than 16 years; patients receiving monotherapy). CTS may also be used to explore trial protocols involving other AEDs to explore the impact of trial design choices on the ability to determine its exposure-response, depending on different possible drug properties. Furthermore, it has been posited that placebo response is similar between clinical trials, thus allowing the simulation of a virtual placebo trial arm, which considerably reduces burden on patients and trial resources. In the case of uncertainty on the placebo effect (or variability thereof), a reduced sample of confirmatory placebo control subjects could be included, instead of the one-to-one randomisation scheme as used in most trials. It should be noted that, as our model was based on data of patients receiving lamotrigine as adjunctive therapy, the observed placebo effect, and potency and maximum effect of lamotrigine may not necessarily be applicable to settings of lamotrigine or AEDs as single primary therapy. However, given the lack of (differences in) interaction between LMT and the existing treatments in our populations, and the large maximum LMT efficacy observed in this otherwise treatment resistant population, extrapolation of our findings to treatment naïve patients may perhaps be feasible.

The target dose of LMT in adults receiving monotherapy is 200 mg per day, whereas those patients receiving concomitant valproic acid, resulting in

reduced LMT clearance, should receive 100 mg of LMT per day and those receiving LMT clearance inducers such as carbamazepine, phenobarbital, and phenytoin should receive 400 mg of LMT per day. To reduce seizure activity from baseline by at least 50%, a steady-state LMT concentration of 2.3 or 1.3 mg/L is required for PO or PGTC seizures respectively, corresponding to an LMT dose of 125 or 70 mg per day respectively (for a typical 70-kg adult patient). However, for higher reductions of seizure activity, increasingly higher steady-state concentrations and thus higher doses are required. Based on our findings here, we may stratify for epilepsy type and baseline seizure activity to derive more specific dosing recommendations (Table 4). Our data was based on studies in patients whom already showed insufficient response to other AEDs, therefore, setting our target to full seizure freedom was not feasible, as the maximum efficacy of LMT based on our population estimates leads to a reduction of seizure activity to slightly more than one every year. Instead, doses given in this table are based on the need to reduce seizure activity (lambda) to below one per month. As can be observed from Table 4, recommended doses required to achieve the pre-set reduction in those with seizure frequencies above 1 every 2 days become increasingly potentially toxic. In treatment-naïve patients, setting the treatment goal to complete seizure freedom should still be the norm.

Our recommendations are derived from population estimates of parameters, thus adjustments may still be needed in the individual patient, and given the large variability on Emax, a significant portion of patients may still perform better than expected.

Table 4. Implementation of a model-based dosing algorithm. In this table we illustrate how seizure frequency at the start of treatment can be used as covariate for dose selection. Doses were rounded to possible combinations of the nearest possible tablet strengths available for extended-release lamotrigine, which are 25, 50, 100, and 200 mg. Doses should be multiplied by 0.5 (halved) when given in combination with valproic acid, and multiplied by 1.76 for comedication with carbamazepine or 2.29 for comedication with phenytoin.

Seizure frequency (day^{-1})	Dose for PO seizures (mg/day)	Dose for PGTC seizures (mg/day)
0.1	200	125
0.2	450	250
0.3	600	375
0.4-0.6	800-1100	500-775
0.7-0.9	1200-1650	950-1350

5. Conclusion

We have shown that the use of a drug-disease model along with appropriate data integration does allow the characterisation of exposure-response relationships for lamotrigine. We have done so by illustrating the performance of different approaches, all of which appear to describe the time course of seizure activity before and after administration of a treatment (i.e., placebo and lamotrigine) in PO and PGTC patients. Clinically, our analysis reveals the implications of interindividual seizure frequency for the choice of dose. Given the large interindividual variability in maximum response, our analysis also makes clear that treatment optimisation in the clinic does require close monitoring of the patient during titration before conclusive recommendations can be made for optimisation of the regimen. The applicability and validity of these findings need to be confirmed in prospective studies, including different seizure types.

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CHAPTER 8

EXPOSURE-RESPONSE RELATIONSHIP AND DOSE RATIONALE FOR LAMOTRIGINE IN CHILDREN AGED 1-24 MONTHS