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

Dijkman, S.C. van

The research leading to this thesis has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 261060 (Global Research in Paediatrics – GRiP Network of Excellence). The work was performed at the Division of Pharmacology of the Leiden Academic Centre for Drug Research, Leiden University, Leiden, The Netherlands.

The printing of this thesis was supported by:

GlaxoSmithKline
Juhl Family Farm

Cover and layout by Kate Juhl
Printed by Ipskamp Printing

ISBN: 978-94-028-0838-4

PERSONALISED PHARMACOTHERAPY IN PAEDIATRIC EPILEPSY:

THE PATH TO RATIONAL DRUG AND DOSE SELECTION

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden
op gezag van Rector Magnificus prof. mr. C.J.J.M. Stolker
volgens besluit van het College voor Promoties
te verdedigen op woensdag 29 november 2017
klokke 10:00 uur

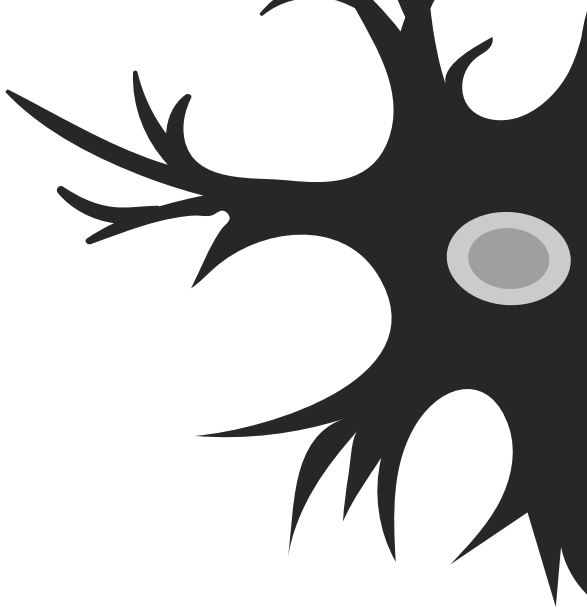
door

Sven Christiaan van Dijkman

geboren te Amsterdam, Nederland
in 1984

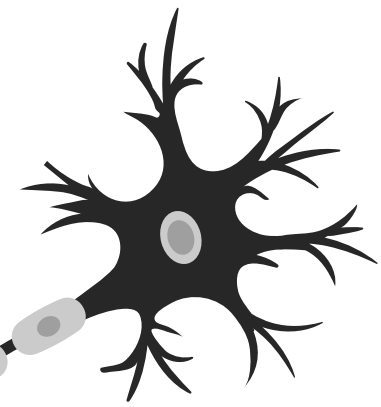
Promotor	Prof. Dr. M. Danhof	Universiteit Leiden
Co-promotor	Prof. Dr. O.E. Della Pasqua	University College London
Promotiecommissie	Prof. Dr. H. Irth, voorzitter	Universiteit Leiden
	Prof. Dr. J.A. Bouwstra, secretaris	Universiteit Leiden
	Prof. Dr. J.W. Sander	University College London
	Prof. Dr. E. Perucca	Università di Pavia
	Prof. Dr. R.A.A. Mathôt	Universiteit van Amsterdam
	Prof. Dr. C.A.J. Knibbe	Universiteit Leiden
	Prof. Dr. H.J. Guchelaar	Universiteit Leiden

TABLE OF CONTENTS



SECTION I

GENERAL INTRODUCTION



CHAPTER 1

PHARMACOTHERAPY IN PEDIATRIC EPILEPSY: FROM TRIAL AND ERROR TO RATIONAL DRUG AND DOSE SELECTION – A LONG WAY TO GO

Pharmacotherapy in pediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go

Sven C. van Dijkman, Ricardo Alvarez-Jimenez, Meindert Danhof, Oscar Della Pasqua

Expert Opinion on Drug Metabolism & Toxicology, 2016

SUMMARY

Introduction: Whereas ongoing efforts in epilepsy research focus on the underlying disease processes, the lack of a physiologically-based rationale for drug and dose selection contributes to inadequate treatment response in children. In fact, limited information on the interindividual variation in pharmacokinetics and pharmacodynamics of anti-epileptic drugs (AEDs) in children drive prescription practice, which relies primarily on dose regimens according to a mg/kg basis. Such practice has evolved despite advancements in paediatric pharmacology showing that growth and maturation processes do not correlate linearly with changes in body size. **Areas covered:** In this review we aim to provide 1) a comprehensive overview of the sources of variability in the response to AEDs, 2) insight into novel methodologies to characterise such variation and 3) recommendations for treatment personalisation. **Expert Opinion:** The use of pharmacokinetic-pharmacodynamic principles in clinical practice is hindered by the lack of biomarkers and by practical constraints in the evaluation of polytherapy. The identification of biomarkers and their validation as tools for drug development and therapeutics will require some time. Meanwhile, one should not miss the opportunity to integrate the available pharmacokinetic data with modelling and simulation concepts to prevent further delays in the development of personalised treatments for paediatric patients.

Article highlights

- Despite the development of therapeutic guidelines for the treatment of epileptic seizures, AED selection and dose rationale for children remains empirical.
- The use of dosing regimens in mg/kg does not correct for age-related changes in pharmacokinetics and pharmacodynamics in children, especially if one considers the use of polytherapy with two or more AEDs.
- Inter- and intra-individual differences in pharmacokinetics and pharmacodynamics of AEDs need to be taken into account for the personalisation of treatment in paediatric epilepsy.
- Whilst the identification of predictive biomarkers remains a challenging endeavour, quantitative clinical pharmacology methods can provide guidance for both anti-epileptic drug and dose selection. These methods allow for evidence synthesis, integration, and extrapolation of findings across different age groups, enabling better clinical decision-making and improved therapeutic response in children.

1. Introduction

Epilepsy is a debilitating syndrome with an estimated 68 million people worldwide affected by it, which places the disease in the 7th position in terms of impact on disability and premature mortality among mental health, neurological, and substance-use disorders[1,2]. In addition, it takes the 19th rank out of 53 items accounting for the total costs for medical care generated in the area of neurology [3]. Whereas global figures may differ, recent prevalence data in the USA show that nearly 25% were children aged below 15 years of age [4].

Effective treatment and management of epileptic seizures has an important and direct impact on the quality of life of patients, especially those in the paediatric group. Despite the implementation and advancement of

therapeutic guidelines, achieving such results remains a challenging objective. This situation prevails in the face of increasing understanding of the progression of the disease after onset in different age groups and introduction of regulatory requirements for the evaluation of efficacy and safety of AEDs in children [5,6].

1.1 Current drug and dose selection rationale in paediatric epilepsy

Various guidelines exist on the diagnostic, management and treatment of epilepsies. However, only a few of them have focused on the use of antiepileptic drugs (AEDs) in children [7-9]. In fact, the British National Institute for Health and Care Excellence (NICE) guideline on epilepsy in children is the only document based on extensive review of the evidence for differences in efficacy and safety of each AED between types of epilepsy [9]. Even though recommendations are supported by evidence arising from randomised controlled trials, shortcomings are still evident. Many studies have been performed to show differences in efficacy and safety between seizure types, but no effective predictors have yet been found for differences in efficacy and safety within the same seizure type. This is likely the consequence of symptom-based criteria, which remain the foundation for diagnosis and AED treatment selection. In addition, most paediatric trials rely on an "add-on approach", with patients who may have more severe or refractory forms of epilepsy, which leads to inadequate evidence regarding the efficacy of monotherapy in treatment naive patients. This shortcoming is often compounded by the definition of response (clinical endpoint) in most clinical trials, which is based on a binary measure: responder (i.e., patients who show at least 50% of reduction in seizures compared to baseline) vs. non-responder. Dichotomisation of the response into two categories can be detrimental for the characterisation of dose-exposure-response relationships, especially if one considers that pharmacokinetic data are not collected systematically in efficacy trials.

Whereas limited understanding of the exposure-response relationships might be mitigated by the clinical requirement for up and down-titration or tapering of the dose. In addition to reducing side effects and withdrawal symptoms, tapering procedures offer an opportunity to factor in the effect

of interindividual pharmacokinetic and pharmacodynamic variability. Yet, this information is not fully integrated to support treatment personalisation. Currently, most formularies still rely on anecdotal (empirical) evidence of efficacy and safety in children. Dose recommendations in formularies, such as the Netherlands *Kinderformularium* or the British National Formulary for Children overlook the role of covariate factors and other sources of variability in pharmacokinetics and pharmacodynamics [10,11]. Clearly, there is a substantial amount of pharmacokinetic data regarding the use of AED in children, but even when taking into account correlations with weight and age, unexplained variability appears to remain high [12-14]. Similar challenges are faced when considering the adjustment of maintenance doses of AEDs. In spite of the use of therapeutic drug monitoring (TDM), which is widely accepted in paediatric epilepsy compared to adults, AED levels are checked against a therapeutic window, which was originally determined in adults. Moreover, these therapeutic ranges ignore known to covariate effects, which may cause variability in exposure and potentially in the exposure-response relationship.

One should also note the impact of variability in the status of the disease at the time of diagnosis and its progression, which are a hurdle for improved therapeutics and may possibly be associated with the unnecessary exposure of paediatric patients to AEDs for years after the seizures have remitted [15]. Thus, the combination of unexplained variability in pharmacokinetics, pharmacodynamic and disease leaves clinicians without a clear dosing algorithm, other than the option to taper and adjust doses based on the clinical symptoms.

The challenges a clinician faces to select the drug and dose regimen are illustrated in numerous publications on the efficacy and safety of AEDs in children [16-18]. In the next paragraphs we will highlight how dosing algorithms can be used as a valuable therapeutic tool before switching treatment or progressing to polytherapy.

1.2 Personalised treatment of epileptic seizures: advancing clinical practice

The ultimate goal of a (personalised) therapeutic intervention is to ensure a positive, if not optimal, balance between the expected benefits and risks of the treatment , taking into account the costs and the inherent uncertainties about favourable and unfavourable effects [19, 20]. This concept is particularly relevant when dealing with chronic diseases such as epilepsy, but little effort has been made to evaluate the impact of a one-size fits all approach on the overall effectiveness of antiepileptic drugs. In fact, one needs to recognise that heterogeneity in the disease makes it a case for exploring treatment options beyond current guidelines. For instance, some patients may achieve complete seizure remission with higher doses before adding on a second drug, but evaluation of higher doses requires more than empirical titration. It should be guided by dosing algorithms, which take into account the role covariate factors associated with inter- and intra-individual variability in pharmacokinetics and pharmacodynamics.

Unfortunately, formal assessment of the advantages of dosing algorithms for personalised treatment with AEDs is fraught with difficulties as it imposes the evaluation of changes in the benefit-risk balance (BRB). The determination of the BRB of a treatment requires precise, detailed information on the relationships between the dose, exposure and its favourable and unfavourable effects on the symptoms and signs of the disease. Given that the BRB of AEDs is not characterised in a quantitative manner during drug development, evidence arising from clinical practice may be too limited to allow accurate decision-making. Consequently, establishing criteria for the choice of the drug and the dose for the treatment of epileptic seizures in children cannot be performed adequately without quantifying the contribution of different sources of variability to heterogeneity in PK, PD, and disease, as discussed in previous paragraphs. Opportunities exist however to explore each of these factors (one by one and in combination) and subsequently evaluate the implications of different treatment options on the overall BRB. This can be achieved by means of model-based meta-analytical approaches including extrapolation and

simulation scenarios in which patient characteristics, drug properties and disease features are integrated [19,21,22].

The aims of this review are therefore to 1) discuss the impact of known sources of variability in PK, PD, and disease and 2) explore how quantitative clinical pharmacology concepts can be used to support the development of dosing algorithms to ensure that treatment choice and dosing rationale for paediatric patients are as effective as possible. We show that some improvement may be achieved in spite of the limitations of current diagnosis criteria, lack of biomarkers and poor understanding of the mechanisms of action of AEDs. To this end, a structured literature search was performed in conjunction with supporting material from clinical guidelines and regulatory documentation on the assessment of efficacy and safety of drugs in the paediatric population. The Pubmed search included MESH terms as well as individual and combined keywords. An overview of the initial search strategy is provided in Figure 1, where selection criteria are listed in a hierarchical manner to capture publications describing paediatric epilepsy, personalisation of treatment, pharmacokinetics, pharmacodynamics, pharmacogenetics, and biomarkers. Reviews as well as perspective papers were included in the analysis if relevant paediatric details were provided. When necessary, a separate search algorithm was used to identify publications on specific issues such as methodologies for data extrapolation and assessment of benefit-risk balance in children. If no relevant literature was retrieved, additional terms were included or excluded. The initial search resulted in a total of 145 articles, of which 56 were selected after screening the abstracts for relevance. These were complemented by an additional 70 publications, which were obtained from secondary queries and interactions with experts in paediatric clinical pharmacology.

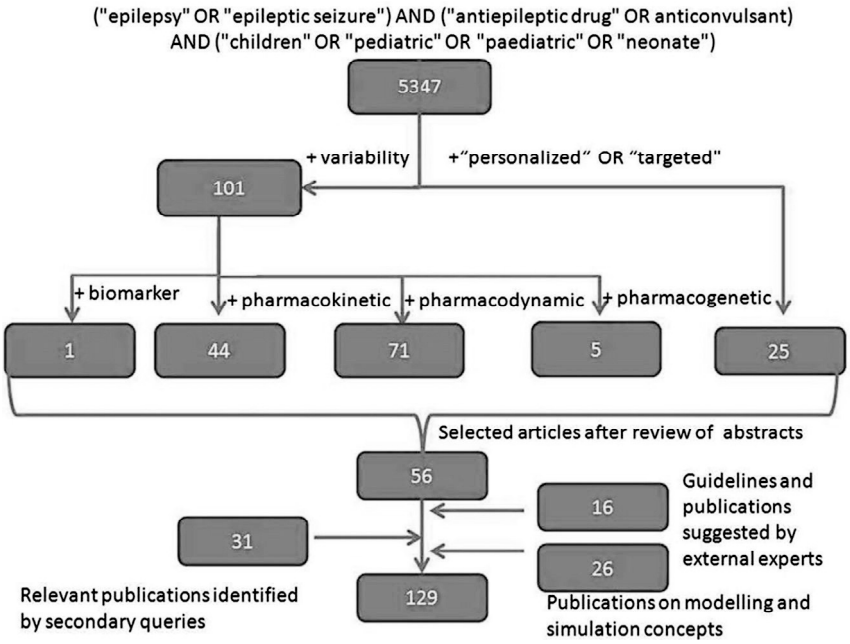


Figure 1. The diagram depicts the search strategy, including MESH terms and keywords used to select the publications included in this review.

2. Intrinsic sources of variability and heterogeneity in response to AEDs

Numerous hurdles have contributed to the emphasis in current practice regarding the use of seizure reduction (i.e., clinical response) for switching treatment and monitoring of systemic drug levels as the basis for modifying or individualising the dose and dosing regimen. Sadly, the notion that plasma levels, even at steady state, may not reflect differences in target exposure or pharmacodynamics is unfamiliar to most prescribing physician. This limitation is also critical for the development of new AEDs, as the evaluation of dose-response in clinical trials relies primarily on the assumption of target plasma levels and a predefined therapeutic range. In the next sections, we will discuss the implications of variability in pharmacokinetics, pharmacodynamics and in relevant physiological factors for the personalisation of treatment.

2.1 Pharmacokinetics

The pharmacokinetics of a drug is determined by up to four physiological processes, namely absorption, distribution, metabolism and excretion (ADME). Metabolism and excretion are usually summarised by systemic clearance (plasma volume being cleared of the drug per time unit; CL). Summary measures of drug disposition is often limited to the so-called secondary pharmacokinetics parameters such as peak concentration (Cmax), trough concentration (Cmin), and mean steady state (Css/Cavg) concentrations, as well as the area under the concentration vs. time curve (AUC). It is important to note that secondary parameters are derived from primary PK parameters. For instance, following extravascular administration, peak concentrations depend on absorption rate, and volume of distribution, whilst Css and AUC are directly related to clearance. From a therapeutic perspective, response to AEDs is most likely explained by the average exposure or trough concentrations, with acute and some chronic side effects primarily being determined by peak concentrations. Hence, variability in the processes that determine drug disposition may affect treatment response. In this respect, one needs to consider that some of these ADME processes are incomplete or immature at birth and young age, especially in pre-term infants [23,24] (Table 1). Despite the impact of these factors on drug exposure, in most cases they are not included into the dose rationale for children.

Details on the differences in the pharmacokinetics of specific AEDs in children can be found elsewhere [23, 25]. In the next paragraphs we describe the main factors determining the differences in ADME between adults and children, and overall variability in the PK of AEDs.

Table 1. Pharmacokinetic characteristics of commonly used antiepileptic drugs (*adapted from [24]*).

Drug	Time to steady state (d)	Half-life (h)	Tentative therapeutic range[a]		Major route of elimination
			(µmol/L)	(µg/mL)	
Felbamate	3-5	14-22	125-250	30-60	Oxidation and renal excretion
Gabapentin	2	5-7	70-120	12-20	Renal excretion
Lamotrigine	3-15	8-33	10-60	2.5-15	Glucuronide conjugation
Levetiracetam	2	7-8	35-120	8-26	Renal excretion and hydrolysis
Oxcarbazepine	2-3	8-15	50-140[b]	12-35	Keto-reduction, then glucuronide conjugation of MHD
Pregabalin	2	6-7	NE	2.8-8.2	Renal excretion
Tiagabine	2	7-9	50-250[c]	20-100[d]	Oxidation
Topiramate	4-6	20-30	15-60	5-20	Renal excretion, oxidation
Vigabatrin	1-2	5-8	NA	NA	Renal excretion
Zonisamide	5-12	50-70	45-180	10-38	Glucuronide conjugation, acetytation, oxidation and renal excretion

a The lower limit of the therapeutic range is of limited value, because many patients do well at serum concentrations below this limit.
b Monohydroxy derivative.
c nmol/L.
d ng/mL.
MHD = monohydroxy metabolite; **NA** = not applicable; **NE** = not established

2.1.1 Drug distribution: differences between plasma and target site concentrations

Plasma protein binding can be an important factor determining differences in pharmacokinetics, both with respect to drug distribution and clearance. In theory, only unbound drug concentrations distribute to the brain. Some authors have focused therefore on the free concentrations or free fraction of AEDs (for example carbamazepine [26], phenytoin [27], valproate [28]). In these publications, the free plasma concentration of the drug was found to better reflect the concentrations of the extracellular space and the brain's interstitial fluid. However, brain distribution can be complex and variable depending on factors related to active transport mechanisms, disease-related changes in tissue permeability and other co-morbidities. For instance, Clinkers et al. studied the influence of epileptic seizures on the concentration of oxcarbazepine in the hippocampus and in plasma in a rat

model. [29]. Concentrations reached higher values in the interstitial space within the pilocarpine-induced acute seizures region and were even higher when oxcarbazepine was given in combination with a P-glycoprotein (Pgp) inhibitor. Most importantly, these differences were observed without significant changes in drug levels in plasma. These results illustrate the complex role of the functioning of the blood brain barrier (BBB) as a determinant of the target exposure. Indeed, up-regulation of the efflux transporter Pgp has been indicated as one of the possible explanations for the development of apparent tolerance [30].

Whereas active transport processes may determine tissue distribution, high variability in drug exposure can exist even between closely located areas in the brain. This was already described in 1978 in patients who had surgery after receiving carbamazepine in regular stable doses [31]. Rambeck et al. [32] analysed plasma, cerebrospinal fluid (CSF) and extracellular space (ECS) concentrations in to-be-excised live temporal brain tissue (*in vivo* with a microdialysis probe and *ex vivo* directly in the removed tissue) in patients refractory to treatment. As expected, brain extra-cellular concentrations were lower compared to plasma and CSF, which demonstrates that the assumption of equal concentrations in CSF and ECS in one well distributed homogenous compartment is unjustified [33]. A general lack of information regarding differences in drug distribution in children, and particularly in infants and toddlers, (i.e., in the developing brain), as compared to adults renders the interpretation of treatment failure quite challenging, as lack of efficacy may not be a matter of refractoriness to therapy, but rather a pharmacokinetic problem.

2.1.2 Clearance: influence of genotype, size, and maturation

Inter-individual, and intra-individual variability in drug elimination processes mostly results from differences in the availability of the drug at the clearing organ, changes in the clearing capacity due to varying intrinsic clearance, and the size of the organ.
Although it is known that organ perfusion varies with age [34], specific quantitative information regarding hepatic and renal changes are still sparse in some groups of the pediatric population. Consequently, it is unclear to what degree variability in organ perfusion determines the changes in clearance between adults and children. Similarly, very limited information is available regarding AED protein binding in young children and its implications for differences in systemic clearance between adults and children [35,36].

Intrinsic clearance can also be influenced by polymorphisms in genes coding for metabolising enzymes which may lead to significant differences in hepatic clearance of many AEDs [37], with increase or reduction in metabolic capacity resulting in different phenotypes [38]. Similarly, renal clearance can be affected by differences in the expression level of renal transporters [39,40]. Whilst the impact of such genetic differences can be accounted for when defining the dose and dosing regimen, genotyping or phenotyping are not used in standard practice when initiating or changing therapy, and is most probably not encouraged in children. Apart from the differences in the genetic make-up of the clearing organ, age-dependent changes also affect the amount of drug that can be cleared. As a child grows organs develop both in terms of size and metabolic capacity (i.e., enzyme activity). It has been postulated that the influence of increasing size on clearance can, at least in part, be accounted for by adjusting for body weight. However, the relation between size (e.g. body weight) and elimination rate has been demonstrated to be non-linear. This implies that dosing in mg/kg does not accurately correct for the underlying differences [41]. In fact, unless explicit differences have been identified in the underlying pharmacokinetic-pharmacodynamic relationship, dose adjustment in children should aim at achieving comparable exposure or similar PK p rofile across the target population, irrespective of body

weight or age. One needs to be aware that whereas the use of weight-banded dosing regimens may be necessary to compensate for such nonlinearity, drug-drug interactions may have a higher impact on clearance than the effect of body size (Figure 2) [42–45].

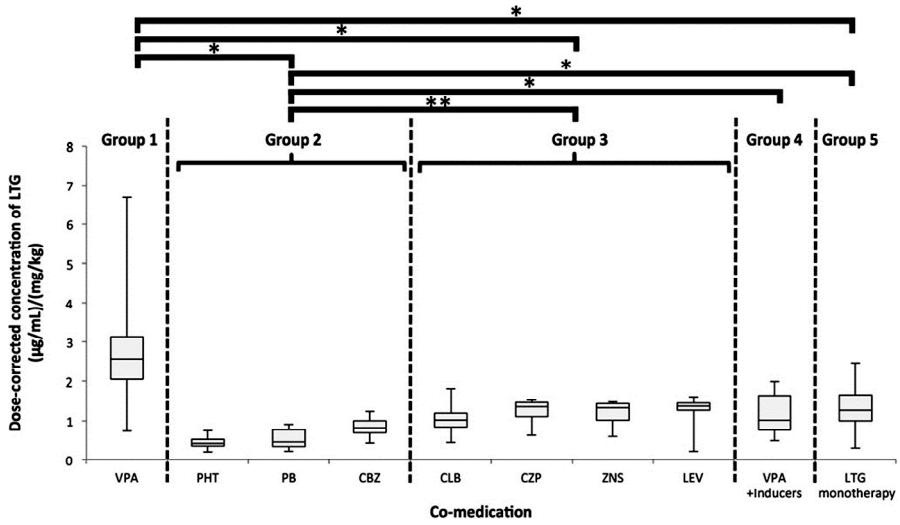


Figure 2. An example of the complex interaction between multiple covariates on the clearance of lamotrigine. In this diagram lamotrigine dose-corrected concentrations (DCC) are stratified by groups: Group 1, samples with VPA co-medication; Group 2, samples with LTG metabolic inducers (inducers) (CBZ, PHT, or PB); Group 3, samples with antiepileptic drugs other than VPA and inducers (CBZ, PHT, or PB); Group 4, samples with VPA and inducers (CBZ, PHT, or PB); and Group 5, samples with LTG monotherapy. The bottom and top of each box show the 25th and 75th percentiles, respectively. The horizontal line in each box indicates the median. The groups are indicated by the dotted lines. The horizontal lines in the upper part of the figure indicate significant differences between groups (*$p < 0.001$, **$p = 0.01$). Among patients with VPA (Group 1) and inducers (Group 2), the DCC of LTG is lower in cases under 6 years old (*adapted from [42]*)

2.2 Pathophysiology and pharmacodynamics

Every brain is unique in its structure, connectivity, plasticity, and neurotransmitter homeostasis. As a result, wide intra- and inter-individual variation is observed in the response to CNS active drugs. Differences in physiology, whether genetic, congenital or acquired, can both give rise to epileptic seizures and affect one's ability to respond to treatment. In fact, over the course of the disease, these differences as well as the progression of the underlying (patho-)physiological processes can change the way the brain responds to seizures, and consequently to therapy. In other words, variability in physiology begets variability in disease progression and treatment response, which in turn beget changes in physiology. Disentangling this circular web of interactions is perhaps the most challenging of the issues plaguing the field of AED therapy. Whereas characterising such interactions on an individual patient level may be unrealistic in the foreseeable future, personalisation of treatment may be achieved by identifying disease-specific factors that are age-related or common to subgroups in the population. The impact of such concepts has been illustrated in a recent investigation by Pellock and collaborators who showed that evidence of efficacy in partial-onset seizures (POS) in adults can be used to predict drug response in children [5]. Yet, in other childhood epilepsies that persist or evolve to adulthood, changes in pathophysiology are not yet understood well enough to allow individual prediction of outcome.

Another challenging aspect in the characterisation of interindividual differences is the nature of the interaction between drug and receptor or target. From a pharmacological point of view, pharmacodynamics (PD) describes the interaction between a drug and its target or receptor and the transduction mechanisms leading to a change in function. PD processes are a major determinant of the efficacy/safety profile of AEDs, but little is known about their (molecular) mechanisms. This is partly due to the fact that most AEDs have been discovered on the basis of phenotypic screening at a time when brain imaging and other innovative functional protocols were not available. Moreover, drug development in epilepsy has traditionally aimed at evaluating efficacy in adults. Only recently, changes in

regulatory requirements have defined the need to characterise the efficacy and safety of AEDs in children. Such a sequential approach may however be inappropriate to address childhood-specific epilepsies.

2.2.1 Assessment of anti-epileptic drug response: symptoms *versus* functional measures of brain activity

In spite of the advances in imaging technologies, the evaluation of brain physiology *in vivo* remains a challenging undertaking. Although EEG is regularly used to identify pathological signs and confirm diagnosis, patients are not routinely subjected to a long-term biochemical and/or electrophysiological evaluation throughout the course of the disease and its treatment. Medical history (i.e. occurrence of seizures) rather than measurement of physiological endpoints is used to support clinical evaluation and decision making regarding the choice of drug and dosing regimens.

Clearly, the lack of data regarding the correlation between AED exposure, pharmacological effects (i.e. biomarkers) and therapeutic response (i.e. seizure reduction or suppression) makes it difficult for a physician to predict which treatment, and which exposure level, will work best for an individual patient or group. Close monitoring of the variation in response between patients over the course of treatment time is required to understand the role of differences in brain physiology. Such a monitoring imposes the availability of biomarkers which are sufficiently sensitive to detect variations in response as well as to predict treatment failure or toxicity. To date, the only known valid antiepileptic drug biomarker is HLA-B*1502, which is a strong predictor of Stevens-Johnson syndrome in patients of specific Asian backgrounds taking carbamazepine [46]. No other parameters exist with sufficient predictive performance for efficacy.

Another point to consider in paediatric epilepsy is the role of neuronal maturation in the progression of epilepsy. Maturation and neurological development are processes that take place during growth. Changes in the expression of voltage gate dependent ion channels as well as structural changes associated with growth can have an impact on the sensitivity of the

brain to a drug and consequently on the magnitude of drug effects [47]. Similarly, the time of diagnosis and initiation of AED therapy are potential causes of variability in treatment response. For example, the clinical management of seizures in the new-born has remained unchanged in spite of evidence that "classic" medications (phenobarbital and phenytoin) are largely ineffective (with more than half of the population being non-responders for both drugs) and potentially neurotoxic [48]. Most symptomatic seizures in neonates are due to hypoxic-ischemic encephalopathy and do not persist beyond the first few days of life. Due to this natural improvement, any prompt intervention would appear effective and even curative. Such an apparent efficacy, which is wrongly attributed to the drug could be relevant across many types of epilepsy and result in AEDs being used more often than necessary, especially in the case of the developing brain of a new-born infant. This is particularly worrying if one takes into account the effect of AEDs on cognitive development and growth [49–53].

2.2.2 Disease progression and maturation

In paediatric epilepsy, it is clearly the natural progression of disease varies not only between patients, but also between and within epilepsy subtypes and syndromes [54,55]. For instance, benign epilepsy with centrotemporal spikes (BECST) typically occurs between the age of 3 – 14 years of age and resolves by age 17 despite the incidence of cognitive and behavioural disorders [56]. By contrast, Lennox-Gastaut syndrome begins between the age of 1-6, with seizures that generally do not respond well to treatment [57] Schmidt *et al.* estimated that without intervention, 20-44% of untreated epilepsies remit within one to two years [58]. Of the remaining patients, around 60% will respond favourably to therapy and the rest will present an insidious or recurrent syndrome in which approximately half of this subpopulation will not respond to treatment. Unfortunately, the authors seem to pay little attention to the differences between types of epilepsy and their aetiology [59,60]. Even more controversial are the prognostic factors for response to treatment, as only around 11% of patients with lack of efficacy to the first AED will respond to the second treatment option [15]. Without relevant biomarkers it is impossible to

predict disease progression and/or treatment response. Consequently, clinical decisions regarding treatment choice and dose selection are determined by the disease status at time of the diagnosis or intervention.

2.2.3 Target receptor polymorphisms, density, and adaptation

Many AEDs are believed to share a common mechanism of action through the interaction at the receptor level, usually an ion channel on the surface of the target neurons [61]. In addition, it can be assumed that *caeteris paribus* the higher the target engagement the stronger the signal being transmitted or blocked. Consequently, the exposure-response curve of an AED *in vivo* will vary depending on the availability (density) of receptors [62]. Additional variability may arise from polymorphisms of target receptors (which can be caused by differences in the aetiology of epilepsy) as well as from variable binding kinetics at the target. Indeed, changes to binding kinetics can alter drug potency, which in turn affects the dosing requirements [63].

From a clinical perspective, it should be highlighted that epileptic patients often experience a decreased drug effect over the course of treatment, which cannot be explained by the aforementioned processes or mechanisms. This reduction may be a gradual process, but often occurs suddenly, possibly after discontinuation and reinstatement of drug therapy. One of the potential causes of pharmacoresistance is down/up regulation of the target receptors [64–66]. In these circumstances, whereas increases in the dose may off-set the effects of down-regulation, higher drug exposure may lead to side effects, preventing achievement of satisfactory response levels. Pharmacoresistance has been reported to affect about 23% of paediatric patients [67], whom respond better to surgical intervention than adults. [68].

3. Extrinsic sources of variability and heterogeneity in response to AEDs

Apart from the biological factors implicated in previous sections, some extrinsic factors limit our understanding of the PKPD relationships of AEDs and consequently may affect treatment choice and dose selection for the paediatric population. Here we focus on the implications of food-drug and drug-drug interactions, as well as on the impact of variable treatment adherence.

3.1 Drug-food interaction and formulation variability

Most used AEDs have been off-patent for some time and thus generic versions exist in all kinds of formulations. Although the pharmacologically active substance is the same, and bioequivalence studies should provide evidence for similar exposure to the drug, different formulations have been introduced, which are intended to modify drug release profile and as such can lead to faster or slower absorption possibly resulting in different peak concentrations [69] and consequently in a different safety profile [70]. This issue can be compounded by small differences in the bioavailability (fraction of the dose that is absorbed and reaches the systemic circulation) of AEDs (Figure 3)[71]. For example, the bioavailability of carbamazepine is considered to be 80% on average, but ranges considerably [72]. In the case of gabapentin, bioavailability is inversely proportional to the taken dose, resulting in reduced increases in exposure with increasing doses [73]. Finally, absorption and first pass metabolism can be influenced by food intake and beverages, such as grapefruit juice [74]. These factors are difficult to control but can contribute to overall variability in the exposure to AEDs. Thus, to minimise the influence of absorption kinetics on the disposition of AEDs, many extended-release formulations have been developed for adult patients, which reduce peak/trough concentration ratios while maintaining similar overall exposure. By contrast, extended release tablet formulations are not always an option in children, as swallowing such tablets can be too difficult for younger patients. This

limitation could be overcome by specially designed liquid extended-release formulations [75].

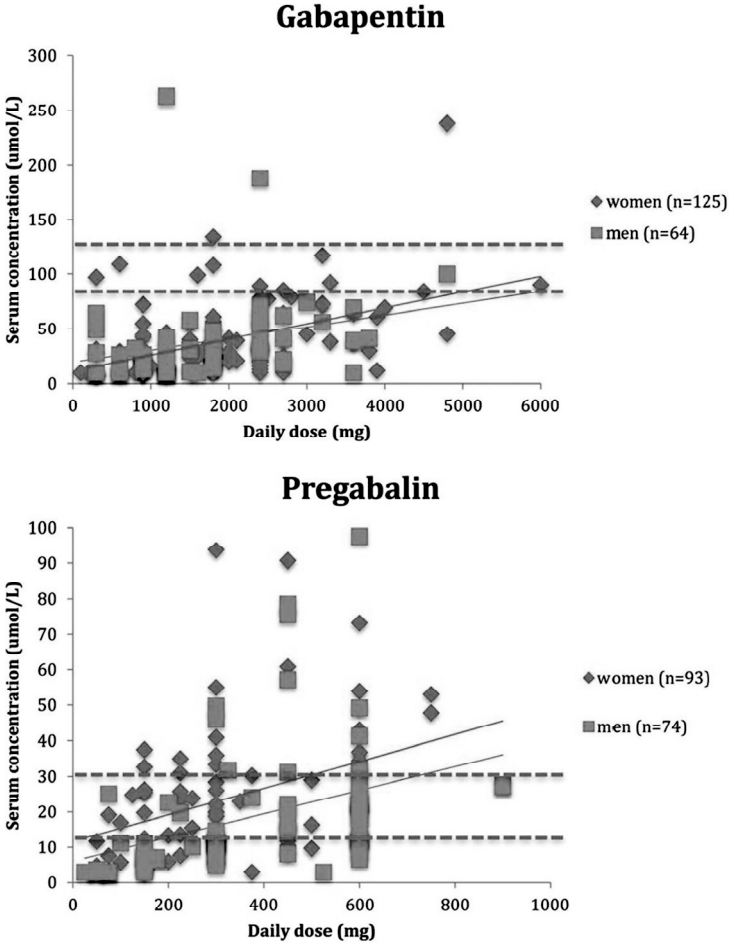


Figure 3. (a) Dose and concentration relationship of (a) gabapentin (n = 189), ref. range (70–120 mmol/L) and (b) pregabalin (n = 167), ref. range (10–30 mmol/L) (*with permission from [71]*).

3.2. Drug combinations and drug-drug interactions

Current clinical guidelines recommend drug combination or polytherapy only in those cases in which monotherapy is proven to be insufficiently effective. In the case of effective polytherapy, it is suggested to taper off the previous treatment to achieve monotherapy over a longer time interval. Monotherapy is therefore assumed to be the best treatment choice, but this practice does not take into account the possibility of pharmacodynamic interactions, and in particular, synergy, for which some evidence exists [76–78]. Combining drugs with a different mechanism of action may offer the best chance of achieving synergistic interactions, although there is scarce evidence for this concept from clinical trials [79]. These claims occur despite the lack of consensus on whether patients might benefit of an alternative drug or multiple AEDs [80]. On the other hand, pharmacokinetic drug-drug interactions (DDI) have been identified for many AEDs. Consequently, it may be challenging to disentangle changes in drug effects due to a pharmacodynamic interaction from the effects associated with changes in the exposure due to the primary AED. Given safety and ethical constraints, the characterisation of possible pharmacodynamic interactions remains difficult in a clinical setting.

3.2 Adherence to treatment

Treatment with AEDs often leads to cognitive, behavioural and physical adverse effects [81]. When such effects are experienced as burdensome, it is likely that a patient will not comply with the prescribed regimen and take short or longer drug holidays, leading to poor persistence and eventually discontinuation of treatment [82]. Whereas some of these adverse effects can be prevented or reversed by adjusting the dose correctly for the individual patient or group, limited information is available on the impact that drug holidays have both on the efficacy and safety profile of AEDs. This issue is further compounded in paediatric epilepsy, as adherence does not involve on the patients themselves, but parents or caregivers who can also interfere with drug intake. In fact, random missingness of the dose during a single day of treatment can already decrease exposure levels significantly. A recent study has found that approximately a quarter of the paediatric

patients are nonpersistent in taking their prescribed AED therapy, but the impact of variable adherence on treatment outcome was not evaluated [83].

Given that poor adherence is often not disclosed by patients, physicians may attribute a potential loss of efficacy to disease or pharmacodynamic factors, rather than to variation in drug exposure due to variable patterns of drug intake. In this case, patients may be recommended a dose increase or an alternative treatment, which may result in increased incidence of adverse effects [82]. Open, honest communication between physician, patients and parents when necessary is therefore critical to minimise the risk of inaccurate treatment decisions [84].

4. Conclusion

Children are not small adults and it is known that syndromes in paediatric epilepsy undergo variable progression and changes in the natural course of the disease due to neurodevelopment. Changes in pharmacokinetic, pharmacodynamic and physiological processes associated with maturation and developmental growth determine the differences in response to AED treatment in this population. Many of these changes occur concurrently, preventing accurate prediction of the response (and prognosis) at an individual patient level. An integrated approach, supported by potential biomarkers and dosing algorithms is needed to ensure appropriate selection of drug(s) and dose for a specific patient or group of patients. Regardless the large amount of data collected on existing and new AEDs, knowledge is not sufficiently integrated to support the implementation of treatment personalisation. This lack of integration prevails, despite efforts by health technology assessment organisations to establish the effectiveness of available medicines. Guidelines such as NICE rely on published evidence, which may lag considerably behind the introduction of a new medicinal product into clinical practice. Moreover, such guidelines are not fit-for-purpose, i.e., do not specifically focus on subgroups in such a way that fully supports the use of personalised treatments in children.

To allow paediatricians to better decide on which AED(s) to prescribe and at which dose, a novel approach is required that takes into account the aforementioned complexities of epilepsy [85]. A promising, readily available methodology for the selection of a drug and dosing regimen is PKPD and disease modelling [86]. However, to be an effective resource for treatment personalisation, biomarkers must be identified that are sensitive to the disease state and progression, so that efficacy and toxicity of drugs can be better characterised in clinical practice. Undoubtedly, the availability of biomarkers would also represent an advancement to diagnosis, minimising the need for a trial-and-error approach to pharmacotherapy [87–90]. In our expert opinion, we explore how the application of model-based algorithms may achieve these goals.

5. Expert Opinion

5.1. Definition of treatment response and assessment of efficacy and safety

Seizure frequency or similar continuous measures be considered as primary endpoints for the assessment of efficacy. The use of number of responders, i.e., patients achieving a decrease in seizure count of at least 50% at the end of the study relative to baseline and the percentage of the population that achieves such “seizure control” compared to placebo or a control treatment are not sufficiently informative. Such a dichotomisation of the response results in a loss of information, as it does not allow the characterisation of the drug effect at the individual patient level. As a result, personalisation of treatment, including dosing recommendations cannot be derived unless a broad dose range is tested and stratified for. Such a requirement is unrealistic as more patients would be required for adequate evaluation of response in a clinical trial. This limitation is further compounded by bias in the comparison between experimental and control treatments when applying the aforementioned response criteria [91].

In addition to the use an endpoint which offers more granularity to the evaluation of efficacy, experimental protocols need to be revisited. Typically, the efficacy of new AEDs is tested in a so-called “add on” trial

design, in which patients who are refractory to treatment receive the new drug. This complicates the interpretation of the results for a variety of reasons. First, it introduces selection bias in drug potency and on the required dose recommendations. In patients who are refractory to treatment, response is expected to be less than in non-refractory patients. Moreover, the observed response is the result of a combination of the direct effect of the drug and/or an interaction with the background treatment. As a result, interactions must be taken into account to establish the magnitude of the effect of the new drug in the absence of other AEDs. These limitations apply *a fortiori* in children. Ethical considerations make it virtually impossible to evaluate efficacy and safety in children according to typical Phase IIb dose ranging studies.

5.2 Understanding and predicting variability

L.B. Sheiner envisioned a learning-confirming paradigm [92] in which available prior information is first used to *learn* by prediction or extrapolation using modelling and simulation techniques (evidence synthesis), where possible taking into account multiple sources of information (integration). An experiment can then be optimised to address the gaps in knowledge (evidence generation), the outcome of which is then used to *confirm* the predictions and build new theories and models (Figure 4). More specifically with regard to the use of AEDs in paediatric epilepsy, accurate predictions of treatment response may be achieved as a result of systematic integration of data on pharmacokinetics, pharmacodynamics and disease [93]. Such an approach may have direct implications for the implementation of personalised treatments, including dosing algorithms for paediatric patients.

The use of PKPD and disease models relies on current understanding of the disease and pharmacology. Usually, one endeavours to describe the biological system of interest with sufficient detail to ensure accurate predictions for a range of possible interventions. This process relies on a set of assumptions is often referred to as parameterisation and is aimed at identifying descriptors of the physiological or pharmacological effects in a simple, but yet robust manner. For instance, using a PK model instead of

collecting and summarising drug concentrations only, it is possible to predict the time course of the drug concentrations following drug administration of different doses and dosing regimens, as well as better account for the impact of covariates such as body weight or age. Similarly, PKPD and disease models provide the basis for the assessment of the interaction between drug and biological system, taking into account the progression or changes associated with the disease itself. Such parameterisation also allows one to quantify the impact of influential factors on parameter values and describe them as covariates. The incorporation of covariates into a PKPD or disease model has an important advantage in that it enhances the prediction of response for specific groups of patients [94–96]. In conjunction with clinical trial simulations, model-based techniques offer an excellent opportunity for the evaluation of novel therapies [97] as well as personalisation of the dosing regimen for children [98].

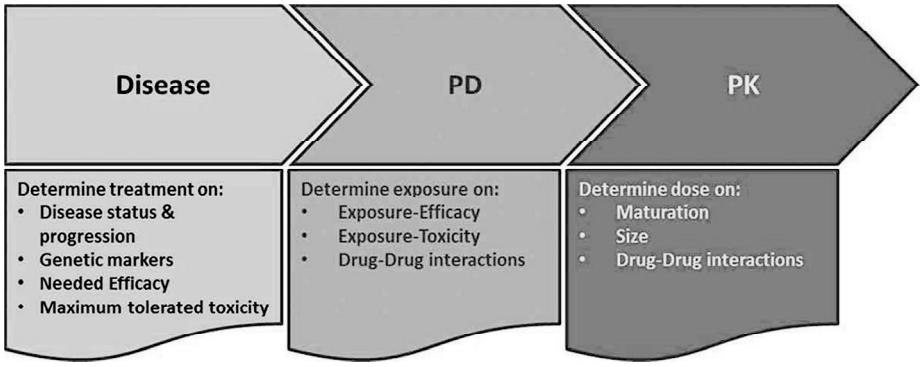


Figure 4. Information on disease processes, pharmacodynamics and pharmacokinetics must be integrated to ensure accurate personalisation of AED treatment and rational dose selection in children. Whereas interindividual differences in disease and pharmacodynamics of AEDs play an important role in treatment selection, understanding of the effect of developmental growth and maturation processes is essential for the selection of the paediatric dosing regimen.

5.2.1 Personalised treatment

Clinical guidelines for epilepsy [99] still rely on diagnostic criteria which are primarily determined by symptoms, Consequently, AED treatment selection is based on the underlying epileptic syndrome, as defined by the type of epileptic seizures (e.g. partial, primary or secondary generalised, absence, etc.) and age (adults, children, etc.), with aetiology playing only a minor role. For each syndrome group, multiple lines of treatment are considered. Given the heterogeneity in the aetiology of the disease within each group, it is likely that the different treatment options simply reflect the uncertainty about the interindividual differences in response.

A more mechanistic approach is required for the classification of seizures, as it would facilitate the distinction between AEDs which can modify the disease from those which act on symptoms [100]. The use of disease modelling can also contribute to another pressing issue, i.e., the nature and magnitude of the effect of drug-drug interactions. It has been proposed that combining AEDs with different mechanisms of action might have a synergistic effect compared to combining those with a similar mechanisms of action, but no research has conclusively supported this idea [101]. By contrast, others have suggested a more practical approach of exploring doses and combinations in difficult refractory cases [102]. A more aggressive pre-emptive intervention may very well be the answer to treatment resistant epilepsy, but no systematic studies are available to support this hypothesis. Despite concerns about the use polytherapy, the concept is appealing especially in children if evidence can be gathered of the implications of early interventions with multiple AEDs. Advancements will only become tangible after sensitive biomarkers have been identified. In conjunction with disease modelling, biomarkers may also allow one to discriminate the contribution of one of more compounds to the overall response and determine whether AEDs affect disease progression.

In the absence of biomarkers, long term longitudinal (observational) studies represent an important step to further characterise the pros and cons of a given intervention. It is regrettable that no attempts have been made to apply disease modelling concepts to (pharmaco)epidemiological studies.

Despite the retrospective nature of such an approach, important insight may be gained about predictors and determinants of response in children.

5.2.2 Personalised dose and dosing regimen

As previously stated, 10-20% of refractory patients can benefit from dose adjustments [15], but little discussion exists in the literature regarding appropriate dosing in non-refractory patients. In fact, it is likely that in numerous cases the lack of response to AEDs may occur due to inadequate dosing, whereas other patients may experience adverse events due to overexposure. Efforts from therapeutic drug monitoring have not addressed this issue and caused PK considerations to be misinterpreted during clinical decision about the dose and dosing regimen of AED. Most importantly, limited attention is given to the role of covariates that are known affect PK and potentially alter the efficacy and safety profile of an AED.

Since therapeutic concentration ranges for each AED are available in literature, such data can be used with PK models, including the contribution of covariates to identify suitable titration and maintenance dosing algorithms. Unfortunately, these therapeutic concentration ranges were generally determined in the adult population, making their relevance for the different epilepsy subtypes in the paediatric population questionable. The development of dosing algorithms is particularly important for the paediatric population, irrespective of the lack of further data on exposure-response and exposure-toxicity relationships. A major benefit from this approach is the opportunity to provide recommendations for dosing adjustment taking into account complex drug-drug interactions in a strictly quantitative manner; this issue is poorly addressed by current therapeutic guidelines. In this context, simulation scenarios can also be explored to predict the response to drug combinations also in refractory patients. Whilst one needs to acknowledge the role of disease progression over time in paediatric epilepsy, efforts to ensure comparable exposure to drugs, irrespective of their age or body weight, represent a more robust approach than trial and error in a vulnerable patient population.

We also note that despite the considerable number of publications aimed at PK modelling of AED, most authors offer this as a somewhat technical description of ADME properties of the drugs. Most publications lack insight into core clinical pharmacology issues and do not expand their analysis and interpretation to meet clinical needs such as dose rationale and implications for prescription practice. In summary, the information available is not being integrated and most importantly, the lack of a "big picture" regarding core clinical pharmacology principles seems to perpetuate the gaps in data generation, i.e., missing information is not being generated. Figure 4 depicts the steps required to ensure personalised treatment, with a stronger rationale for drug and dose selection. Clinical dosing could be enhanced by algorithms, which are more efficient than typical titration procedures and therapeutic drug monitoring (TDM). Combined with dried blood spot or saliva analysis techniques, the burden of TDM on the paediatric patient could be minimised. [103,104] The benefits of a model-based approach are illustrated in a simulation study [supplement 1, to be downloaded from the online version of this article], using published data as an example of what dosing algorithms can represent to clinical practice in paediatric epilepsy [105]. Clearly, effective implementation of dosing algorithms imposes further integration of existing and new evidence on the efficacy and safety of AEDs. It also demands for extrapolation tools and evidence generation based on more informative experimental protocols. The potential impact to such efforts is highlight in the following paragraphs.

5.3 Evidence synthesis

5.3.1 Integration of historical and new evidence

One of the most powerful characteristics of model-based approaches is the possibility of integrating information from different sources and combining them with statistical concepts to make predictions about new scenarios, beyond the experimental evidence available from the data itself. Given the complexity of epilepsy's many interacting factors, these techniques represent a valuable research tool in this field. Currently, its use remains, however, limited to pharmacokinetic data analysis.

5.3.2 Extrapolations

Translational medicine can be defined as extrapolating findings from basic science and quickly making them useful for practical applications that enhance human health [106]. Whilst its implementation is often limited to stand-alone experimental protocols, translational steps can be achieved by the use of model-based extrapolations [107,108], The use of extrapolations based on clinically and biologically plausible assumptions can make translational medicine a valid and powerful tool. The approach involves appropriate scrutiny by simulation exercises enabling the integration of different types of data, such as pre-clinical *in vitro* (cell lines, tissue, organs), *in vivo* (mice, rats, dogs, etc.) and clinical data [109, 110]. Of interest is the role that extrapolations can have to characterise differences and similarities between paediatric and adult patients [111-113]. As recently defined by the European Medicines Agency (EMA), extrapolation may be generally defined as: "Extending information and conclusions available from studies in one or more subgroups of the patient population (source population), or in related conditions or with related medicinal products, to make inferences for another subgroup of the population (target population), or condition or product, thus reducing the need to generate additional information (types of studies, design modifications, number of patients required) to reach conclusions for the target population, or condition or medicinal product" [6].

It should be clear that the primary rationale for extrapolation is to avoid unnecessary studies in children. However, extrapolations are not generally acceptable as a default approach (Table 2). As discussed previously, an interesting finding in epilepsy is the extrapolation of efficacy results in adults to predict a similar adjunctive treatment response in 2- to 18-year-old children with partial onset seizure [5].

Table 2. Acceptability of different extrapolation approaches for the prediction of disease progression, pharmacodynamics and pharmacokinetics between and within species.

Extrapolation of	From	To	Acceptability	References
Disease mechanisms and PD	animals	humans	Unclear	[57,58,98,101,102]
Disease progression and PD with similar aetiology	adults	children	Possibly	[100,103]
Disease progression and PD with different aetiologies	adults	children	Not acceptable	[104]
Pharmacokinetics (allometrically)	animals	humans	Possibly	[105]
Pharmacokinetics (allometrically)	adults	children >3yo	Probably	[8,106,107]

>3yo: older than 3 years

5.4 Evidence generation

An important shortcoming of the primary measure of efficacy is the fact that seizure reduction from baseline does not reflect changes in epileptic activity in the brain in a strictly quantitative manner nor does it relate to the mechanism of the drug on such processes. In fact, a more careful evaluation of this criterion may not be comparable across all subpopulations [114]. Clearly, early, sensitive biomarkers and endpoints are essential to accurately characterise interactions of drug(s) and disease. One needs to establish how drug effects interact with the underlying disease and explore whether longitudinal changes in such endpoints can be used to predict long term response to treatment. So far, very few attempts have been made to identify predictors of response or treatment failure; such investigations have however relied on seizure reduction or establish the potential prognostic rather than predictive value of the variables of interest (Figure 5) [115]. Therefore we strongly support the views that clinical

research protocols need to integrate clinical measures to markers of physiological and pharmacological effects of AEDs. In this context, imaging techniques need to be coupled to the evaluation of efficacy in clinical trials. Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) represent promising opportunities, but their evaluation as biomarkers in epilepsy has not yet been fully explored [116–118] and may be too burdensome to use in paediatric epilepsy.

A final point to consider in evidence generation is the informative value of data, which should include, rather than exclude relevant covariates and influential factors on exposure-response relationships. Numerous examples exist where early adoption of modelling and simulation has led to better trial design, in particular with regard to the dose selection and characterisation of influential factors on PK , PD and response [121,122]. Although successful studies have been conducted to derive paediatric dosing based on empirical designs, others failed and possibly could have been successful based on modelling and simulation [123–125]. In summary, clinical researchers and regulators need to acknowledge the limitations of traditional protocols to evaluate efficacy and safety of AEDs in children [126–128]. Effective implementation of personalised treatment for the paediatric population requires concerted efforts to ensure that experimental data are generated and integrated beyond traditional statistical hypothesis testing. Lessons can be learned from recent developments in oncology [129], where clinical trials, treatment and dose selection have undergone major advancements both conceptually and clinically over the last decade.

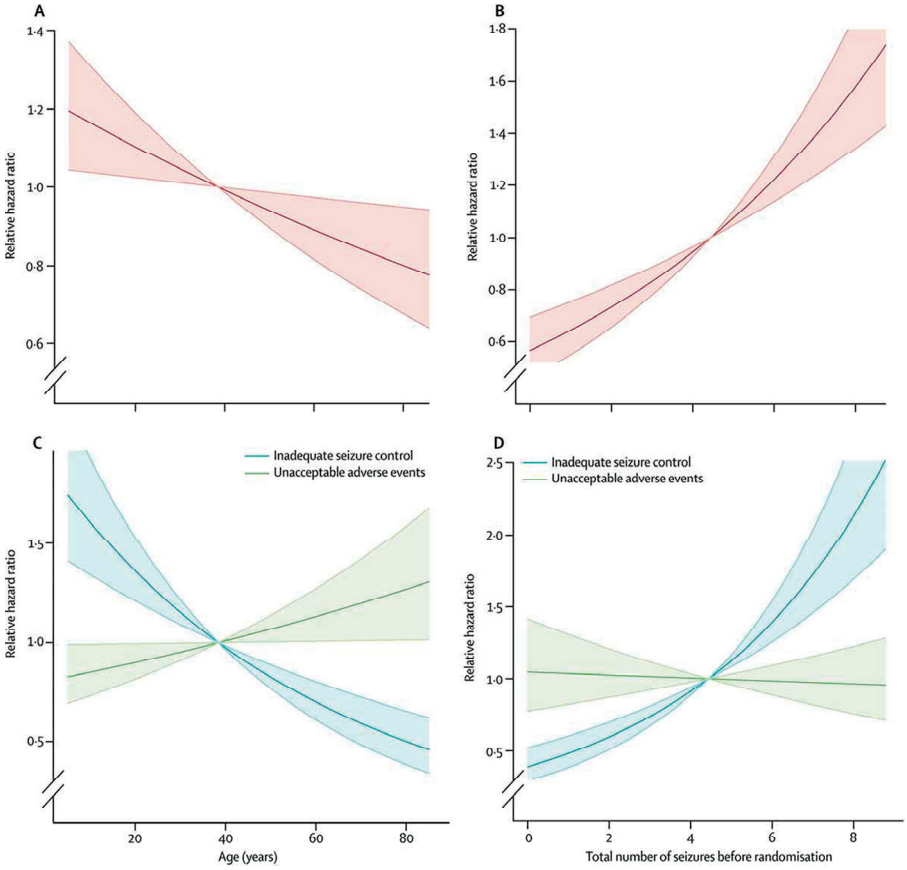


Figure 5. In this example, plots show the relative hazard ratio for age and total number of seizures before randomisation for the time to treatment failure. Hazard ratio estimates with 95% CIs are shown for overall time to treatment failure, for age (A) and total number of seizures (B), and for time to treatment failure because of inadequate seizure control and because of unacceptable adverse events, for age (C) and total number of seizures (D). Ideally, biomarkers should be identified that can be used as predictors of response or failure without the need to measure the reduction in seizure frequency.

References

1. Ngugi AK, Bottomley C, Kleinschmidt I, et al. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia 2010;51:883–90.

2. England MJ, Liverman CT, Schultz AM, et al. Epilepsy across the spectrum: Promoting health and understanding. Committee on the Public Health Dimensions of the Epilepsies. Institute of Medicine (ed)., Washington, DC, The National Academies Press, 2012, p 19-47.

3. Olesen J, Gustavsson A, Svensson M, et al. The economic cost of brain disorders in Europe. Eur. J. Neurol. 2012;19:155–62.

4. Cardarelli WJ, Smith BJ. The Burden of Epilepsy to Patients and Payers. Am. J. Manag. Care 2010;16:331–336.

5. Pellock JM, Carman WJ, Thyagarajan V, et al. Efficacy of antiepileptic drugs in adults predicts efficacy in children: a systematic review. Neurology 2012;79:1482–9.

6. European Medicines Agency. Concept paper on extrapolation of efficacy and safety in medicine development. EMA/129698/2012 2012;

7. Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: Management of an unprovoked first seizure in adults. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2015; 84: 1705-1713.

8. French JA, Kanner AM, Bautista J, et al. Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy. Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2004; 62:1252-1260

9. National Institute for Health and Clinical Excellence (NICE). The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. London (UK): National Institute for Health and Clinical Excellence (NICE); 2012 Jan. 117 p. (Clinical guideline; no. 137).

10. Kinderformularium. Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen (NKFK), 2016 (https://www.kinderformularium.nl/, last accessed on 15 May 2016).

11. Paediatric Formulary Committee. BNF for Children. London: BMJ Group, Pharmaceutical Press, and RCPCH Publications; 2016

12. Cella M, Knibbe C, de Wildt SN, et al. Scaling of pharmacokinetics across paediatric populations: the lack of interpolative power of allometric models. Br. J. Clin. Pharmacol. 2012;74:525–35.

13. Cella M, Zhao W, Jacqz-Aigrain E, et al. Paediatric drug development: Are population models predictive of pharmacokinetics across paediatric populations? Br. J. Clin. Pharmacol. 2011;72:454–464.6.

14. Anderson BJ, Holford NHG. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu. Rev. Pharmacol. Toxicol. 2008;48:303–32.

15. Stagi S, Lasorella S, Piccorossi A, et al. Cessation of epilepsy therapy in children. Expert Rev. Neurother. 2016;16:549–559.

16. Min K, Hur Y, Yu H, et al. Initial response to antiepileptic drugs in patients with newly diagnosed epilepsy. J. Clin. Neurosci. 2014;21:923–926.

17. Kwan P, Brodie MJ. Epilepsy after the first drug fails: substitution or add-on? Seizure 2000;9:464–8.

18. Sillanpää M, Schmidt D. Predicting antiepileptic drug response in children with epilepsy. Expert Rev. Neurother. 2011;11:877–85; quiz 886.

19. Bellanti F, van Wijk RC, Danhof M, Della Pasqua O. Integration of PKPD relationships into benefit-risk analysis. Br. J. Clin. Pharmacol. 2015;80:979–991.

20. EMA. Benefit-risk methodology project tools and processes for regulatory benefit-risk. 2011;44:1–33.

21. Holmes E, Plumpton C, Duerden M, Marson T, Hughes D. New advice on switching antiepileptic drugs might be a false economy. BMJ. 2013; 347:f7471.

22. Plumpton CO, Yip VL, Alfirevic A, Marson AG, Pirmohamed M, Hughes DA. Cost-effectiveness of screening for HLA-A*31:01 prior to initiation of carbamazepine in epilepsy. Epilepsia. 2015; 56: 556-63.

23. Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age. Clin. Pharmacokinet. 2006;45:351–363.

24. Johannessen SI, Tomson T. Pharmacokinetic variability of newer antiepileptic drugs: when is monitoring needed? Clin. Pharmacokinet. 2006;45:1061–75.

25. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. Clin Pharmacokinet. 2013; 52: 627-45.

26. Deleu D, Aarons L, Ahmed IA. Population pharmacokinetics of free carbamezipine in adult Omani epileptic patients. Eur. J. Clin. Pharmacol. 2001;57:243–248.

27. Deleu D, Aarons L, Ahmed IA. Estimation of population pharmacokinetic parameters of free-phenytoin in adult epileptic patients. Arch. Med. Res. 2005;36:49–53.

28. Ueshima S, Aiba T, Makita T, et al. Characterization of non-linear relationship between total and unbound serum concentrations of valproic acid in epileptic children. J. Clin. Pharm. Ther. 2008;33:31–8.

29. Clinckers R, Smolders I, Michotte Y, et al. Impact of efflux transporters and of seizures on the pharmacokinetics of oxcarbazepine metabolite in the rat brain. Br. J. Pharmacol. 2008;155:1127–1138.

30. Löscher W, Schmidt D. Experimental and clinical evidence for loss of effect (tolerance) during prolonged treatment with antiepileptic drugs. Epilepsia 2006;47:1253–84.

31. Friis ML, Christiansen J, Hvidberg EF. Brain concentrations of carbamazepine and carbamazepine-10,11-epoxide in epileptic patients. Eur. J. Clin. Pharmacol. 1978;14:47–51.

32. Rambeck B, Jürgens UH, May TW, et al. Comparison of brain extracellular fluid, brain tissue, cerebrospinal fluid, and serum concentrations of antiepileptic drugs measured intraoperatively in patients with intractable epilepsy. Epilepsia 2006;47:681–694.

33. Christensen J, Højskov CS, Dam M, Poulsen JH. Plasma concentration of topiramate correlates with cerebrospinal fluid concentration. Ther. Drug Monit. 2001;23:529–35.

34. Wu C, Honarmand AR, Schnell S, et al. Age-Related Changes of Normal Cerebral and Cardiac Blood Flow in Children and Adults Aged 7 Months to 61 Years. J. Am. Heart Assoc. 2016;5:e002657.

35. Koyama H, Sugioka N, Uno A, et al. Age-related alteration of carbamazepine-serum protein binding in man. J. Pharm. Pharmacol. 1999;51:1009–1014.

36. Heine R Ter, van Maarseveen EM, van der Westerlaken MML, et al. The Quantitative Effect of Serum Albumin, Serum Urea, and Valproic Acid on Unbound Phenytoin Concentrations in Children. J. Child Neurol. 2013;29:803–810.

37. Lopez-Garcia MA, Feria-Romero IA, Fernando-Serrano H, et al. Genetic polymorphisms associated with antiepileptic metabolism. Front. Biosci. (Elite Ed). 2014;June:377–386.

38. Chang Y, Yang L, Zhang M, Liu S-Y. Correlation of the UGT1A4 gene polymorphism with serum concentration and therapeutic efficacy of lamotrigine in Han Chinese of Northern China. Eur. J. Clin. Pharmacol. 2014;941–946.

39. Urban TJ, Brown C, Castro R, et al. Effects of genetic variation in the novel organic cation transporter, OCTN1, on the renal clearance of gabapentin. Clin. Pharmacol. Ther. 2008;83:416–421.

40. Piana C, Antunes NDJ, Pasqua O Della. Implications of pharmacogenetics for the therapeutic use of antiepileptic drugs. Expert Opin. Drug Metab. Toxicol. 2014;10:341–358.

41. Anderson BJ, Holford NHG. Mechanistic Basis of Using Body Size and Maturation to Predict Clearance in Humans. Drug Metab. Pharmacokinet. 2009;24:25–36.

42. Takeuchi T, Natsume J, Kidokoro H, Ishihara N. The effects of co-medications on lamotrigine clearance in Japanese children with epilepsy. Brain Dev. 2016;

43. Mikaeloff Y, Rey E, Soufflet C, et al. Topiramate pharmacokinetics in children with epilepsy aged from 6 months to 4 years. Epilepsia 2004;45:1448–52.

44. Bouillon-Pichault M, Jullien V, Bazzoli C, et al. Pharmacokinetic design optimization in children and estimation of maturation parameters: example of cytochrome P450 3A4. J. Pharmacokinet. Pharmacodyn. 2011;38:25–40.

45. Vovk T, Jakovljević MB, Kos MK, et al. A nonlinear mixed effects modelling analysis of topiramate pharmacokinetics in patients with epilepsy. Biol. Pharm. Bull. 2010;33:1176–82.

46. Glauser TA. Biomarkers for antiepileptic drug response. Biomark. Med. 2011;5:635–641.

47. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N. Engl. J. Med. 2000;342:314–319.

48. Painter M, Scher M, Stein A, et al. Phenobarbital compared with Phenytoin for the Treatment of Neonatal Seizures. N. Engl. J. Med. 1999;341:485–489.

49. Bittigau P, Sifringer M, Genz K, et al. Antiepileptic drugs and apoptotic neurodegeneration in the developing brain. Proc. Natl. Acad. Sci. U. S. A. 2002;99:15089–94.

50. Meador KJ, Baker G a., Browning N, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): A prospective observational study. Lancet Neurol. 2013;12:244–252.

51. Lee H-S, Wang S-Y, Salter DM, et al. The impact of the use of antiepileptic drugs on the growth of children. BMC Pediatr. 2013;13:211.

52. Banach R, Boskovic R, Einarson T, Koren G. Long-term developmental outcome of children of women with epilepsy, unexposed or exposed prenatally to antiepileptic drugs: a meta-analysis of cohort studies. Drug Saf. 2010;33:73–9.

53. Farwell J, Lee Y, Hirtz DG, et al. Phenobarbital for febrile seizures—effects on intelligence and on seizure recurrence. N. Engl. J. Med. 1990;322:364–369.

54. Nicoletti A, Sofia V, Vitale G, et al. Natural history and mortality of chronic epilepsy in an untreated population of rural Bolivia: A follow-up after 10 years. Epilepsia 2009;50:2199–2206.

55. Okuma T, Kumashiro H. Natural History and Prognosis of Epilepsy : Report of a Multi-institutional Study in Japan. Epilepsia 1981;22:35–53.

56. Vannest J, Tenney JR, Gelineau-morel R, et al. Cognitive and behavioral outcomes in benign childhood epilepsy with centrotemporal spikes. Epilepsy Behav. 2015;45:85–91.

57. Montouris GD, Wheless JW, Glauser TA. The efficacy and tolerability of pharmacologic treatment options for Lennox-Gastaut syndrome FDA-Approved Medications. 55:10–20.

58. Schmidt D, Sillanpää M. Evidence-based review on the natural history of the epilepsies. Curr. Opin. Neurol. 2012;25:159–63.

59. Sloviter RS. The neurobiology of temporal lobe epilepsy: too much information, not enough knowledge. C. R. Biol. 2005;328:143–153.

60. Bender RA, Baram TZ. Epileptogenesis in the developing brain: what can we learn from animal models? Epilepsia 2007;48 Suppl 5:2–6.

61. Kwan P, Sills GJ, Brodie MJ. The mechanisms of action of commonly used antiepileptic drugs. Pharmacol. Ther. 2001;90:21–34.

62. Ploeger BA, van der Graaf PH, Danhof M. Incorporating Receptor Theory in Mechanism-Based Pharmacokinetic-Pharmacodynamic (PK-PD) Modeling. Drug Metab. Pharmacokinet. 2009;24:3–15.

63. Hung C-C, Chen C-C, Lin C-J, Liou H-H. Functional evaluation of polymorphisms in the human ABCB1 gene and the impact on clinical responses of antiepileptic drugs. Pharmacogenet. Genomics 2008;18:390–402.

64. Weaver DF, Pohlmann-Eden B. Pharmacoresistant epilepsy: unmet needs in solving the puzzle(s). Epilepsia 2013;54 Suppl 2:80–5.

65. Vega-hern A, Felix R. Down-Regulation of N-Type Voltage-Activated Ca 2 + Channels by Gabapentin. 2002;2002:185–190.

66. Byrnes JJ, Miller LG, Greenblatt DJ, Shader RI. Chronic benzodiazepine administration. Biochem. Pharmacol. 1991;42:S99–S104.

67. Berg AT, Rychlik K. The course of childhood-onset epilepsy over the first two decades : A prospective , longitudinal study. 2014;56:40–48.

68. Francione S, Liava A, Mai R, et al. Drug-resistant parietal epilepsy : polymorphic ictal semiology does not preclude good post-surgical outcome. 2015;17:32–46.

69. Yamada M, Welty TE. Generic Substitution of Antiepileptic Drugs: A Systematic Review of Prospective and Retrospective Studies. Ann. Pharmacother. 2012;46:304–304.

70. Crawford P, Feely M, Guberman A, Kraemer G. Are there potential problems with generic substitution of antiepileptic drugs? A review of issues. Seizure 2006;15:165–176.

71. Johannessen C, Beiske G, Baftiu A, et al. Experience from therapeutic drug monitoring and gender aspects of gabapentin and pregabalin in clinical practice. Seizure Eur. J. Epilepsy 2015;28:88–91.

72. Marino SE, Birnbaum AK, Leppik IE, et al. Steady-state carbamazepine pharmacokinetics following oral and stable-labeled intravenous administration in epilepsy patients: effects of race and sex. Clin. Pharmacol. Ther. 2012;91:483–8.

73. Chen C. Meta-analyses of dose-exposure relationships for gabapentin following oral administration of gabapentin and gabapentin enacarbil. Eur. J. Clin. Pharmacol. 2013;69:1809–1817.

74. Krauss GL, Caffo B, Chang YT, et al. Assessing bioequivalence of generic antiepilepsy drugs. Ann. Neurol. 2011;70:221–228.

75. Mishra B, Sahoo BL, Mishra M, et al. Design of a controlled release liquid formulation of lamotrigine. Daru 2011;19:126–37.

76. Jonker DM, Voskuyl RA, Danhof M. Synergistic combinations of anticonvulsant agents: what is the evidence from animal experiments? Epilepsia 2007;48:412–34.

77. Lee JW, Dworetzky B. Rational Polytherapy with Antiepileptic Drugs. Pharmaceuticals 2010;3:2362–2379.

78. Stafstrom CE. Mechanisms of action of antiepileptic drugs: the search for synergy. Curr. Opin. Neurol. 2010;23:157–63.

79. Sake J-K, Hebert D, Isojärvi J, et al. A pooled analysis of lacosamide clinical trial data grouped by mechanism of action of concomitant antiepileptic drugs. CNS Drugs 2010;24:1055–68.

80. Stephen LJ, Brodie MJ. Antiepileptic drug monotherapy versus polytherapy: pursuing seizure freedom and tolerability in adults. Curr. Opin. Neurol. 2012;25:164–72.

81. Zaccara G, Giovannelli F, Giorgi FS, et al. Analysis of nocebo effects of antiepileptic drugs across different conditions. J. Neurol. 2016;

82. Faught E. Adherence to antiepilepsy drug therapy. Epilepsy Behav. 2012;25:297–302.

83. Aylward BS, Rausch JR, Modi AC. An Examination of 1-Year Adherence and Persistence Rates to Antiepileptic Medication in Children With Newly Diagnosed Epilepsy. 2015;40:66–74.

84. Smithson WH, Hukins D, Colwell B, Mathers N. Developing a method to identify medicines non-adherence in a community sample of adults with epilepsy. Epilepsy Behav. 2012;24:49–53.

85. Castro FA De, Piana C, Simões BP, et al. Busulfan dosing algorithm and sampling strategy in stem cell transplantation patients. Br. J. Clin. Pharmacol. 2015;80:618–629.

86. Margineanu DG. Systems biology impact on antiepileptic drug discovery. Epilepsy Res. 2012;98:104–15.

87. Danhof M, Alvan G, Dahl SG, et al. Mechanism-based pharmacokinetic-pharmacodynamic modeling-a new classification of biomarkers. Pharm. Res. 2005;22:1432–7.

88. Engel J, Pitkänen A, Loeb JA, et al. Epilepsy biomarkers. Epilepsia 2013;54 Suppl 4:61–9.

89. Chen X, de Haas S, de Kam M, van Gerven J. An Overview of the CNS-Pharmacodynamic Profiles of Nonselective and Selective GABA Agonists. Adv. Pharmacol. Sci. 2012;2012:134523.

90. Santen G, van Zwet E, Bettica P, et al. From trial and error to trial simulation III: a framework for interim analysis in efficacy trials with antidepressant drugs. Clin. Pharmacol. Ther. 2011;89:602–7.

91. Schobben F, Hekster Y, van Zwieten-Boot B. Outcome measures for the assessment of new antiepileptic drugs. Pharm. World Sci. 1997;19:223–226.

92. Sheiner LB. Learning versus confirming in clinical drug development. Clin. Pharmacol. Ther. 1997;61:275–291.

93. Pennell PB, Peng L, Newport DJ, Ritchie JC, et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. Neurology. 2008 May 27;70(22 Pt 2):2130-6.

94. Csajka C, Verotta D. Pharmacokinetic-pharmacodynamic modelling: History and perspectives. J. Pharmacokinet. Pharmacodyn. 2006;33:227–279.

95. Lalonde RL, Kowalski KG, Hutmacher MM, et al. Model-based drug development. Clin. Pharmacol. Ther. 2007;82:21–32.

96. Danhof M, de Jongh J, De Lange ECM, et al. Mechanism-based pharmacokinetic-pharmacodynamic modeling: biophase distribution, receptor theory, and dynamical systems analysis. Annu. Rev. Pharmacol. Toxicol. 2007;47:357–400.

97. Lee JY, Garnett CE, Gobburu JVS, et al. Impact of pharmacometric analyses on new drug approval and labelling decisions: a review of 198 submissions between 2000 and 2008. Clin. Pharmacokinet. 2011;50:627–35.

98. Knibbe C a J, Danhof M. Individualized dosing regimens in children based on population PKPD modelling: are we ready for it? Int. J. Pharm. 2011;415:9–14.

99. National Institute for Health and Care Excellence. Epilepsies: diagnosis and management (CG137). Available at: http://www.nice.org.uk/guidance/cg137.

100. Coombes S, Terry JR. The dynamics of neurological disease: Integrating computational, experimental and clinical neuroscience. Eur. J. Neurosci. 2012;36:2118–2120.

101. Deckers CL, Hekster YA, Keyser A, et al. Reappraisal of polytherapy in epilepsy: a critical review of drug load and adverse effects. Epilepsia 1997;38:570–5.

102. French JA, Faught E. Rational polytherapy. Epilepsia 2009;50 Suppl 8:63–8.

103. Milosheska D, Grabnar I, Vovk T. Dried blood spots for monitoring and individualization of antiepileptic drug treatment. Eur. J. Pharm. Sci. 2015;75:25–39.

104. Patsalos PN, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs by use of saliva. Ther. Drug Monit. 2013;35:5–29.

105. Girgis IG, Nandy P, Nye JS, et al. Pharmacokinetic-pharmacodynamic assessment of topiramate dosing regimens for children with epilepsy 2 to 10 years of age. Epilepsia 2010;51:1954–1962.

106. Woolf SH. The meaning of translational research and why it matters. JAMA 2008;299:211–3.

107. Danhof M, de Lange ECM, Della Pasqua OE, et al. Mechanism-based pharmacokinetic-pharmacodynamic (PK-PD) modeling in translational drug research. Trends Pharmacol. Sci. 2008;29:186–91.

108. Donovan MD, Boylan GB, Murray DM, Cryan JF, Griffin BT. Treating disorders of the neonatal central nervous system: pharmacokinetic and pharmacodynamic considerations with a focus on antiepileptics. Br J Clin Pharmacol. 2016; 81:62-77.

109. Brochot A, Zamacona M, Stockis A. Physiologically based pharmacokinetic/pharmacodynamic animal-to-man prediction of therapeutic dose in a model of epilepsy. Basic Clin. Pharmacol. Toxicol. 2010;106:256–62.

110. Guillemain I, Kahane P, Depaulis A. Progress in Epileptic Disorders Workshop on AED trials Animal models to study aetiopathology of epilepsy : what are the features to model ? Epileptic Disord. 2012;14:217–225.

111. Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics 2011;128:e1242–9.

112. Chiron C, Dulac O, Pons G. Antiepileptic drug development in children: considerations for a revisited strategy. Drugs 2008;68:17–25.

113. Kang HE, Lee MG. Approaches for predicting human pharmacokinetics using interspecies pharmacokinetic scaling. Arch. Pharm. Res. 2011;34:1779–88.

114. Stefan H, Lopes da Silva FH, Löscher W, et al. Epileptogenesis and rational therapeutic strategies. Acta Neurol. Scand. 2006;113:139–55.

115. Bonnett L, Smith CT, Smith D, et al. Prognostic factors for time to treatment failure and time to 12 months of remission for patients with focal epilepsy : post-hoc , subgroup analyses of data from the SANAD trial. Lancet Neurol. 11:331–340.

116. Ronan L, Alhusaini S, Scanlon C, et al. Widespread cortical morphologic changes in juvenile myoclonic epilepsy: evidence from structural MRI. Epilepsia 2012;53:651–8.

117. Laufs H, Duncan JS. Electroencephalography/functional MRI in human epilepsy: what it currently can and cannot do. Curr. Opin. Neurol. 2007;20:417–23.

118. Kim S, Salamon N, Jackson HA, et al. PET imaging in pediatric neuroradiology: current and future applications. Pediatr. Radiol. 2010;40:82–96.

119. Wang Y, Bhattaram VA, Jadhav PR, et al. Leveraging prior quantitative knowledge to guide drug development decisions and regulatory science recommendations: impact of FDA pharmacometrics during 2004-2006. J. Clin. Pharmacol. 2008;48:146–56.

120. Mid E, Sf W, Burghaus R, et al. Good Practices in Model-Informed Drug Discovery and Development : Practice , Application , and Documentation. 2016;93–122.

121. Piana C, Surh L, Furst-recktenwald S. Integration of Pharmacogenetics and Pharmacogenomics in Drug Development : Implications for Regulatory and Medical Decision Making in Pediatric Diseases. 2012;704–716.

122. Cohen AF. Developing drug prototypes: pharmacology replaces safety and tolerability? Nat. Rev. Drug Discov. 2010;9:856–65.

123. Harnisch L, Shepard T, Pons G, Della Pasqua O. Modeling and Simulation as a Tool to Bridge Efficacy and Safety Data in Special Populations. CPT Pharmacometrics Syst. Pharmacol. 2013;2:e28.

124. Jadhav PR, Kern SE. The need for modeling and simulation to design clinical investigations in children. J. Clin. Pharmacol. 2010;50:121S–129S.

125. Wilby J, Kainth A, Hawkins N, et al. Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation. Health Technol. Assess. (Rockv). 2005;9:Executive summary.

126. Glauser T, Ben-menachem E, Bourgeois B, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia 2006;47:1094–120.

127. Perucca E. Designing clinical trials to assess antiepileptic drugs as monotherapy: difficulties and solutions. CNS Drugs 2008;22:917–38.

128. Perucca E. When clinical trials make history: demonstrating efficacy of new antiepileptic drugs as monotherapy. Epilepsia 2010;51:1933–5.

129. Della Pasqua O. PKPD and Disease Modeling: Concepts and Applications to Oncology. In: Kimko HH, Peck CC, eds. Clinical Trial Simulations: Applications and Trends. Springer New York, : 281–310.

CHAPTER 2

SCOPE AND INTENT OF INVESTIGATIONS

Scope and intent of investigations

1. Introduction

Reference to epilepsy and epileptic seizures can be found in Assyrian texts, almost 2,000 B.C. [1]. However, it was not until the 18th and 19th century that medicine started the delineation of pathophysiology of epilepsy and the topographic localization of epileptic seizures. Unfortunately, at that time, the notion of interindividual and biological variation was far from the concepts defining the work on epileptogenesis, aetiology, and taxonomy of epilepsy. In fact, John Hughling Jackson's definition of epilepsy in 1873 was limited to the ictal phase of the disease ("Epilepsy is the name for occasional, sudden, excessive, rapid and local discharges of grey matter") [2].

The possibility of non-surgical interventions, based on pharmacological principles started only in 1857, when the anticonvulsant and sedative traits of potassium bromide were identified. Potassium bromide became a choice treatment for humans with epileptic seizures until the 1912 discovery of phenobarbital. The next drug introduced in the therapy of epilepsy was phenytoin in 1938. Phenytoin became the first-line medication for the prevention of partial and tonic-clonic seizures and for acute cases of epilepsies or status epilepticus, giving an alternative therapeutic choice for patients not responding to bromides or barbiturates. During the 1950s, new drugs came up such as carbamazepine in 1953 [3], primidone in 1954, ethosuximide in 1958 [4], and sodium valproate in 1963 [5]. Despite such a progress, none of these drugs have undergone the scrutiny of randomised clinical trials at the time of approval, or considered the need to establish different treatment options in children as compared to adults. By contrast, over the last two decades the field continued to evolve, with a considerable number of molecules introduced into clinical practice based on controlled clinical studies.

The so called newer antiepileptic drugs such as vigabatrin (1989), lamotrigine (1990), oxcarbazepine (1990), gabapentin (1993), felbamate (1993), topiramate (1995), tiagabine (1998), zonisamide (1989 in Japan and 2000 in the USA), levetiracetam(2000), stiripentol (2002), pregabalin (2004), rufinamide (2004), lacosamide (2008), eslicarbazepine (2009), and perampanel (2012), have all shown to meet regulatory criteria for efficacy and safety.

In parallel to the availability of novel drugs, various clinical guidelines have been introduced that are aimed at improved diagnostics, management and treatment of epilepsies, with a few of them considering the need to define a different treatment rationale in children [6–8]. However, a careful review of the history of epilepsy along with the evolution of treatment guidelines reveals that the focus on diagnostics and taxonomy of epileptic seizures may have distracted researchers from the principles that underpin modern clinical pharmacology and therapeutics, i.e., the relevance of characterising exposure response relationships and quantifying the impact of different (intrinsic and extrinsic) factors on exposure and response variability. In this context, it is not surprising that despite the notion that differences in drug levels may be associated with therapeutic failure or adverse events, limited attention has been given to the use of quantitative clinical pharmacology methods as a tool for dose selection. Therapeutic drug monitoring was introduced in 1960, when Buchtal and Svensmark introduced the measurement of antiepileptic drug levels in the blood [9], but its use in clinical practice has remained an undesirable requirement. Most importantly, data collected during therapeutic drug monitoring has been linked to an empirical decision process, with trough plasma concentrations often confounded by other covariate factors.

As discussed in **Chapter 1**, it is clear that inter- and intra-individual differences in pharmacokinetics and pharmacodynamics of AEDs need to be taken into account for the personalisation of treatment in paediatric epilepsy. Evidence of efficacy in a clinical trial, does not imply that individual patients will show optimal response in clinical practice or that the same dose and dosing regimen(s) will be appropriate for all patients, in particular, if one considers paediatric patients. In brief, the assumption

current limitations in the understanding of the exposure-response relationships can be mitigated by up and down-titration or tapering of the dose, appears to be flawed. Dose selection based on such procedures does not account for age-related changes in pharmacokinetics and pharmacodynamics in children, especially when dealing with polytherapy with two or more AEDs. In fact, dose recommendations in formularies, such as the Netherlands Kinderformularium or the British National Formulary for Children overlook the role of covariate factors and other sources of variability in pharmacokinetics and pharmacodynamics [10,11]. Moreover, in spite of the use of therapeutic drug monitoring (TDM), which is widely accepted in paediatric epilepsy compared to adults, AED levels are checked against a therapeutic window, which was originally determined in adults.

A range of arguments has been used to explain the lack of such a systematic evaluation of the exposure-response relationships for antiepileptic drugs. First, treatment and dose recommendations make their way into clinical guidelines and formularies according to evidence-based principles (Figure 1). However, the approaches currently available to establish the level and quality of evidence supporting therapeutic and clinical choices do not consider the pharmacological basis for an intervention. Whereas phase II dose ranging studies are aimed at defining dose rationale in phase III trials, these studies are not necessarily optimised to account for potential covariate effects on pharmacokinetics and/or pharmacodynamics. Subsequently, after drug approval in the primary target population, empirical evidence from randomised clinical trials, systematic reviews and meta-analyses does not necessarily provide insight into the underlying exposure-response relationship or clinical implications of covariate effects for the dose rationale. Second, it is not possible to control and stratify all factors contributing to variability in a clinical trial. Given that evidence is limited to the sampled population, it is not difficult to anticipate the challenges in quantifying the impact of inclusion and exclusion criteria. Third, the lack of biomarkers or effective predictors of response to treatment. This shortcoming is often compounded by the definition of response itself (clinical endpoint), which is based on a binary measure: responder (i.e., patients who show at least 50% of reduction in seizures compared to baseline) vs. non-responder. Dichotomisation of the response

into two categories can be detrimental for the characterisation of dose-exposure-response relationships.

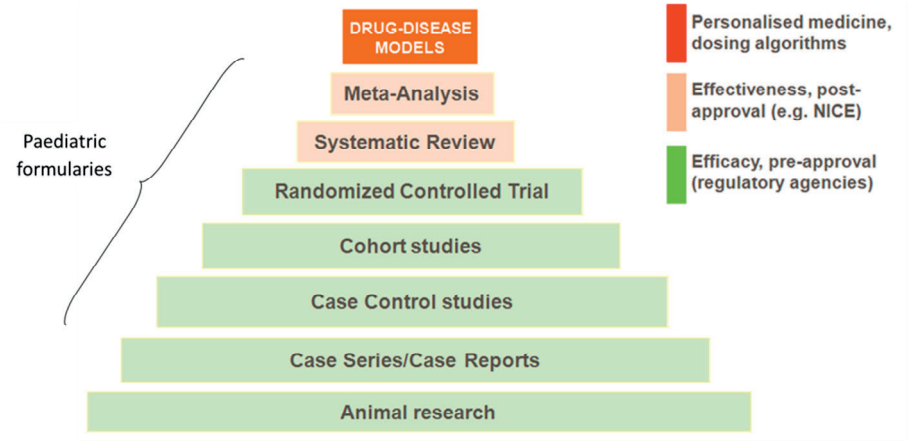


Figure 1. Evidence pyramid supporting treatment choice, target patient population and dose rationale. Different experimental data (evidence generation) and inferential methods (evidence synthesis) are used during the evaluation of efficacy and effectiveness of drugs in clinical practice. In contrast to systematic reviews and meta-analyses, drug-disease models provide a framework to assess the implications of multiple interacting factors, taking into account the underlying exposure-response relationships as well as drug-, disease and patient-specific characteristics. (adapted from Murad et al. [12])

Based on the aforementioned, any attempt to optimise treatment in paediatric epilepsy requires an integrated approach in which the implications of multiple interacting factors are taken into account. To that purpose, the theoretical concepts presented in **Chapter 1** will form the basis for the experimental work proposed in this thesis, which are described in the subsequent paragraphs in this chapter. Using a parametric approach along with data from a paradigm compound (lamotrigine), we aim to demonstrate how model-based dosing algorithms can be developed and implemented in clinical practice. For the sake of clarity, factors that determine treatment response and variability will be categorised into

disease, drug and patient-related factors. In order to illustrate the contribution of modelling and simulation as a tool for more effective evidence synthesis and better decision making regarding the dose selection, work presented in this thesis will be divided into three main sections, namely:

- **Section II (Knowledge integration)**, in which a compilation of the available pharmacokinetic and pharmacokinetic-pharmacodynamic models is presented along with details regarding the identification and parameterisation of the effect of intrinsic (e.g., disease, age-related) and extrinsic (e.g., drug interactions) factors on the exposure and response to AEDs.
- **Section III (Model-based dosing algorithms)**, where the magnitude of covariate effects and requirements for personalised regimens in paediatric epilepsy are evaluated using simulation scenarios under the assumption of comparable target therapeutic exposure ranges in adults and children.

- **Section IV (Evidence generation and evidence synthesis)**, where a pharmacokinetic and a drug-disease model are developed using a population-wide approach for the characterisation of exposure and exposure-response relationships in adults and children. In conjunction with scaling and extrapolation principles, a model-based dosing algorithm is then proposed for the optimisation of treatment response in children.

The main features and steps of the approach that will be discussed throughout the different chapters in this thesis are summarised in Figure 2. As sketched out in the diagram, we attempt to reverse-engineer the process, by identifying the elements in the causal chain between treatment and response. We first explore the feasibility and impact of personalised treatment with AEDs using a model-based approach. These principles are illustrated for a range of drugs for which covariate effects have been identified and parameterised into pharmacokinetic models. This exercise aims to show the advantages of inferential methods over empirical dose selection. It also provides an opportunity to evaluate the impact of

combining different approaches to characterise interindividual differences, such as the use of therapeutic drug monitoring. Given the limited application of modelling and simulation in clinical research with AEDs, we select a paradigm compound to demonstrate how drug-disease models can be used with population-wide data to accurately characterise pharmacokinetics, exposure-response relationships and covariate effects in the target population. Taking into account its therapeutic indication in partial onset and primary generalised tonic-clonic seizures, the choice of lamotrigine as a paradigm compound offers insight into all the necessary elements required for the implementation of model-based dosing algorithms. It can be anticipated that the similar principles and parameterisation can be applied to other antiepileptic drugs.

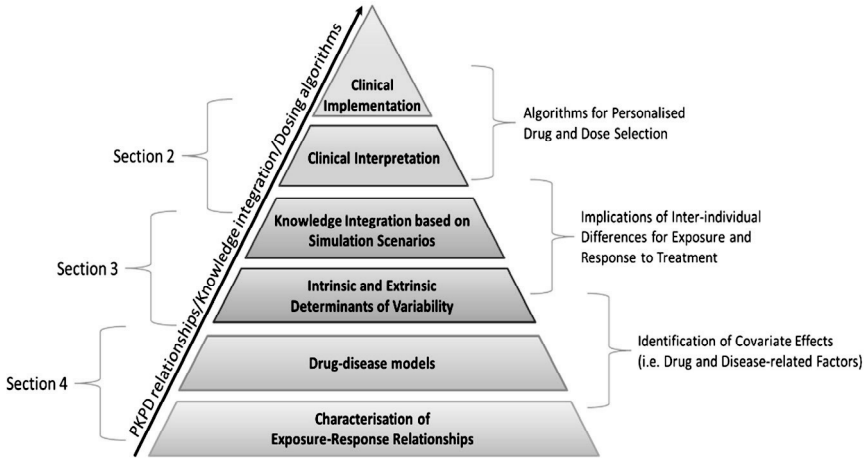


Figure 2. Diagram describing the different steps and themes presented in this thesis, which are required for the implementation of model-based algorithms aimed at the personalisation of the treatment of paediatric patients with epilepsy.

We anticipate that the concepts presented here offer more than just an opportunity for the optimisation of the treatment of paediatric patients. Our approach may provide answers to a range of clinical questions regarding the drug and dose selection. We endeavour to address the following:

1) Based on current clinical practice, ***can interindividual differences in exposure to AEDs and inadequate response in some patients be explained by size and age-related covariate factors?***

2) Assuming similar exposure-response relationships and target therapeutic range in adults and children, ***what are the implications of the commonly recommended empirical dosing in mg/kg?***

3) Given that the vast majority of drug-drug interaction studies are performed in adults ***can one assume similar effects in the paediatric population?***

4) ***Can model-based dosing algorithms minimise the need for treatment switch and combination therapy?***

5) Assuming comparable exposure-response relationships in adults and children, ***which data are required and which criteria should guide the selection and personalisation of paediatric doses?***

6) Assuming different exposure-response relationships in adults and children, ***which data are required and which criteria should guide the selection and personalisation of paediatric doses?***

An outline of the scope of the research and details on the implementation of the different sections are presented in the next paragraphs.

Section II - Knowledge integration

The development and therapeutic use of anti-epileptic drugs (AEDs) is encumbered by a number of complex interactions, involving pharmacokinetics (PK), pharmacodynamics (PD), and disease heterogeneity [13]. Some of the complexities are related to the episodic nature of the disease, the non-continuous nature of clinical measures of efficacy (endpoints), whereas others arise directly from the poor understanding of exposure-response relationships, which is further compounded by variable disease progression. Some of these complexities have been discussed previously in **Chapter 1** and make evident the need for further knowledge integration if one aims to optimise treatment and dosing regimens. They also have implications for the design of clinical trials and the analysis of the resulting data.

If model-based dosing algorithms are to be developed for personalisation of treatment with AEDs, it is essential to establish which covariate factors (intrinsic and extrinsic sources of variability) contribute to changes in exposure and response to AEDs. Taking into account sample size requirements, we assume that nonlinear mixed effects modelling is a sufficiently robust methodology to characterise covariate effects and establish the correlations between model parameter and covariate factor. Therefore, our research starts in **Chapter 3** with a comprehensive review of the pharmacokinetic and pharmacodynamic models for anti-epileptic drugs in adults, children and neonates. Publications in which model-based methodologies have been applied to describe exposure and response to the most commonly used AEDs, including carbamazepine, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine (and metabolite MHD), phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide will be identified and summarised. During data extraction, focus will be given to details regarding model parameterisation and evidence of predictive performance for subsequent application of the model in the evaluation of personalised or individualised therapy. In addition, a full tabular overview of model parameterisation will be provided, including details on the modelling approach, relevant parameter values and code syntax. Those who are unfamiliar with the principles of pharmacokinetic

and pharmacokinetic-pharmacodynamic modelling are invited to review some key references, in which clinical applications and impact of model-based approaches are outlined [14–17]. Given the objectives of our investigation, data will be split into three categories, namely adults (> 16 years), infants, children and adolescents (paediatric patients, age 1 month - 16 years), and pre-term and term new-borns (neonates, age 0 – 1 month). It should become evident whether knowledge about parameter distributions and covariate effects is currently being used to select dosing regimens for an individual patient before the start of treatment, i.e., by taking into account patient specific characteristics.

Section III - Model-based dosing algorithms

Whilst it can be anticipated that limited evidence is available of the exposure-response relationships for AEDs in adults and children other than clinical data from efficacy trials, this does not need to represent a hindrance for the evaluation of the concepts underpinning the use of model-based dosing algorithms. In **Chapter 4**, we will assess the benefits and advantages of model-based dosing algorithms by exploring the clinical relevance of covariate effects, with special focus on the consequences of intrinsic sources of variability on pharmacokinetics. An assumption is made with regard to the therapeutic exposure ranges defined for adults, i.e., that these levels do reflect the desirable target levels in children. In addition, we hypothesise that for a given seizure type, the PKPD relationships are similar in adults and children. Using simulation scenarios and optimal design concepts we will attempt to identify suitable titration schemes and dosing algorithms and possibly personalise the treatment of seizures for the 11 most commonly used AEDs. In addition to a reference regimen based on a standard dose for all patients, a series of scenarios will be considered in which doses are adjusted according to i. individual clearance estimates (CL), as predicted by population PK models, and ii. individual clearance estimates, obtained by therapeutic drug monitoring according to different sampling schemes. Attainment of steady-state target exposure will be used as performance criterion. It can be anticipated that the implementation of model-based titration and dosing algorithms may be of particular relevance for 10-20% of patients who still show unresolved seizures when their target

dose has been achieved. This approach may also allow the identification of individuals within the group of patients who would respond to optimised regimens, but currently remain refractory to treatment and are said to have drug-resistant epilepsy.

Another important aspect in clinical practice, which should be considered in the development of model-based dosing algorithms, is the need for combination therapies. Despite evidence on the role of pharmacoresistance and progression of the underlying pathological processes, the lack of response can be partly explained by inter-individual variability in the pharmacokinetics. The impact of such variability can be particularly important in the paediatric population, where exposure may vary due to maturation processes and developmental growth [13,18,19]. In addition, children who do not adequately respond to first-line treatment are given multiple AEDs in combination, which can lead to pharmacokinetic and pharmacodynamic drug-drug interactions (DDIs). Bearing in mind current clinical practice, in **Chapter 5** we aim to assess the impact of DDIs on the exposure to AEDs and establish the need for further dose adjustment for combination therapies. Using simulation techniques, a range of scenarios will be evaluated for 11 of the most commonly used AEDs, including different drug combinations and dose levels for both adult and paediatric patients. For each scenario, virtual patients will be simulated taking into account interindividual differences in clinical and demographic characteristics. We aim to identify the dose or dose levels that maximise the fraction of patients that reach and remain within the target exposure range for each drug. The impact of DDIs on the systemic exposure of the first-line or alternative first-line AED will be subsequently assessed based on clinically relevant dosing regimens and combinations. Here again we hypothesise that for a given seizure type, the PKPD relationships are similar in adults and children. In addition, we assume that differences in individual sensitivity to individual drug effects are captured by the proposed target range, whereas resistance to treatment would impose exposure to higher drug concentrations, which are likely to be associated with poor tolerability. We anticipate that our analysis will assist the review of clinical guidelines, taking into account the role of covariate factors in future dosing recommendations. Most importantly, it will provide clinicians further

insight into the role of PK variability in the overall efficacy and safety profile of AEDs.

Clearly, our ability to evaluate the implications of interindividual variability in pharmacokinetics and pharmacodynamics of AEDs and identify covariates or predictors of exposure and response depends on the quality of evidence. As the work described in the first two sections of this thesis relies primarily on the published literature, it should be highlighted that many of the studies involved non-controlled observational data obtained from clinical practice, whereas the collection of pharmacokinetic data in the case of clinical trials is usually a secondary or even exploratory objective.

In addition, with a few exceptions, the vast majority of the population pharmacokinetic modelling reported in the clinical literature lack stringent validation procedures, which support their prospective utilisation for simulations and/or prediction purposes. In fact, there appears to be no single example in neurology of the implementation of such concepts. In the next section of this thesis we will focus therefore on the use of approaches that ensure optimised evidence generation and improved assessment of the dose rationale for the paediatric population.

Section IV - Optimised evidence generation and evidence synthesis

The design and execution of clinical trials in adult patients with epilepsy is generally perceived as challenging. Restrictions exist on the type of patients that may be included; trials are required to apply a design where add-on medication is given to patients who have already unsuccessfully received multiple other treatments. Moreover, the pre-existing AEDs are generally not stopped before or during the trial. Consequently, these trial protocols are not designed to provide insight into exposure-response relationships or disentangle possible pharmacodynamic drug-drug interactions. As such, bias may occur regarding the efficacy and safety of the dose and dosing regimen under investigation. This situation usually complicates the extrapolation of study findings to a wider patient population.

In fact, the evaluation of pharmacokinetics and response is often limited to a statistical summary of the clinical endpoints along with the predefined statistical hypothesis test results. The primary endpoint is generally the percentage of patients that achieve treatment success, defined as a reduction in seizure frequency of at least 50% compared to baseline. Other (primary and secondary) endpoints include the time to first seizure, average population change in seizure frequency, probability of side-effects, etc. The analysis of seizure count data is complex and typical, non-parametric approaches are not suitable to describe individual patterns of response. These methods tend to weight response based on seizure frequencies over a time-period, which leads to the loss of information available for the characterisation of intra- and inter-individual variability, as well as eventual covariate factors or predictors. If a trial includes the evaluation of pharmacokinetics, data are usually summarised using non-compartmental methods, which limit the description of pharmacokinetic properties to total exposure with the area under the concentration vs. time curve (AUC), peak concentration, elimination by terminal half-life, etc. Interindividual variability in these analyses is captured by standard deviation of the parameters.

The issues highlighted above are compounded by additional practical and ethical constraints when considering the design and execution of clinical trials in children with epilepsy. Consequently, the value of new data is tremendously higher than in a standard protocol involving adults. Yet, little attention has been paid to the role of methodologies that support evidence synthesis, whilst keeping the burden for the children to a minimum. Therefore, we propose to integrate evolving concepts in paediatric clinical pharmacology into the evaluation of the dose rationale for children. In a very simplistic manner, it can be said that three scenarios can be used to determine the rationale for paediatric clinical trials: 1) if differences between adults and children exist in disease and its progression, which cannot be predicted from data obtained in adults, then pharmacokinetic and efficacy data must be generated in children to establish the effective dose and dosing regimen; 2) if the disease and its progression can be deemed comparable across populations (or are considered different in children, but can be predicted from data obtained in adults) and the same

clinical endpoints are used to assess response in adults and children, then bridging concepts can be applied. In this situation, collection of pharmacokinetic and eventually pharmacodynamic data in children in conjunction with evidence of exposure-response relationship (and consequently of the efficacious exposure levels) in adults should be sufficient to define the dose rationale for the paediatric population; 3) in some cases it is also conceivable that pathophysiological processes and pharmacological mechanisms are sufficiently understood to allow full extrapolation of efficacy findings from the adult population without the need to generate efficacy data in children. In these circumstances, pharmacokinetic data in children should be used in conjunction with evidence of exposure-response relationship (and consequently of the efficacious exposure levels) in adults to adjust for differences in drug disposition and formulation to be used in the paediatric population. In all three cases the quality of the data collected is crucial to establish not only the effect size of a treatment, but also to define the dose rationale.

Whilst historically, evidence of different types of epileptic seizures and consequently differences in the diagnosis of epilepsy have been used justify the need for efficacy trials in children, limited efforts have been made to establish whether exposure-response relationships are indeed different between the two populations. Consequently, this has hampered the evaluation and potential implementation of bridging and extrapolation concepts. Using lamotrigine as a paradigm compound, we attempt to characterise exposure-response relationship of lamotrigine in adults and explore the feasibility of extrapolating efficacy based on the attainment and maintenance of target exposure.

First, in **Chapter 6**, we propose the use of a population-wide approach, in which pharmacokinetic data from patients from 0.2 - 91 years of age are pooled together, for an integrated analysis of the effect of covariates on the pharmacokinetics of lamotrigine. From a methodological perspective, allometric concepts will be used to describe the effect of age- and size-related differences on the pharmacokinetics of lamotrigine. If needed, a maturation function will be considered to describe changes in CL in infants and toddlers. Given the limited range of dose levels used for companion

drugs in combination therapy, drug-drug interactions will be parameterised as discrete covariates. Assuming a common target therapeutic range in adults and children, we illustrate how the covariate effects can be characterised and validated using a model-based approach. In addition to standard diagnostics and goodness-of-fit criteria, the predictive performance of the model will be evaluated using internal and external validation procedures, including numerical predictive checks, normalized prediction distribution error (NPDE) and nonparametric bootstrapping of the parameter estimates obtained with the final model. This is a critical aspect of the implementation of model-based dosing algorithms, as evidence of predictive performance has not been the focus of publications aimed primarily at the estimation of relevant model parameters. Metrics of predictive performance provide insight into other important validation criteria for the proposed dosing algorithms, such as sensitivity and specificity [20–22].

After having identified relevant covariate effects on the pharmacokinetics of lamotrigine, the next obvious step is the assessment of the exposure-response relationships of lamotrigine. In **Chapter 7**, we attempt to evaluate innovative modelling approaches to describe drug effects on episodic seizure events and identify clinically plausible influential factors affecting response in adult patients. Given the possibility to explore parameterisations in which drug- and disease-specific properties can be assigned to distinct parameters, we also aim to assess whether different exposure-response relationships are required to predict treatment response in partial onset and primary generalised tonic-clonic seizures. To this purpose data from clinical trials of lamotrigine, in which pharmacokinetics and efficacy were assessed in adults, will be pooled and analysed. In spite of the limited number of doses used during the maintenance phase, data obtained during the titration phase will be included in the analysis. It will be assumed that drugs effects are not delayed relative to the onset of treatment, i.e., that difference in response during titration is driven primarily by changes in exposure.

From a methodological perspective, instead of evaluating treatment response based on a dichotomous or binary measure (e.g decrease > 50% seizure rate), we propose to use mathematical concepts that are appropriate for the description of count data, as is the case for seizure frequency, which are usually described as numbers of events per interval. Naturally, zero event/count is also a possibility, especially in the case of efficacy, where antiepileptic drugs suppress all seizures [23–25]. Mathematically, a useful place to start modelling event-count data is the Poisson distribution. Count events can also be described by hazard functions. Hazard describes the instantaneous rate of the events and determining whether and how this hazard varies with covariates, including treatment effect, is typically the aim of the data analysis. However, in the case of epileptic seizures it is likely that time affects the hazard, i.e., the hazard is not constant, a repeated time to event analysis may be required.

The most important count model is the Poisson model, but the assumption of a Poisson distribution implies equality of the mean and the variance [26]. This property does not seem to apply to seizure events. Using a hierarchical modelling we attempt to address the so-called overdispersion phenomenon and estimate parameters that describe the event rate. Conceptually, the treatment effect is handled as a covariate effect, i.e., treatment alters the parameter(s) describing the probability and rate of events.

Given the chronic, episodic nature of epileptic seizures, we will also attempt to explore alternative methodologies, which enable characterisation of the underlying pathophysiological process and its progression (i.e., period of ictal activity followed by non-ictal intervals). Such an episodic process may also be described by multi-state models. In medicine, and more specifically in epilepsy, the states can describe conditions like healthy (non-seizure), seizure, worsening or complication of disease. Markov models and in particular hidden Markov models allow us to link the disease states (hidden layer) to the observed clinical symptoms (open layer) by means of statistical distributions. Hence, each state may be assigned to a clinically defined endpoint and may well have a pathophysiological analogue. Hidden Markov models (HMMs) have been successfully applied to model chronically recurring infections, such as herpes [27], and episodic diseases such as

migraine [28–30]. If necessary, stochastic methods will also be evaluated to ensure accurate characterisation of intra-individual variability over the course of treatment. Ultimately, these techniques provide us with the appropriate tools to assess whether differences in exposure only explain variability in response, or whether there are real differences in the underlying exposure-response relationship due to the different seizure types.

Lastly, in **Chapter 8**, we will illustrate the application of modelling and simulation concepts for the evaluation of treatment response and possible extrapolation of the dose from adults to infants and toddlers [31]. Data from children aged 1-24 months with partial type seizures receiving lamotrigine as adjuvant therapy will be used in this analysis. Based on the parameters describing the underlying exposure-response relationship and on covariate effects known to affect drug disposition we will apply clinical trial simulations to define the dose rationale for this population and explore opportunities to optimise prospective clinical trials in this population [8,32]. Of interest in this group of patients is the possibility to establish whether potential (biologically plausible) differences in disease alter the underlying exposure-response relationship or whether other factors explain differences in the clinical response phenotype, such as baseline seizure frequency, placebo effect or prior treatment failure. Our final goal is to show that model-based dosing algorithms can also be used as a design tool during drug development, supporting clinical pharmacology efforts such as bridging and extrapolation studies [33–35].

The last section of this thesis provides an integral summary of the findings and conclusions from the investigations presented throughout the previous chapters. In **Chapter 9**, we focus on the consequences of inaccurate dose selection and the implications of model-based dosing algorithms to guide the dose rationale for paediatric patients, In this concluding chapter, we revisit the concept of personalised medicine and attempt to shed light on the need to assess exposure-response relationships during the evaluation of efficacy and safety of novel molecules. We make clear that the current clinical paradigm (in which evidence generation is based solely on statistically significant separation from placebo or comparator arm) is

inefficient for the personalisation of treatment, and in particular for establishing the dose rationale for children. In addition, concrete recommendations are made for improving protocol design and data analysis of paediatric trials with antiepileptic drugs in which pharmacokinetics and efficacy are evaluated. We acknowledge that many methodological aspects remain to be explored, which relate to the heterogeneity of the disease in adults and children. This is presented along with the limitations imposed by the lack of intermediate measures or markers of pharmacology, which restrict the opportunities for characterising antiepileptic activity in humans before embarking into expensive and often complex clinical trials.

We anticipate that advancement of pharmacotherapy with antiepileptic drugs will require a different regulatory framework and a shift in the current clinical reasoning, with further attention to the so-called *level of evidence* needed for the assessment of pharmacokinetics, safety and efficacy and how model-based inferential methods can be applied to the analysis and interpretation of clinical findings.

References

1. Magiorkinis E, Sidiropoulou K, Diamantis A. Hallmarks in the history of epilepsy : Epilepsy in antiquity. Epilepsy Behav. 2009;17(1):103–8.

2. Sidiropoulou K, Diamantis A, Magiorkinis E. Hallmarks in 18th- and 19th-century epilepsy research. Epilepsy Behav. 2010;18(3):151–61.

3. Schindler W, Blattner H. Über Derivate des Iminodibenzyls Iminostilben-Derivate. Helv Chim Acta. 1961;44(3):562–753.

4. Vossen R. Uber die antikonvulsive Wirking von Succinimiden. Dtsch Medizinische Wochenschrift,. 1958;83:1227–1230.

5. Meunier H, Carraz G, Neunier Y, Eymard P, Aimard M. Propriétés pharmacodynamiques de l'acide n-dipropylacetique. Therapie. 1963;18:435–8.

6. Krumholz A, Wiebe S, Gronseth GS, Gloss DS, Sanchez AM, Kabir AA, et al. Evidence-based guideline : Management of an unprovoked first seizure in adults American Academy of Neurology and the American Epilepsy Society. 2015;

7. French JA, Kanner AM, Bautista J, Abou-khalil B, Harden CL, Theodore WH, et al. Efficacy and Tolerability of the New Antiepileptic Drugs , I : Treatment of New-Onset Epilepsy : Report of the TTA and QSS Subcommittees of the American Academy of Neurology and the American Epilepsy Society. Epilepsia. 2004;45(5):401–9.

8. National Institute for Health Care and Excellence. Clinical guideline [CG137]. Epilepsies: diagnosis and management. 11 jan 2012 [Internet]. [cited 2016 Oct 6]. Available from: https://www.nice.org.uk/guidance/ cg137/resources/epilepsies-diagnosis-and-management-35109515407813

9. Buchthal F, Svensmark OLE. Aspects of the Pharmacology of Phenytoin (Dilantina) and Phenobarbital Relevant to their Dosage in the Treatment of Epilepsy. 1(30).

10. Kinderformularium. Nederlands Kenniscentrum voor Farmacotherapie bij Kinderen (NKFK). 2016.

11. Paediatric Formulary Committee. BNF for children. London: BMJ Group, Pharmaceutical Press, and RCPCH Publications; 2016.

12. Murad MH, Asi N, Alsawas M, Alahdab F. New evidence pyramid. 2016;(August):125–8.

13. van Dijkman SC, Alvarez-Jimenez R, Danhof M, Della Pasqua O. Pharmacotherapy in pediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go. Expert Opin Drug Metab Toxicol. 2016;12(10):1143–56.

14. Sheiner LB, Steimer J-L. Pharmacokinetic/Pharmacodynamic Modeling in Drug Development. Annu Rev Pharmacol Toxicol. 2000;40(1):67–95.

15. Krekels EHJ, Van Den Anker JN, Baiardi P, Cella M, Cheng KY, Gibb DM, et al. Pharmacogenetics and paediatric drug development : issues and consequences to labelling and dosing recommendations Pharmacogenetics and paediatric drug development : issues and. Expert Opin Pharmacother. 2007;8(12):1787–99.

16. Bellanti F, Della Pasqua O. Modelling and simulation as research tools in paediatric drug development. Eur J Clin Pharmacol. 2011 May;67 Suppl 1:75–86.

17. Zineh I, Woodcock J. Clinical Pharmacology and the Catalysis of Regulatory Science : Opportunities for the Advancement of Drug Development and Evaluation. 2013;(January):515–25.

18. Thomson AH, Brodie MJ. Pharmacokinetic Optimisation of Anticonvulsant Therapy. Clin Pharmacokinet. 1992;23(3):216–30.

19. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. Clin Pharmacokinet. 2013 Aug;52(8):627–45.

20. Parikh R, Mathai A, Parikh S, Sekhar GC, Thomas R. Understanding and using sensitivity , speci Þ city and predictive values Positive Predictive Value (PPV). (February 2008).

21. Ghaaliq A, Mb L, Frca C, Mccluskey A, Chb MB. Clinical tests : sensitivity and specificity. 2008;221–3.

22. Brooks E, Tett SE, Isbel NM, Staatz CE. Population Pharmacokinetic Modelling and Bayesian Estimation of Tacrolimus Exposure: Is this Clinically Useful for Dosage Prediction Yet? Clin Pharmacokinet. 2016;55(11):1295–335.

23. Plan EL. Modeling and simulation of count data. CPT pharmacometrics Syst Pharmacol. 2014;3(August 13):e129.

24. Zucchini W, MacDonald IL, Langrock R. Hidden Markov Models for Time Series: An Introduction Using R, Second Edition. Chapman and Hall/CRC; 2016.

25. Deng C, Plan EL, Karlsson MO. Approaches for modeling within subject variability in pharmacometric count data analysis: dynamic inter-occasion variability and stochastic differential equations. J Pharmacokinet Pharmacodyn. 2016;43(3):305–14.

26. Scott JG. Logit , Poisson , and Cox regression models : summary notes. :1–7.

27. Crespi CM, Cumberland WG, Blower S. A Queueing Model for Chronic Recurrent Conditions under Panel Observation. 1993;(March 2005):193–8.

28. Maas HJ, Danhof M, Della Pasqua OE. Prediction of headache response in migraine treatment. Cephalalgia. 2006 Apr;26(4):416–22.

29. Anisimov V V, Maas HJ, Danhof M, Pasqua O Della. Analysis of responses in migraine modelling using hidden Markov models. 2007;(March):4163–78.

30. Maas HJ, Snelder N, Danhof M, Pasqua O Della. Prediction of attack frequency in migraine treatment.

31. Sillanpää M, Schmidt D. Predicting antiepileptic drug response in children with epilepsy. Expert Rev Neurother. 2011 Jun;11(6):877–85; quiz 886.

32. Jadhav PR, Kern SE. The need for modeling and simulation to design clinical investigations in children. J Clin Pharmacol. 2010 Sep;50(9 Suppl):121S–129S.

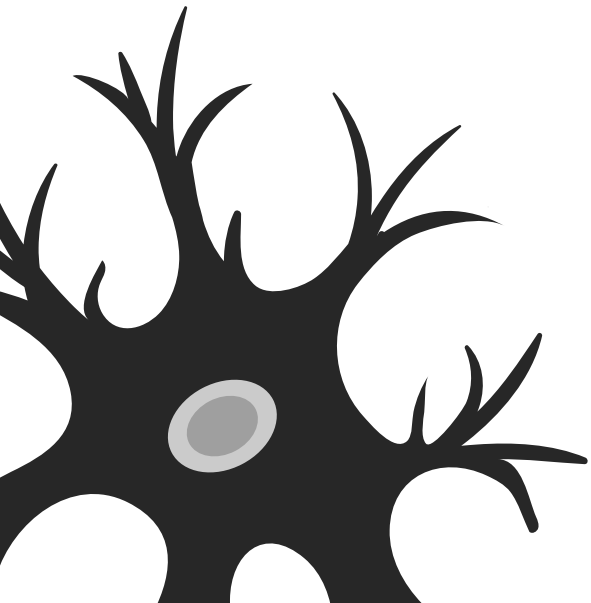
33. Anderson BJ, Holford NHG. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol. 2008 Jan;48:303–32.

34. Articles S, Cella M, Danhof M, Pasqua O Della. articles Bridging Strategies for Drug Combinations in Pediatric Indications. Clin Pharmacol Ther. 2009;91(4):726–33.

35. Bellanti F, Di Iorio VL, Danhof M, Della Pasqua O. Sampling Optimization in Pharmacokinetic Bridging Studies: Example of the Use of Deferiprone in Children With β-Thalassemia. J Clin Pharmacol. 2016;56(9):1094–103.

SECTION II

KNOWLEDGE INTEGRATION



CHAPTER 3

PHARMACOKINETIC AND PHARMACODYNAMIC MODELS FOR ANTI-EPILEPTIC DRUGS IN ADULTS, CHILDREN, AND NEONATES

Pharmacokinetic and pharmacodynamic models for anti-epileptic drugs in adults, children and neonates

Sven C. van Dijkman, Ricardo Alvarez-Jimenez, Celine H. Lemoine, Francesco Bellanti, Meindert Danhof, Oscar E. Della Pasqua

Submitted for publication to Clinical Pharmacokinetics

SUMMARY

There is no general consensus regarding the optimal dosing strategies for anti-epileptic drugs (AEDs). Empirical guidelines have been developed to guide physicians, but the use of AEDs remains to be improved, especially in young children. On the other hand, numerous pharmacokinetic (PK) and pharmacodynamic (PD) models for AEDs have been published, which could be used as basis for more efficient personalised dosing algorithms. In this systematic review we aim to provide a comprehensive overview of the PK and PKPD models for the most commonly used AEDs. A PubMED search was performed to identify PK and PKPD models describing systemic exposure and response to carbamazepine, clonazepam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine (and metabolite MHD), phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide. Searches resulted in 1827 articles, of which 173 contained models for review. Data were extracted and summarised into tables including the demographics, model parameter values, and covariate factors. Model codes were subsequently re-created and several simulation scenarios were performed to illustrate the implementation of dosing algorithms, taking into account clinically relevant covariates. Our findings show that despite the changes in the paediatric legislation, the use of PK modelling remains limited in young children and neonates. Most strikingly is the absence of data on the PKPD relationships of AEDs in patients. Whereas optimal dosing is not a requirement for the approval of medicines, the lack of PKPD models appears to perpetuate trial and error in clinical practice, hindering the identification of suitable dosing algorithms for patients with epilepsy.

Key Points

- Given that the PKPD relationships of most anti-epileptic drugs has not been characterised, identification of improved dosing algorithms remains challenging for most patients with epilepsy.
- Despite the evidence of covariate effects on the pharmacokinetics of anti-epileptic drugs, approved doses and dosing regimens have not been optimised to take such covariate effects into account.
- The lack of PKPD models appears to perpetuate trial and error in clinical practice, especially in young children (<2 years) and neonates.

1. Introduction

Seizure control forms the basis for the treatment of epilepsy, although not everyone with the condition will need to be treated. For a large number of patients, treatment of epileptic seizures often requires long-term pharmacotherapy with anti-epileptic drugs (AEDs). However, due to our limited ability to predict disease progression and poor understanding of individual exposure-response relationships, clinical guidelines rely upon the use of empirical titration to response, i.e., a typical patient is started at a safe low dose that is gradually increased until the seizure reduction is achieved or dose-limiting adverse events occur. Despite the use of an apparently cautious approach, titration and tapering procedures render it difficult to identify optimal doses, as treatment choices do not fully account for the underlying variability in pharmacokinetics (PK), pharmacodynamics (PD), and pathophysiology [1]. In fact, variability in the exposure-response relationship results in some patients experiencing side-effects already at sub-therapeutic concentrations, while some do not respond to treatment even at supra-therapeutic concentrations. This situation has led to the perception that therapeutic drug monitoring (TDM) may have limited value and consequently clinicians should better closely follow the observed response [2]. TDM use has been further discouraged by the international league against epilepsy (ILAE) except for a few specific circumstances [3]. Their suggestion is that TDM has relevance as a marker of the AED

concentration range at which an individual patient has achieved seizure freedom, so that when for some reason (e.g. aging, pregnancy, polypharmacy), changes in exposure occur, dose adjustments can be made to ensure attainment and maintenance of previously efficacious drug levels. Consequently, current pharmacotherapy guidelines do not provide clinicians with any other patient specific recommendations than the approved dose range for which efficacy has been demonstrated in clinical trials. As such, it remains impossible to prospectively select doses taking into account intrinsic (e.g., tolerance, co-morbidities) and extrinsic (e.g. drug-drug interactions) factors known to affect the exposure and response to AEDs. This situation also prevents better use of AEDs as prophylactic therapy in acute conditions, such as head trauma, or in febrile seizures in neonates.

Clearly, the importance of dosing algorithms, rather than generic dosing recommendations cannot be overlooked in epilepsy, as concepts such as personalised medicine evolve into daily clinical practice. A number of examples are available across different therapeutic areas, which illustrate how dosing algorithms have been implemented to optimise treatment, thereby increasing efficacy and reducing the risk of adverse events in the target patient population [4–7]. Similar concerns regarding the start and maintenance dose of AEDs also apply to the onset of treatment with drugs known to have a narrow therapeutic window or in cases where delayed the overall treatment response is delayed relatively to the start of the therapeutic intervention. Of note is the role of covariate effects, particularly among those individuals who are at the extreme of the covariate distribution, such as in the case of age (e.g. new-borns and elderly), organ function or phenotype (e.g. poor and fast metabolisers). As indicated above, the current dosing recommendations for AEDs do not incorporate pharmacokinetic or pharmacodynamic factors that could affect AED-dose requirements. Knowledge of the extent to which these factors affect treatment response could help in the prediction of personalised and possibly individualized loading and maintenance doses and dosing regimens. In this context, model-based algorithms may offer a unique opportunity for the advancement of pharmacotherapy with AEDs. Some of the key principles underpinning the use of such algorithms have been

recently described by de Castro et al. [4], who show the implementation of a model-based dosing algorithm for busulfan in patients undergoing bone marrow transplantation. Similarly, various initiatives have been taking place to establish the predictive performance of different dosing algorithms for anticoagulants [8]. Moreover, in paediatric oncology, the identification of covariate effects on the pharmacokinetics of doxorubicin has raised awareness of clinical community and resulted in efforts that ensure prospective validation of proposed dosing algorithms, leading to a regulatory process and subsequent label changes [9]. The implementation of such principles in clinical practice is further highlighted by individualised treatment strategies which integrate Bayesian inference and control theory (e.g. the use of TDM for robust estimation of patient-specific parameters) with *in-silico* approaches such as model-based simulations [10]. Such efforts remain elusive in the field of epilepsy.

Here, we aim to provide a comprehensive overview of the published PK and PKPD models for first and second line AEDs. Focus will be given to the model parameterisation and evidence of predictive performance for subsequent application in the evaluation of personalised or individualised therapy. Those who are unfamiliar with the principles of pharmacokinetic and pharmacokinetic-pharmacodynamic modelling are invited to read some key references, in which clinical applications and impact of model-based approaches are outlined [11–14]. It should become evident that one of the main reasons for the predictive performance of model-based algorithms is that PK, PKPD, and disease models do not only establish a defined correlation between dose, exposure, and response. In addition to the underlying parameter distributions, the hierarchical structure of population models also allows variability to be characterised both within and between patients. The availability of such a framework for AEDs offers the opportunity to personalise treatment *a-priori*, i.e. to select dosing regimens based on covariates before the start of treatment. It also enables individualisation of treatment by incorporating patient specific data on exposure and response.

2. Methods

According to Meyer et al. [15] the most commonly used AEDs for long-term seizure control are: carbamazepine (CBZ), clonazepam (CLNZ), ethosuximide (ETHS), gabapentin (GBP) and its prodrug gabapentin enacarbil (GBP-E), lamotrigine (LMT), levetiracetam (LVT), oxcarbazepine (OXC) and its main pharmacologically active metabolite monohydroxy derivative (MHD), phenytoin (PHT), topiramate (TPM), valproic acid or valproate (VPA) and zonisamide (ZNS). Given the scope of our review drugs prescribed solely for the treatment of status epilepticus (i.e., diazepam and lorazepam) were excluded from this list. Furthermore, phenobarbital (PHB) was included, as it is the first line treatment in neonatal epilepsy and it is still considered a first-line treatment for partial and generalized tonic–clonic seizures in developing countries by the World Health Organization [16],[17].

Based on this initial AED selection, a structured search strategy was implemented in PubMED to identify PK and PKPD modelling details. Search criteria included preselected MESH terms, software tool and compound name. Searches were performed with search string: (((PK OR PKPD OR PK/PD OR PK-PD) AND (model OR population)) OR (NONMEM OR MONOLIX)) AND [DRUG NAME]. An exception was made for valproic acid, where [DRUG NAME] was substituted with ((valproic acid) OR valproate). Searches were restricted to clinical data and compartmental modelling approaches, where available. Publications including detailed data analysis and model structure were selected as the source for subsequent data abstraction. Any gaps regarding drug disposition characteristics or pharmacological activity were complemented where necessary, by (parameter) information from additional publications on the pharmacokinetics and pharmacodynamics of each compound. Note that the PubMED search engine automatically includes pharmacokinetics when searching for “PK”, pharmacodynamics when searching for “PD”, etc. Our initial search resulted in a total of 1827 articles, from which 173 articles were found to include PK or PKPD modelling details (**Fig. 1**, **Table 1**). As no relevant articles were found for ethosuximide, this compound was excluded from subsequent steps.

Despite evidence of age-related differences in the prevalence of seizure types, and the availability of recommended classification of paediatric patients based on age groups [18,19], data were abstracted and been split where possible into three categories, namely adults (> 16 years), infants, children and adolescents (paediatric patients, age 1 month - 16 years), and pre-term and term new-borns (age 0 – 1 month). This selection takes into account the patient population included in the original analysis reported in the publications, as well as age groups for which data was not available. Relevant model parameters and covariate factors were summarised for each population, including a description of their impact on dose and dosing regimen. Given the objective of this review, i.e., the identification of opportunities for the implementation of model-based dosing algorithms, data were presented in a structured, hierarchical manner, namely pathophysiology, pharmacodynamics, and pharmacokinetics. This was complemented by the inclusion of the main, probable and possible pharmacological targets for each AED, as proposed by Kwan et al. [20], and by therapeutic ranges reported by the ILAE [3]. In addition to the summary findings in the results section, a full tabular overview of the available PK and PKPD models was included in as supplemental material. Each file contains details on the modelling approach and relevant parameter values, including model structure, the relevant code syntax for prospective use of the model, and the internal and/or external validation, where available.

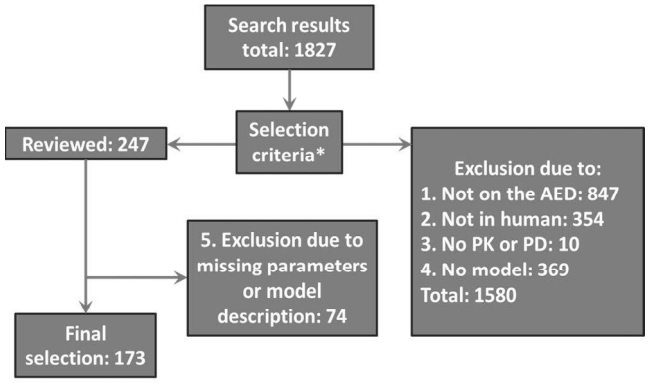


Fig. 1 Diagram of the search strategy including MESH terms used to systematically derive the literature included in this review. *Selection criteria were the description of a human PK, PD or PKPD model in the article.

Table 1 Literature search results and overview of the modelling approach and parameter values for each drug. Each supplemental file includes model structure, the relevant code syntax for prospective use of the model, and the internal and/or external validation, where available. An additional supplement is provided in which details of the methodology are outlined. Readers are invited to read this file to ensure appropriate interpretation of the modelling results in each supplemental file. **Supplemental files may be downloaded from www.AEDapt.org/PKPDmod.zip**

Drug	Number of articles†	No. of patients included for modelling purposes‡
Carbamazepine (CBZ)	29/358	5656
Clonazepam (CLNZ)	5/63	543
Ethosuximide	0/18	-
Gabapentin (GBP)	5/87	2051
Lamotrigine (LMT)	22/112	4407
Levetiracetam (LVT)	9/68	2841
Oxcarbazepine (OXC)	6/47	2020
Phenobarbital (PHB)	16/311	1158
Phenytoin (PHT)	37/361	3612
Topiramate (TPM)	11/65	2347
Valproic Acid (VPA)	30/313	5609
Zonisamide (ZNS)	3/24	342
Total	**173/1827**	**30586**

† Number of selected articles/number of articles found using the search criterion, based on searches on the 26th of July 2016. ‡ The utmost care was taken to make sure data that was used in multiple studies was not counted multiple times; however, this cannot be guaranteed due to the number of papers and a lack of reporting in some of the original papers.

3. Results

3.1 Carbamazepine

General (adult) pharmacology: Carbamazepine (CBZ) is a first-generation AED indicated for partial and tonic-clonic seizures. Its principal target is the voltage-gated Na+ channel.

PKPD relationships: No data available in the published literature other than evidence of efficacy in clinical trials at the approved doses [20]. No PKPD model has been identified for CBZ that provides evidence of the relationship between exposure and response. To date, only one attempt has been made to correlate peak concentrations (Cmax) with the occurrence of typical side effects such as dizziness, headaches, ataxia, nausea, etc. [21]. Its therapeutic concentration window is 4-12 mg/L [3]

Pharmacokinetics in adults: There has been controversy regarding the development of auto-induction of its metabolism [22–27]. While some reports suggest a negative correlation between dose and CBZ concentration/dose ratios [28–30] or a positive correlation between dose and CL values derived using such ratios [31,32], which are both indicators of auto induction, other publications do not seem to support that finding [21,33,34]. CBZ metabolism is thought to be induced within 20 to 30 days after the start of treatment or when co-administered with other drugs and enzyme inducers [23,32,35–37] and clearance is expected to increase until it reaches saturation [37]. A pharmacokinetic model describing metabolic induction indicated that differences in metabolic activity are detectable up to 2 weeks after the treatment is stopped [38].

PHB, PHT and VPA are usually considered to influence CBZ clearance to a clinically relevant degree, although the magnitude of the effect of such interactions varies between models [34,36,39–42]. Given the differences in model building between studies, it is difficult to determine whether the magnitude of the effect is really different. In the few cases in which such the magnitude of drug-drug interactions was investigated, no significant differences were found [34,41]. In addition, it is unclear whether differences in clearance between ethnicities exist. In most studies PK has only been assessed on one ethnicity at a time.

Pharmacokinetics in children: Many publications have evaluated the PK of CBZ in cohorts including adults and children [39,41–45], and children only [31,32,40,46]. Although each model took into account the impact of age and body weight, this was implemented differently in each investigation, which does not allow a direct comparison of the results. While the impact of auto-induction has not been universally included in models for adults, this does seem to be the case in most models including paediatric patients. Moreover, PK drug-drug interactions have been described across different age ranges. Bondareva et al. [47] showed that Bayesian dose adjustments based on TDM samples can dramatically improve dosing regimens by reaching drug concentrations within the therapeutic range, even though it is not yet clear whether similar therapeutic ranges should be used in children as in adults. Similarly, the apparent lack of evidence for ethnic differences in PK may also apply to children, but there is no data to support this assumption.

Pharmacokinetics in neonates: Tulloch et al. reported that "*determining an 'ideal' carbamazepine dose for neonates is difficult*" [48]. Their review on the PK of AEDs in neonates shows how sparse is the information on the ontogeny of metabolic pathways of CBZ and many AEDs. There has been an attempted to describe the maturation of CBZ clearance in neonates [49], but the model could not adequately predict concentrations in new patients, possibly due to the lack of covariate effects and small sample size available for the development of the model. A case report has mentioned the possibility to use CBZ in neonatology with good results [50], but the incidence of liver related toxicity [51,52] calls for more evidence before CBZ can be used effectively and safely in neonates.

3.2 Clonazepam

General (adult) pharmacology: Clonazepam (CLNZ) is an anxiolytic benzodiazepine derivative and has been used as a first-generation AED for myoclonic epilepsy, Lennox-Gastaut syndrome, infantile spasms and status epilepticus. Its principal target is the $GABA_A$ receptor, and its mechanism of action is similar to other benzodiazepines [20]. Chronic administration of

CLNZ often results in the development of tolerance, probably due to a reduction in binding sites by downregulation of GABA receptors [53]. This tolerance occurs in around 30% of patients, with an onset between 1-6 months after treatment initiation. Due to the development of tolerance, and the relatively strong adverse effects such as dysphoria and drowsiness that can occur even when exposures are maintained within the therapeutic range, CLNZ is only indicated for long term treatment in difficult-to-manage cases.

PKPD relationships: No data available in the published literature other than the evidence of efficacy in clinical trials at the approved doses. No PKPD models exist for CLNZ that provides evidence of the relationship between exposure and response. The therapeutic range for its antiepileptic effects is believed to lie between 0.02-0.07 mg/L [3], This range must be interpreted with caution as linking high serum concentrations of CLNZ to adverse effects has proven difficult.

Pharmacokinetics in adults: The pharmacokinetics and the interactions with other anti-epileptic drugs have been reported long ago in the 1980s [54,55]. However, the first models describing the PK of clonazepam in detail after administration of clonazepam as monotherapy or in combination with other AED were published much later [56–58]. It was shown that CLNZ clearance increased by 22% and 14%, when given in combination with CBZ and VPA respectively. A decrease in CLNZ exposure was reported in combination with phenobarbitone, presumably as a result of increased clearance, but the magnitude of change in clearance was not calculated. Inspection of the reported results suggest an increase in CL of up to 50% [59].

CLNZ clearance is dose-independent within the therapeutic concentration range, but shows a nonlinear relationship with body weight, which needs to be taken into consideration when determining individual doses. By contrast, the volume of distribution was determined to be linearly related to body weight [60]. In addition, as its absorption is highly variable, high peak concentrations may occur which result in adverse events in some patients. In this regard, a physiologically-based PK model was able to describe the absorption profile and thus might be useful to prevent toxic CLNZ levels

[61].. Given the aforementioned characteristics, CLNZ doses in mg/kg/day have been found to correlate well with steady-state concentrations. Consequently, prediction of maintenance doses based on a target steady-state concentration is possible and to a reasonable degree could be derived even without modelling. The challenge remains the variable absorption profile, which requires extended-release formulations or the physiologically-based models to prevent toxic levels. However, the available models do not fully account for the nonlinear relationship between CLNZ CL and body weight, making predictions eventually biased in children.

Pharmacokinetics in children: No specific paediatric models are available, despite the fact that models developed by Yukawa and collaborators included data that included children even younger than 1 year of age [56–58]. In addition, data shows that serum concentrations in children were found to correlate linearly with the dose, which points to (near-) dose proportionality in paediatric patients. A dose between 0.1-0.2 mg/kg usually should result in therapeutic concentrations, although as mentioned before, this does not eliminate the risk of adverse events. This target range contrasts with the doses proposed by Dahlin et al., who showed treatment response and less adverse events with an even lower dose of CLNZ [62].

Pharmacokinetics in neonates: There is very limited PK data in the neonatal population. As in older children, CLNZ clearance in neonates seems to be affected by body weight., even though patients with a post-natal age lower than 7 days exhibited a reduction in clearance of 50-70% compared to older infants [63]. The tested dose range of CLNZ seemed equally effective in this population as in older patients, despite evidence of patients being refractory the first line medication for neonatal seizures, i.e., phenobarbital. In absence of any other investigation in the neonatal population, dose and dosing regimens are currently based on the recommendations of 0.1 mg/kg by André et al. [63].

3.3 Gabapentin

General (adult) pharmacology: Gabapentin (GBP) is a second-generation AED indicated for partial seizures. Its mechanism of action is not fully understood, but is antiepileptic effect is presumably related to the inhibition of HVA Ca2+ channels. In addition, interactions at voltage-gated Na+ channels and an effect on GABA turnover are believed to contribute to the therapeutic efficacy [20]. ***PKPD relationships:*** No detailed modelling data are available in the published literature other than the evidence of efficacy in clinical trials at the approved doses. To date, there is only one PKPD model has based on hidden Markov Poisson function that correlates exposure to GBP (expressed in terms of total dose) with reduction in seizure frequency [64], and another one describing the probability of side effects (i.e., dizziness and somnolence) associated with systemic exposure (i.e., AUCs). This model shows that values higher than 200 mg/L·h (corresponding to a Css of roughly 8 mg/L) result in a 10% and 5% probability of dizziness and somnolence, respectively [65].

A wide therapeutic range has been identified for GBP, ranging between 2-20 mg/L [3]. Despite this wide interval, the incidence of adverse events is low. In fact, the absolute maximum tolerated dose has not been identified. One case was reported where the ingestion of 49 grams of GBP resulted in supra-therapeutic GBP plasma level of 62 µg/ml approximately 8 hours after ingestion, which was associated with only mild side effects (dizziness, lethargy) and no other clinically relevant abnormalities [66].,

Pharmacokinetics in adults: The PK of GBP after intravenous administration may be best described by a three-compartment model with linear elimination [67]. By contrast, oral GBP PK has been described most often by a one-compartment model with first-order absorption and elimination [65,68,69], of which only one [68] included the nonlinear bioavailability relative to increasing dose levels [70]. The nonlinearity in the oral absorption of GBP is explained by a saturation of the l-amino acid transporter in the gut. Some models take such saturation into account, allowing calculation of the percentage of the dose that will actually be absorbed [68,70], **Fig. 2** shows the relationship between the daily dose and absorbed fraction. From this correlation, we can assume that doses over

2000 mg/day do not result in significantly higher systemic exposure. GBP protein binding in plasma is very low and 95% of the circulating levels are excreted renally, resulting in no known PK drug-drug interactions with other AEDs during polytherapy. Nevertheless, potential interactions with other renally-cleared AEDs, such as levetiracetam and vigabatrin, may exist and dose adjustments should probably be considered in case of renal insufficiency or failure [71]. Because of its renal elimination route, GBP clearance is linearly correlated with creatinine clearance. Body weight influences both clearance and volume of distribution, either directly [69,72] or indirectly according to nonlinear relationships (allometry) or based on estimates of BSA and creatinine clearance [68]. Factors such as transporters, genotype or ethnic background do not seem to influence the disposition of GBP.

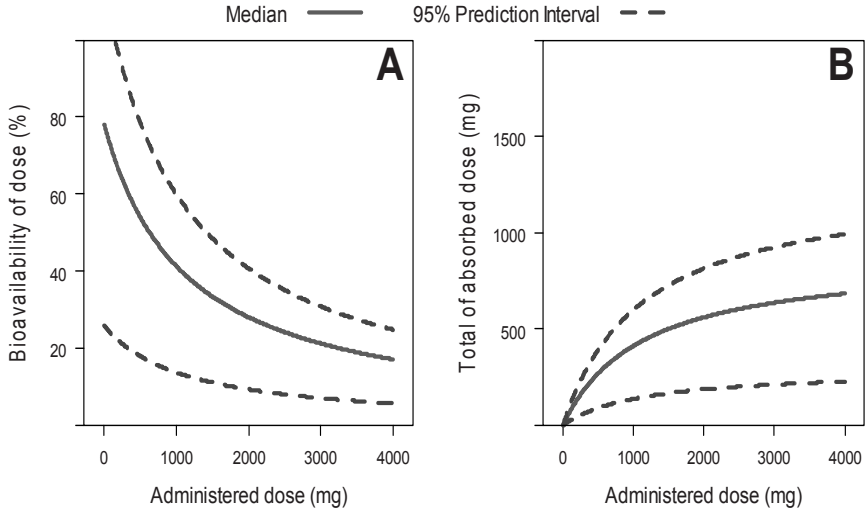


Fig. 2 Relationship between administered gabapentin dose (x-axis both panels) and the absorbed fraction (y-axis panel A) or total absorbed amount (y-axis panel B). Profiles are simulations based on the meta-analysis of Chen [70].

Pharmacokinetics in children: PK models for children have identified body weight as the most important covariate on the clearance and volume of distribution of GBP [69,73,74]. In addition, clinically relevant differences in clearance have been found between children from different ethnic groups

[69], which suggests the need for different dose adjustments across ethnic groups, even though no such differences have been reported for adult patients.

Pharmacokinetics in neonates: There is very limited PK data in the neonatal population. The use of GBP is not well documented in neonates, which can be explained by the fact that there are few indications for the use of this drug in this patient group. One case report has been published where a simple non-compartmental analysis of GBP at steady state concentrations was used to predict the dosing regimen for a single neonate with spinal issues resulting from drug abuse by the mother. Their goal was to alleviate pain while minimising the adverse effects such as sedation. The authors proposed a dose of 7 mg/kg once daily, which was predicted to result in a plasma concentration of 2 mg/L, a level which is deemed to be efficacious for pain relief in infants [75].

3.4 Lamotrigine

General (adult) pharmacology: Lamotrigine (LMT) is a second-generation AED indicated for treatment of partial and generalised seizures. The primary molecular target of lamotrigine is the voltage-gated Na+ channel, with a probable activity on HVA Ca2+ channels [20].

PKPD relationships: No data available in the published literature other than the evidence of efficacy in clinical trials at the approved doses. A PKPD model has been developed to assess the effect of LMT on QT interval prolongation, but at therapeutic doses no QT-prolonging effects are observed [76]. Although the originally reported therapeutic exposure range was 0.9- 2.3 mg/L [77], these values were later broadened to 0.9-3 mg/L [78] and it currently considered to lie between 2.5-15 mg/L [3].

Pharmacokinetics in adults: LMT is absorbed nearly completely, but its rate of absorption varies widely and is dependent on the formulation. Its volume of distribution has been normalised body weight, with values of approximately 1.5-2 L/kg [33,79,80]. However, no models have showed evidence of body weight as a covariate on volume of distribution [81–86]. LMT is eliminated by glucuronidation (both UGT-1A4 and UGT-2B7), with

genotype affecting its elimination rate [82]. Elimination is described by a first-order process with most authors reporting clearance values of 2-2.5 L/kg/h. Many drug-drug interactions are known to affect clearance, most notably CBZ (+45%), PHB (+40 to +60%), PHT (+60 to +120%), VPA (-60%), and oral contraceptives (+25%). The manner in which the co-medication affects LMT clearance seems to suggest that they can cancel each other out, e.g. the addition of both PHB and VPA to the LMT regimen may result in no net change in CL. In addition, ethnic differences in LMT clearance were found to have relatively small effect on systemic exposure [83].

Pharmacokinetics in children: Various models have been published in which the PK of LMT has been characterised in children [79,87–91], but none of these were in children younger than 2 years of age. Interestingly, non-modelling literature describes a relatively higher clearance in this same group (when adjusted for weight) compared to adults. Therefore, no function is available that describes changes in drug disposition during the first few years of life. Currently, recommended dose adjustments are based on empirical evidence, with increases between 35%-125% in the dose in mg/kg/day yielding similar exposure as in older children and adults [92].

Pharmacokinetics in neonates: There is very limited PK data in the neonatal population. No models are available for LMT in neonates. It should be highlighted that thanks to its favourable safety profile, LMT is also used during pregnancy. Data from non-compartmental analysis shows that during pregnancy, LMT maternal clearance is significantly increased (approximately 186%) and returns to regular levels shortly after delivery [93]. Given the evidence that LMT has been found to be safe and well tolerated by the developing foetus and new-borns [94], this drug represents a realistic option in neonatology. In infants younger than 4 weeks, therapy has been successfully initiated with a dose of 2 mg/kg per day with a dose increase every week until a maximum dose of 10 mg/kg per day was reached. Good response rates were achieved in this small sample of children [95], with many reports describing very few side-effects and serum concentrations within the normal therapeutic range for neonates who are exposed to LMT during lactation [96–100].

3.5 Levetiracetam

General (adult) pharmacology: Levetiracetam (LVT) is a second-generation AED indicated for partial and generalised seizures, and its principal molecular target is the synaptic vesicle protein 2A, while possible additional targets include HVA Ca2+ channels and GABAa receptors [20].

PKPD relationships: No detailed modelling data are available in the published literature other than the evidence of efficacy in clinical trials at the approved doses. Only one model has been developed by which the dose-response relationship was described for LVT [101]. Based on this model, a daily dose of 1408 mg was found to be 50% efficacious, indicating that this dose yields half the maximum effect of 69% seizure frequency reduction [102] (**Fig. 3**). The LVT therapeutic range lies between 12-46 mg/L [3].

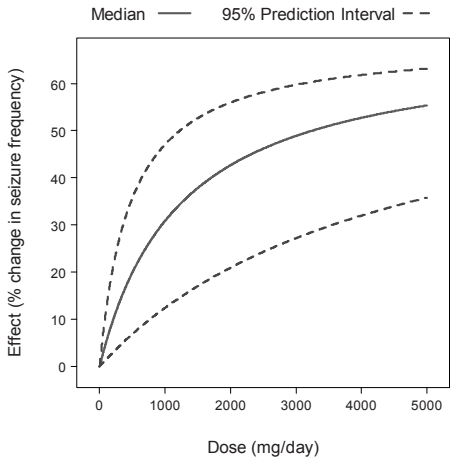


Fig. 3 Relationship between administered LVT dose (x-axis) and effect as percentage of change in seizure frequency compared to baseline (y-axis). Red line: median effect; blue dashed lines: 95% prediction interval of effect. Simulations based on Snoeck et al. [101]

Pharmacokinetics in adults: The PK of LVT has been described by a one compartment model with first-order absorption and elimination, with weight and age as correlated with clearance and volume of distribution

[102]. According to this model, LVT doses of between 1000-4000 mg/day to an adult of 70 kg should result in a typical average Css well within the LVT therapeutic window of 12-46 mg/L.

LVT is minimally metabolised and cleared primarily by renal processes. This leads to very limited potential for PK drug-drug interactions and allows clinicians to use LVT in combination with other AEDs without the need for adjustments in the dose regimen of either drug, even though PD interactions cannot be excluded (which may impose dose adjustments). The covariate found to most affect the clearance and volume of distribution of LVT is weight, although the weight-adjusted clearance differs greatly between studies [102–104]. In some cases creatinine clearance has also been used as predictor of LVT clearance [103,104]. The use of such models may be limited in very young children due to the nonlinear correlation between creatinine clearance, age and renal function [105].

Pharmacokinetics in children: Quite a few models are available that describe the PK of LVT in children [102,106–108]. Similarly to adults, weight was found to be the most important predictor of LVT clearance in children. Reported parameter values from different publications show comparable results, indicating that body weight is a strong covariate and as such can be used to optimize dosing regimens [107,108]. In contrast to the previous drugs, differences in clearance seem to be associated with ethnic differences [106], with very different values being reported for clearance in Chinese children as compared to Caucasians.

Pharmacokinetics in neonates: There is very limited PK data in the neonatal population. One model has been identified, which describes the maturation of LVT clearance during the first week after birth, with CL increase from 0.7 ml/min/kg on the day of birth to 1.33 ml/min/kg seven days thereafter [109]. On the other hand, another model has been developed in which clearance does not vary over time, with values of 1.21 ml/min/kg over the whole postnatal age of 0-32 days [110].

3.6 Oxcarbazepine

General (adult) pharmacology: Oxcarbazepine (OXC) is a second-generation AED indicated for partial and generalised tonic-clonic seizures. Its principal target is considered to be voltage-gated Na+ channels [20]. In contrast to other AEDs, the active moiety responsible for the antiepileptic effects of OXC is its main metabolite, mono-hydroxycarbazepine (MHD).

PKPD relationships: No detailed modelling data are available in the published literature other than the evidence of efficacy in clinical trials at the approved doses. The therapeutic window of MHD is considered to be 3-35 mg/L [3].

Pharmacokinetics in adults: As OXC is rapidly and almost entirely (approximately 95%) metabolised to MHD after oral administration, MHD concentrations can be modelled directly, using a one compartment model with first-order absorption and elimination, without including intermediate OXC concentrations. In addition, MHD and its metabolites show chiral properties with stereospecific metabolism. A multi-compartmental model has been recently developed describing the disposition of r S-MHD and R-MHD along with two major metabolites (S-MHD and R-MHD) [111]. MHD clearance has been correlated with age (peaking around 32 years [33]), gender, and weight. In addition, CYP450 enzyme-inducing drugs (e.g. CBZ, PHB, PHT) have been found to increase MHD clearance by roughly 30%, leading to dose adjustments [112–114]. MHD clearance usually lies between 2-2.5 L/h for a typical 70 kg adult. Whilst no clear differences have been observed between ethnic groups, it should be highlight that the number of patients from different ethnic groups may be limited to investigate such differences [114].

Pharmacokinetics in children: Most available PK models have included some data from different groups in the paediatric population. Consequently, the covariate effects described above for adults still holds true in this population. One exception, however, is a model including patients across the age range of 2 months to 17 years of age, in which clearance and volume of distribution were correlated with body surface area and height, respectively [114]. The relevance of these covariates was evaluated using a population of toddlers [115].

Pharmacokinetics in neonates: There is very limited PK data in the neonatal population. However, Bülau et al. showed that OXC and its metabolite 10-hydroxy-carbazepine pass the placenta barrier. Moreover, these authors showed that MHD is also transferred to a newborn through breastfeeding by mothers using OXC [116]. Based on the concentrations observed in this single neonate, a half-life of f 17 hours has been estimated for MHD, which corresponds to the values observed in older patients.

3.7 Phenobarbital

General (adult) pharmacology: Phenobarbital (PHB) is a first-generation AED indicated for partial and generalised seizures, neonatal seizures and status epilepticus. The principle target of phenobarbital is believed to be the GABAα receptor, with HVA Ca2+ channels and glutamate receptors as possible secondary targets [20]. Although it is approved in the aforementioned epileptic types, it is most prominently used in the treatment of neonatal seizures.

PKPD relationships: No detailed data are available in the published literature regarding the exposure-relationships of PHB other than the evidence of efficacy in clinical trials at the approved doses. One PKPD model has been developed which describes the correlation between PHB plasma concentrations with EEG signals. As this model was built in conjunction with pharmacokinetic modelling of data exclusively in neonates, details are provided below with the pharmacokinetics in neonates. The therapeutic window for PHB is considered to lie between 10-40 mg/L [3].

Pharmacokinetics in adults: PHB has a near-complete bioavailability (>95%) with a fast absorption reaching maximum concentrations between 0.5 and 4 hours [117]. In addition, PHB is eliminated mostly hepatically, with a minor contribution from renal processes. Its PK is described with a one compartment model with first order absorption and elimination. Its volume of distribution is typically directly related to body weight in a linear fashion, whereas clearance is most often non-linearly (allometrically) related to body weight, with an exponent that can range from 0.21-0.45. Drug-drug interactions have been described with CBZ, PHT, and VPA, all of which

decrease PHB CL by up to 47% [118–120]. Furthermore, CYP2C9 polymorphism leads to significant metabolic differences between slow and fast metabolisers [119,121,122]. This could also indirectly explain differences in PHB CL between ethnic groups, as the prevalence of different CYP2C9 phenotypes varies across different populations. Yet, no obvious differences have been detected for typical population estimates for clearance based on Asian and Caucasian patients.

Pharmacokinetics in children: Similar to adults, PHB PK in children can be described using a one compartment model with first order absorption and elimination. Volume of distribution in this population is also directly related to body weight, whereas the nonlinear relationship between CL and body weight is described by a larger exponent than the one estimated in adults (up to approximately 1.9), possibly due ontogeny of hepatic enzymes in very young children. Given the similarity of adult and paediatric models [118,119], the impact of CYP2C9 polymorphism, as well as the interaction with CBZ, PHT, and VPA can be considered to lead to effects of similar magnitude as in adults.

Pharmacokinetics in neonates: There is limited PK data in the neonatal population, but different PK models have been developed with the available data. Among them, a one compartment PK model has been developed in conjunction with allometry and a maturation function to describe the effect of body weight and ontogeny on clearance of PHB. On the other hand Yukawa et al. [123] developed a two-compartment model and first order elimination., in which total body weight was a covariate of the apparent volume of distribution and the post-natal age was correlated with the clearance of PHB. In an update to their model the same authors reported a decrease in PHB's clearance at high concentrations (above 50 mg/L), suggesting the possibility of non-linear (saturable) kinetics in this population [124]. Interestingly, in contrast to the other AEDs, efforts have been made to characterise the concentration-effect relationship of PHB in neonates. A three state Markov model has been used to describe PHB effects on the patterns from amplitude-integrated electro-encephalography (aEEG) patterns [125]. aEEG signals were analysed and categorised into separate states, which allowed the evaluation of the effect of PHB on the transition between three functional patterns or states, namely, burst

suppression (BS); discontinuous normal voltage (DNV) and continuous normal voltage (CNV). (**Fig. 4**). The transition between these states reflects improvement form high to intermediate ictal activity and finally to normal, as typically observed in healthy neonates). Using Markovian concepts, drug exposure is used as a covariate on the transition probabilities, with higher probabilities occurring with higher exposure levels. As shown in Van Den Broek et al. [125], increasing doses of PHB has a small, but significant effect on the transition probability in states 4 and 5 (**Fig. 5**). Based on these results, it becomes evident why the authors suggest the use of a second bolus infusion to patients receiving 20 mg/kg PHB (**Fig. 6**). Model-based simulations reveal that exposure ranges after 20 mg/kg PHB administered as a bolus infusion to neonates may result in PHB concentrations are close to or lower than the desired therapeutic range. It is assumed that exposures associated with levels below 20 mg/kg will have no effect on the transition probabilities.

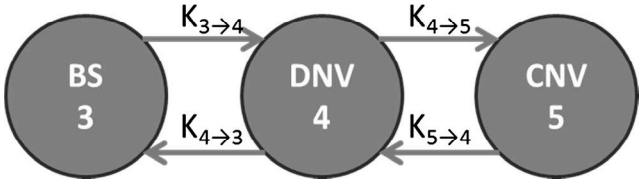


Fig. 4 States and transition rates in the neonatal aEEG Markov model, reproduced with permission from Van Den Broek et al. [125]. BS: burst suppression; DNV: discontinuous normal voltage; CNV: continuous normal voltage. Kx->y: transition rate from state x to state y

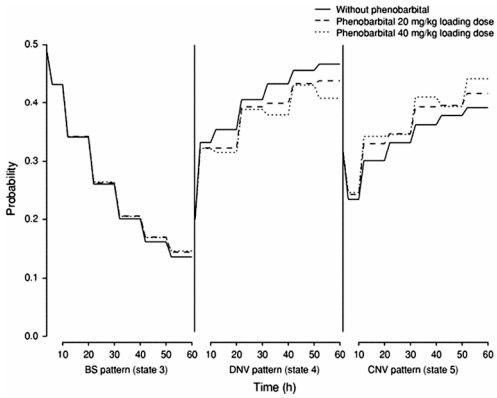


Fig. 5 Probability of a typical neonate showing a burst suppression (state 3, left panel), discontinuous normal voltage (state 4, middle panel) or continuous normal voltage pattern (state 5, right panel) on aEEG evaluation. Probabilities are given for untreated patients (full lines) and patients receiving 20 mg/kg (dashed lines), or 40 mg/kg (dotted lines) of phenobarbital. Reprinted with permission from Van den Broek et al. [125]

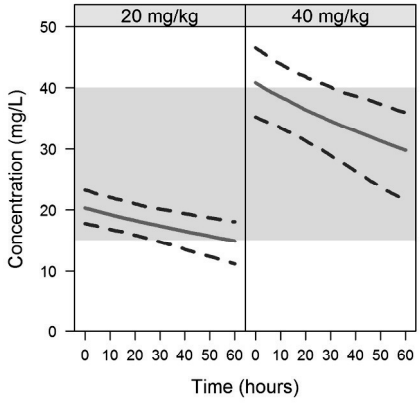


Fig. 6 Pharmacokinetic profiles (median: red solid line; 95% prediction interval: blue dashed lines), based on simulations of 1000 neonates receiving 20 mg/kg PHB (left panel), and 1000 neonates receiving 40 mg/kg PHB (right panel) as a single IV bolus loading dose using the PK model from Van Den Broek et al. [125]. The therapeutic window of PHB is shown as a blue shaded area. Given that concentrations in both dosing scenarios mostly reside within the therapeutic range, the option of giving 40 mg/kg PHB to a neonate should be considered safe in those cases where insufficient efficacy has been reached.

3.8 Phenytoin

General (adult) pharmacology: Phenytoin (PHT) is a first-generation AED indicated for partial and generalised tonic-clonic seizures and status epilepticus. Its principal target is considered to be voltage-gated Na+ channels [20].

PKPD relationships: Despite its wide use in many countries, there is no data available in the published literature other than the evidence of efficacy in clinical trials at the approved doses. Its therapeutic window is considered to lie between 10-20 mg/L [3].

Pharmacokinetics in adults: The bioavailability of PHT is easily influenced by the use of concomitant drugs, dietary choices and GI diseases. If absorption is fast, peak concentrations will increase disproportionally due to its concentration-dependent elimination, which is typically described using Michaelis-Menten kinetics [126,127]. In addition, PHT levels can be very sensitive to changes in, drug distribution (including protein binding) and can be greatly altered by hepatic and renal disease [128]. Such non-linearity in elimination occurs even within the therapeutic range of concentrations. As the ratio of bound and unbound drug in serum is considered to affect the efficacy and toxicity profiles of PHT, various PK models have been developed to better describe the free PHT fraction or take into account factors such as albumin [129–131]. Because of its narrow therapeutic window, small perturbations of PK processes will easily result in under or overexposure to PHT.

Due to saturable clearance, Michaelis-Menten (MM) kinetics is required to describe the elimination of PHT. Valodia et al. [132] showed that models with MM and first order elimination perform better than a model in which MM is not linked to first order elimination. These authors also provide further evidence that this choice of parameterisation can be used to optimise treatment. Body weight, age, gender and ethnicity have been identified as covariates for Vmax and volume of distribution. The differences in the prevalence of CYP2C9/CYP2C19 polymorphisms explains part of the effect of race on Vmax [133–135], which was found to be different in Japanese and Chinese patients, which suggests the need for, genotyping as a tool for dose optimisation. It should be highlighted that

while the role of CYP2C9/CYP2C19 polymorphisms has been examined more thoroughly in the Asian populations, it is yet not fully clear how these variations affect other ethnic (sub)populations.

Pharmacokinetics in children: There are limited examples of pharmacokinetic modelling in children, but theoretically the same considerations regarding drug-drug interactions and metabolic polymorphism described above for adults apply to children. Even though PHT clearance may be described by Michaelis-Menten kinetics in conjunction with first order elimination mechanisms in both adults and children [132], Odani et al. [133] have also used a dose dependent clearance model for PHT in children that could adequately describe the PK without the complexity and computational difficulties of MM kinetics. However, such simplification does not allow prediction of the overall PHT concentrations vs. time curve.

Pharmacokinetics in neonates: There is limited PK data in the neonatal population. Ter Heine et al. [129] showed how serum albumin, urea and VPA can affect PHT concentrations in children and neonates. Based on these findings, these authors suggested monitoring unbound PHT concentrations when treating children, despite the fact that the unbound fraction of PHT was approximately 10% for most patients. A more useful parameterisation is the one proposed by Al Za'abi et al, who have used TDM data from children and neonates in conjunction with allometric scaling and a maturation function, taking into account post-natal age [136]. The model has been subsequently used to simulate different loading and maintenance doses, and define optimised dosing regimens based on mg/kg for different age groups. Interestingly, Frey et al. have shown that it is possible to obtain adequate serum concentrations following the use of oral dosing regimen to pre-term neonates [137].

3.9 Topiramate

General (adult) pharmacology: Topiramate (TPM) is a second-generation AED indicated for partial and generalised seizures. The probable molecular targets for TPM include voltage-gated Na+ channels, HVA Ca2+ channels, GABAa receptors, and glutamate receptors [20].

PKPD relationships: No detailed data are available in the published literature other than the evidence of efficacy in clinical trials at the approved doses. A PKPD model has been developed using a hazard function to describe the correlation between trough concentrations (Cmin) and treatment response in children aged 2-17 and adults aged 18-85 years [138] (**Fig. 7**). A second PKPD model has been reported, which attempts to correlate phonemic fluency (being able to speak well) to drug levels, as a proxy for the occurrence of side-effects [139]. Despite insight into efficacious ranges from these models, the therapeutic range is based on clinical practice and is considered to lie between 5-20 mg/L [3].

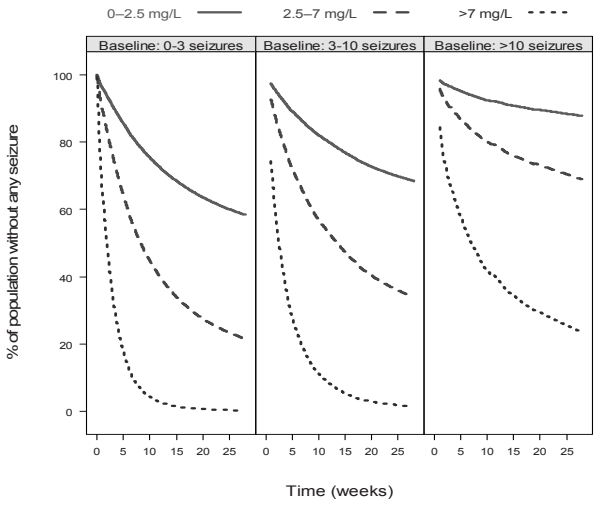


Fig. 7 Median seizure free percentage of the population over time, depending on exposure to TPM at trough (solid line: 0-2.5 mg/L; dashed line: 2.5-7 mg/L; dotted line: above 7 mg/L) and low (left panel), medium (middle panel), or high (right panel) baseline seizure frequency, from a simulation of 1000 typical 4-14 year old patients based on the demographics and model from Girgis et al. [138].

Pharmacokinetics in adults: TPM PK has been successfully modelled both using one- and two compartment models. Absorption is typically fast and bioavailability is approximately 100%. Body weight has been identified as a covariate on the volume of distribution. Some authors have found either dose-dependent clearance or otherwise resorted to Michaelis-Menten elimination to better describe their data. In one study based on single oral doses, apparent clearance was found to be inversely related to the dose. Such findings strongly suggest dose-dependent bioavailability, as observed for GBP [140]. Despite renal excretion being the main route of elimination of TPM, PK drug-drug interactions have been observed with CBZ, PHB, PHT and VPA, which can increase its clearance by 100% or more.

Pharmacokinetics in children: The PK of TPM is fairly well-described in children. As in adults, volume of distribution and clearance are usually related to weight either in a non-linear fashion using allometry or in a linear fashion. Bouillon-Pichault et al. [141] show that a higher dose of TPM should be given to children in order to obtain PK profiles comparable to adults. This is due to the fact that TPM clearance is negatively correlated with age. Girgis et al. [138] have reported an increase in the clearance of TPM of about 200% when used with other AEDs in children between 2-10 years old.

Pharmacokinetics in neonates: There is very limited PK data in the neonatal population, despite TPM being a relatively new AED with considerable number of cases of off-label use by neonatologists and paediatric experts [142]. Recently, interesting details on the PK of TPM were obtained in a study in infants 1-24 months old. The study reveals that TPM has acceptable safety profile, but unfortunately, the influence of factors such as age, weight and co-medication was not evaluated, making it hard to derive specific dose recommendations for individual patients [143]. Even though no neonatal PKPD model is available, evidence from clinical practice suggests that TPM might be more effective for the developing brain, as compared to other AEDs [144,145].

3.10 Valproic acid and Sodium valproate

General (adult) pharmacology: Valproic acid (VPA), or its salt form valproate sodium, is a first-generation AED indicated for partial and generalised seizures. Probable targets for VPA include voltage-gated Na+ channels, LVA Ca2+ channels, and blockade of the GABA turnover [20].

PKPD relationships: No detailed data are available in the published literature other than the evidence of efficacy in clinical trials at the approved doses. Whereas two models have been developed, including data in children, such data has had limited use in clinical practice. The first one is based on logistic regression to describe the probability of achieving a reduction in seizures of at least 50% compared to baseline, depending on age, co-medications, genetic marker (SCN1A) and VPA concentrations [146]. The other correlates the probability of at least 50% reduction in seizures to intellectual disability, genotype (SOD2) and VPA AUC (mg/L*h) [147]. Despite insight into efficacious ranges from these models, the therapeutic range for VPA is based on clinical practice and varies between 50-100 mg/L [3].

Pharmacokinetics in adults: VPA PK is usually described using a one compartment model with first order absorption and elimination. Body weight has been found to be correlated with clearance and volume of distribution by allometry, irrespective of the estimation or use of standard allometric exponents. In addition, VPA dose is often included as a covariate on clearance in an inverse relationship (i.e. total body clearance decreases as the dose increases), indicating auto-inhibition. Presumably this may be a consequence of saturable protein binding, which suggests the need for dose adjustments based on intrinsic rather than total clearance. However, a study by Ahmad et al. did not identify albumin concentration as a predictor of drug clearance [148]. CBZ, CLNZ, and PHB have been reported to increase VPA CL by 36-50% [149–151], 16% [151], and 12% [149,150,152] respectively. On the other hand TPM and PHT have been shown to decrease VPA clearance by 23% [153] and 25% [150] , respectively. Contradictory findings have been reported on the influence of CYP2C9 and CYP2C19 genotypes on population PK parameters. Ogusu et al. did not find any significant effect of genotypes on PK [147]. However, these result contrast

with Jiang et al., who report a significant effect of CYP2C9 and CYP2C19 polymorphisms in Chinese patients [154]. Their analysis suggests that inclusion of genotype as a covariate may provide better predictions than demographic factors only.

Pharmacokinetics in children: Publications based on combined data from adults and children show that a one compartment model with first order absorption and elimination accurately describes the PK of VPA. Clearance and volume of distribution are usually allometrically scaled to weight, with exponents either close to, or fixed to the typical 0.75 and 1, respectively. Most of the aforementioned PK drug-drug interactions reflect data in both adults and children, but a few cases were only children were included, similar findings were observed [151,152,155,156].

Pharmacokinetics in neonates: There is very limited PK data in the neonatal population. Whereas VPA shows good therapeutic response in adults and children, scepticism remains about its benefit in neonates and during pregnancy due to the teratogenic effects demonstrated in utero [157,158]. This contrasts with early case reports[159], which suggest its use in refractory seizures in neonatology [160–162]. Given that the elimination half-life of children younger than 2 months has been reported to be around 60 hrs [163], dose recommendations on the use of VPA in neonates should be “based on patient response” [48]. There is only one PK model developed with data from a single neonate, results are not sufficient to define recommendations for this population [159].

3.11 Zonisamide

General (adult) pharmacology: Zonisamide (ZNS) is a second-generation AED primarily indicated for partial seizures. Its principal target is considered to be voltage-gated Na+ channels, with probable and possible targets being LVA Ca2+ channels, and carbonic anhydrase, respectively [20].

PKPD relationships: No data available in the published literature other than the evidence of efficacy in clinical trials at the approved doses. ZNS’s therapeutic range is between 10-40 mg/L [3]. However, the recommended

therapeutic exposure is reported to be approximately 20 mg/L, while adverse events have been reported to occur at 30mg/L [164].

Pharmacokinetics in adults: Zonisamide is a relatively new drug and not much literature exists on its PK. ZNS has a tendency to bind to red blood cells (RBCs) at a ratio of about 50%/50% (bound/unbound). This binding has an inverse relationship to the total blood concentration. It is known that 30-40% of the drug is excreted unchanged in the urine and the rest is metabolised in the liver. When first marketed in Japan, its PK was described as linear, but when it was tried in the USA, it displayed nonlinear (Michaelis-Menten) kinetics. ZNS is metabolised by CYP3A4, and thus shares a metabolic pathway with other AEDs, such as PHT, CBZ and VPA, which are metabolic inducers of this iso-enzyme. The increased clearance of ZNS resulting from such drug-drug interactions may lead to the requirement for dose adjustments. While no PK model currently describes such interactions or Michaelis-Menten elimination kinetics, TDM should be considered to establish optimal dosage for individual patients. Some studies also indicated that ZNS treatment did not have a clinically relevant impact the PK of PHT [165], VPA [166] and LMT [167], despite the significant changes in the clearance of ZNS itself. However, these investigations did not take into account the implications of inter and intra-subject variability. There is only one population pharmacokinetic model for ZNS, in which authors clearly show high inter-subject variability on Cmax and Cmin, [168].

Pharmacokinetics in children: The PK of ZNS has been described in children by a model which included dose dependent clearance (DDCL) [169]. Their analysis was based on data from children and adults. Body weight was found to correlate with clearance and volume of distribution. The model has been used to perform simulations and derive dosing recommendations for children with weight in the range between 10 and 33 kg,

Pharmacokinetics in neonates: There is very limited PK data in the neonatal population. Kawada et al. [170] describe details on two neonates that were born from mothers who were using ZNS perinatally. The PK of ZNS in these neonates showed first-order kinetics with half-lives of 109 and 61 hours, while in adults the half-life is around 63 hours. These results are not sufficient to define clear dosing recommendations for this population.

4. Discussion

Numerous reviews have been previously published on the pharmacokinetics and efficacy of AEDs [48,171]. However, to our knowledge, this is the first attempt to summarise the available PK and PKPD models and their application in clinical trials and therapeutic use of AEDs. Undoubtedly, non-parametric or non-compartmental summaries of PK and efficacy can provide the basis for comparison of compound characteristics between treatments. Yet, it has not become clear to the clinical community that such summaries are purely descriptive, making it difficult to establish which factors determine the experimental observations, be it pharmacokinetics or clinical endpoints such as seizure reduction.

In contrast to statistical associations, which are often identified by data mining and genetic/genomic research, model-based data analysis are inferential tools aimed at exploring and defining mechanism-based, biologically plausible relationships [172,173]. When appropriately parameterised, PK and PKPD models offer insight into the interactions between the drug and biological system [174]. They also provide an opportunity to evaluate the impact of variability due to intrinsic and extrinsic factors known to affect drug disposition, physiological function or disease [175,176]. This feature makes the use of modelling and simulation a powerful tool to investigate treatment performance. Whilst evidence generation is essential for the advancement of medical practice, evidence synthesis and scenario analysis offer the basis not only for the optimisation of experimental protocols, but also to maximise the therapeutic benefits of a medicine.

Unfortunately, our review shows that despite the relatively high incidence of epilepsy in the overall population and importance of optimising therapeutic interventions with AEDs [177], little effort has been made to characterise PKPD relationships and establish in a strictly quantitative manner the clinical relevance of a myriad of factors known to affect drug disposition and exposure to AEDs. As a consequence, most of the model-based research published to date is exploratory. Very few authors mention the use of modelling results as basis for the dose rationale or personalised regimens.

Irrespective of the limitations highlighted above, a few interesting lessons arise with regard to PK modelling efforts in this area. Most publications refer to compartmental modelling without taking into account the implications of different formulations, which play a critical role when extrapolating data from adults to children and neonates. In addition, with the exception of PHT, none of the modelling approaches consider metabolic saturation or other factors that might lead to nonlinearity between dose and exposure. As covariate effects describing drug-drug interaction are mostly defined as a discrete change to disposition parameters, none of the models allow for a clear assessment of inter-individual differences in the magnitude of these interactions, which may differ considerably between patients or during titration and/or tapering of an add-on drug. Most importantly, no publication has provided insight into the implications of concurrent covariate effects for the dose rationale. From a clinical perspective, understanding the consequences of the interaction between multiple factors, such as body weight, renal function and metabolic inhibition, should be common knowledge to any clinician interested in treating a patient effectively, i.e., with the right drug(s) and dosing regimen(s).

Given our primary interest in the development of dosing algorithms aimed at the optimisation of pharmacotherapy, it is also important to highlight the fact that most models have been developed using nonlinear mixed effects approach as a '*data analysis method*', rather than a 'design or decision-making tool'. Whilst we understand the limitations of clinical protocols and availability of data, best practice principles in quantitative pharmacology research, such as external validation, predictive performance, and sensitivity analysis have not been used for the evaluation of PK and PKPD models described here. Most publications assess the suitability of a model, its parameterisation and accuracy and precision of the parameter estimates based on goodness-of-fit and other diagnostic metrics using the source data or eventually by bootstrapping procedures. This lack of standards along with the limited sample sizes represents an important issue, as prospective use of such models require clear assessment of the impact of model uncertainty and potential biases due to poor accuracy or even poor

precision in parameter estimates, in particular those describing inter and intra-individual variability.

Another important point is the choice of parameterisation for the description of covariate effects. Unless a covariate factor has a major impact on the parameter of interest, the ability to detect a covariate effect and establish the correct relationship or correlation between model parameter and covariate will depend primarily on sample size and on covariate distribution in the population under investigation [178,179]. These considerations are essential when defining the dose rationale for paediatric patients as well as those on drug combinations (polypharmacy). Most published models included weight as a covariate on clearance and volume of distribution, but the correlations between parameter and covariate factor were not always defined by allometric principles. In addition, for drugs that are eliminated both renally and hepatically or exclusively by renal processes, correlations with creatinine clearance were limited to age-related variation, as renally and hepatically impaired patients seem to have been excluded from the analysis. Given the limited number of neonatal patients and young children >2 years of age, during which creatinine clearance will show the largest differences relative to adults, it can be anticipated that the reported estimates may not be sufficiently precise. A similar concern applies to the different parameterisation of a maturation function describing the ontogeny of enzymes in young children.

Lastly, it became evident how limited attention to interacting factors such as ethnicity and genetic polymorphism may be overlooked during covariate model building. The lack of balanced designs along with limited sample sizes makes it difficult, if not impossible to disentangle the effect of ethnicity from the effect of differences in genotype or phenotype. Whereas few models have identified the impact of slow or fast metabolism on clearance, such results cannot be corroborated without further assessment of the effect in *in silico* models. An increasing number of examples are now available across therapeutic areas, which illustrate how information from in silico models can be extrapolated or integrated with population pharmacokinetic models to explore the relevance of polymorphism, ethnicity and drug-drug interactions, taking into account other known sources of inter-individual variability [180,181].

We also recognise that in the absence of PKPD models, it will remain difficult to explore to what extent covariate models will allow identification of explanatory variables describing inter-individual variability in response [182,183]. Nevertheless, the available population PK models provide a starting point for future implementation of model-based approaches, including the evaluation of dosing algorithms. In fact, we have started to evaluate the impact of existing models as a tool for dose optimisation. A set of pharmacokinetic models was used in conjunction with simulation scenarios to establish the need for dose adjustment in adult and paediatric patients who receive AED combinations [184]. Similarly to the investigations performed previously by de Castro et al. [4] and Völler et al. [9], we have used this same set of models to evaluate the performance of different dosing algorithms, including scenarios in which the approach is combined with therapeutic drug monitoring (TDM) [185].

5. Conclusion

In this review we have summarised the available PK and PKPD information available in literature, focussing on model-based evidence where possible. We have unravelled an enormous gap regarding pharmacokinetic-pharmacodynamic relationships is especially problematic, as for these drugs, inadequate response or unacceptable adverse events are the main cause of discontinuation of, or non-adherence to AEDs [186,187]. Thus far, clinicians do not seem persuaded by the fact that in the absence of personalised or even individualised doses, treatment failure is not the only consequence; clinical response may be suboptimal [188]. This issue may not be “fixed” by up and down-titration or tapering procedures.

Without clearly described and validated models, the implementation of personalised medicine principles will remains out of reach. Modelling and simulation is an inferential tool and a powerful method to characterise response at individual and population level when multiple interacting factors are involved. If correctly parameterised, these models will reflect the underlying exposure-response relationships along with the effects covariate factors, allowing for appropriate dose selection. As long as seizure control forms the basis for the treatment of epilepsy patients, neurologist and paediatric neurologists cannot continue to resort to trial and error, to up and down titration. *Post hoc, ergo propter hoc, i.e.* "after this, therefore because of this", is a logical fallacy. We cannot ignore the causal chain between stimulus and response.

References

1. van Dijkman SC, Alvarez-Jimenez R, Danhof M, Della Pasqua O. Pharmacotherapy in pediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go. Expert Opin. Drug Metab. Toxicol. 2016;12:1143–56.

2. St Louis EK. Monitoring antiepileptic drugs: a level-headed approach. Curr. Neuropharmacol. 2009;7:115–9.

3. Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser T a., Johannessen SI, et al. Antiepileptic drugs - best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008;49:1239–76.

4. Castro FA De, Piana C, Simões BP, Lanchote VL, Pasqua O Della. Busulfan dosing algorithm and sampling strategy in stem cell transplantation patients. Br. J. Clin. Pharmacol. 2015;80:618–29.

5. Fang L, Xin W, Ding H, Zhang Y, Zhong L, Luo H, et al. Pharmacokinetically guided algorithm of 5-fluorouracil dosing , a reliable strategy of precision chemotherapy for solid tumors : a meta-analysis. Nat. Publ. Gr. Nature Publishing Group; :1–7.

6. Ma X, Chien JY, Johnson J. Simulation-Based Evaluation of Dose-Titration Algorithms for Rapid-Acting Insulin in Subjects with Type 2 Diabetes Mellitus Inadequately Controlled on Basal Insulin and Oral Antihyperglycemic Medications. :1–8.

7. Zhang Y, Boer ADE, Verhoef TI. Age-stratified outcome of a genotype-guided dosing algorithm for acenocoumarol and phenprocoumon. 2016;454–64.

8. Liu R, Li X, Zhang W, Zhou H. Comparison of Nine Statistical Model Based Warfarin Pharmacogenetic Dosing Algorithms Using the Racially Diverse International Warfarin Pharmacogenetic Consortium Cohort Database. 2015;1–11.

9. Voller S, Hempel G, Wurthwein G, Boddy A V, Krischke M, Andre N, et al. Towards a Model-Based Dose Recommendation for Doxorubicin in Children. 2006;215–23.

10. Jayachandran D, Laínez-Aguirre J, Rundell A, Vik T, Hannemann R, Reklaitis G, et al. Model-based individualized treatment of chemotherapeutics: Bayesian population modeling and dose optimization. PLoS One. 2015;10:1–24.

11. Sheiner LB, Steimer J-L. Pharmacokinetic/Pharmacodynamic Modeling in Drug Development. Annu. Rev. Pharmacol. Toxicol. 2000;40:67–95.

12. Krekels EHJ, Van Den Anker JN, Baiardi P, Cella M, Cheng KY, Gibb DM, et al. Pharmacogenetics and paediatric drug development : issues and consequences to labelling and dosing recommendations Pharmacogenetics and paediatric drug development : issues and. Expert Opin. Pharmacother. 2007;8:1787–99.

13. Bellanti F, Della Pasqua O. Modelling and simulation as research tools in paediatric drug development. Eur. J. Clin. Pharmacol. 2011;67 Suppl 1:75–86.

14. Zineh I, Woodcock J. Clinical Pharmacology and the Catalysis of Regulatory Science : Opportunities for the Advancement of Drug Development and Evaluation. 2013;515–25.

15. Meyer J, Fardo D, Fleming ST, Hopenhayn C, Gokun Y, Ryan M. Generic antiepileptic drug prescribing: a cross-sectional study. Epilepsy Behav. Elsevier B.V.; 2013;26:1–6.

16. WHO. Initiative of support to people with epilepsy. 1990.

17. Kwan P, Brodie MJ. Phenobarbital for the treatment of epilepsy in the 21st century: a critical review. Epilepsia. 2004;45:1141–9.

18. Milh M, Ticus I, Villeneuve N, Hugonencq C, Mancini J, Chabrol B. Epileptic Seizures in Childhood: From Seizure Type to Diagnosis. Arch. Pediatr. 2008;15:216–22.

19. ICH Expert Group. ICH Topic E 11. Clinical investigation of medicinal products in the paediatric population. [Internet]. Int. Conf. Harmon. Tech. Requir. Regist. Pharm. Humans. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/Step4/E11_Guideline.pdf

20. Kwan P, Sills GJ, Brodie MJ. The mechanisms of action of commonly used antiepileptic drugs. Pharmacol. Ther. 2001;90:21–34.

21. Tothfalusi L, Speidl S, Endrenyi L. Exposure-response analysis reveals that clinically important toxicity difference can exist between bioequivalent carbamazepine tablets. Br. J. Clin. Pharmacol. 2008;65:110–22.

22. Cereghino JJ, Meter JC, Brock JT, Penry JK, Smith LD, White BG. Preliminary observations of serum carbamazepine concentration in epileptic patients. Neurology. 1973;23:357–66.

23. Eichelbaum M, Ekbom K, Bertilsson L, Ringberger V a, Rane a. Plasma kinetics of carbamazepine and its epoxide metabolite in man after single and multiple doses. Eur. J. Clin. Pharmacol. 1975;8:337–41.

24. Rawlins MD, Collste P, Bertilsson L, Palmér L. Distribution and elimination kinetics of carbamazepine in man. Eur. J. Clin. Pharmacol. 1975;8:91–6.

25. Troupin a S, Friel P. Anticonvulsant level in saliva, serum, and cerebrospinal fluid. Epilepsia. 1975;16:223–7.

26. Morselli PL, Frigerio a. Metabolism and Pharmacolinetics of Carbamazepine. Drug Metab. Rev. 1975;4:97–113.

27. Levy RH, Pitlick WH, Troupin AS, Green JR, Neal JM. Pharmacokinetics of carbamazepine in normal man. Clin. Pharmacol. Ther. 1975;17:657–68.

28. Battino D, Bossi L, Croci D, Franceschetti S, Gomeni C, Moise A, et al. Carbamazepine Plasma Levels in Children and Adults: Influence of Age, Dose and Associated Therapy. Ther. Drug Monit. 1980;2:315–22.

29. Suzuki Y, Cox S, Hayes J, Walson PD. Carbamazepine Age-Dose Ratio Relationship in Children. Ther. Drug Monit. 1991;13:201–8.

30. Sanchez A, Duran JA, Serrano JS. Steady-State Carbamazepine Plasma Concentration-Dose Ratios in Epileptic Patients. Clin. Pharmacokinet. 1986;11:411–4.

31. Summers B, Summers RS. Carbamazepine Clearance in Paediatric Epilepsy Patients: Influence of Body Mass, Dose, Sex and Co-Medication. Clin. Pharmacokinet. 1989;17:208–16.

32. Iribanegaray D, Buelga S, Sánchez G. Carbamazepine Population Pharmacokinetics in Children : Mixed-Effect Models. Ther. Drug Monit. 1997;19:132–9.

33. Wegner I, Wilhelm AJ, Sander JW, Lindhout D. The impact of age on lamotrigine and oxcarbazepine kinetics: a historical cohort study. Epilepsy Behav. Elsevier Inc.; 2013;29:217–21.

34. Punyawudho B, Ramsay ER, Brundage RC, Macias FM, Collins JF, Birnbaum AK. Population Pharmacokinetics of Carbamazepine in Elderly Patients. 2012;176–81.

35. Deleu D, Aarons L, Ahmed IA. Population pharmacokinetics of free carbamezipine in adult Omani epileptic patients. Eur. J. Clin. Pharmacol. 2001;57:243–8.

36. Jiao Z, Zhong M-K, Shi X-J, Hu M, Zhang J-H. Population pharmacokinetics of carbamazepine in Chinese epilepsy patients. Ther. Drug Monit. 2003;25:279–86.

37. Bertilsson L, Höjer B, Tybring G, Osterloh J, Rane a. Autoinduction of carbamazepine metabolism in children examined by a stable isotope technique. Clin. Pharmacol. Ther. 1980;27:83–8.

38. Punyawudho B, Cloyd JCJC, Leppik IEIE, Ramsay REE, Marino SESE, Pennell PBPB, et al. Characterization of the time course of carbamazepine deinduction by an enzyme turnover model. Clin. Pharmacokinet. 2009;48:313–20.

39. Yukawa E, Aoyama T. Detection of Carbamazepine Drug Interaction by Multiple Peak Approach Screening using Routine Clinical Pharmacokinetic Data. J. Clin. Pharmacol. 1996;36:752–9.

40. Gray a L, Botha JH, Miller R. A model for the determination of carbamazepine clearance in children on mono- and polytherapy. Eur. J. Clin. Pharmacol. 1998;54:359–62.

41. Chan E, Lee HS, Hue SS. Population pharmacokinetics of carbamazepine in Singapore epileptic patients. Br. J. Clin. Pharmacol. 2001;51:567–76.

42. Jiao Z, Shi X-J, Zhao Z-G, Zhong M-K. Population pharmacokinetic modeling of steady state clearance of carbamazepine and its epoxide metabolite from sparse routine clinical data. J. Clin. Pharm. Ther. 2004;29:247–56.

43. Ismail R, Fatah A, Rahman A. Estimation of population pharmacokinetics for carbamazepine in Malaysian patients using the OPT @ computer program ".

44. Reith DM, Hooper WD, Parke J, Charles B. Population pharmacokinetic modeling of steady state carbamazepine clearance in children, adolescents, and adults. J. Pharmacokinet. Pharmacodyn. 2001;28:79–92.

45. El Desoky ES, Sabarinath SN, Hamdi MM, Bewernitz M, Derendorf H. Population pharmacokinetics of steady-state carbamazepine in Egyptian epilepsy patients. J. Clin. Pharm. Ther. 2012;37:352–5.

46. Carlsson KC, Hoem NO, Glauser T, Vinks A a. Development of a population pharmacokinetic model for carbamazepine based on sparse therapeutic monitoring data from pediatric patients with epilepsy. Clin. Ther. 2005;27:618–26.

47. Bondareva IB, Sokolov a V, Tischenkova IF, Jelliffe RW. Population pharmacokinetic modelling of carbamazepine by using the iterative Bayesian (IT2B) and the nonparametric EM (NPEM) algorithms: implications for dosage. J. Clin. Pharm. Ther. 2001;26:213–23.

48. Tulloch JK, Carr RR, Ensom MHH. A Systematic Review of the Pharmacokinetics of Antiepileptic Drugs in Neonates With Refractory Seizures. J. Pediatr. Pharmacol. Ther. 2012;17:31–44.

49. Rey E, D'Athis P, de Lauture D, Dulac O, Aicardi J, Olive G. Pharmacokinetics iof carbamazepine in the neonate and in the child. Int. J. Clin. Pharmacol. Biopharm. 1979;17:90–6.

50. Hoppen T, Elger CE, Bartmann P. Carbamazepine in phenobarbital-nonresponders: experience with ten preterm infants. Eur. J. Pediatr. 2001;160:444–7.

51. Frey B, Braegger CP, Ghelfi D. Neonatal cholestatic hepatitis from carbamazepine exposure during pregnancy and breast feeding. Ann. Pharmacother. 2002;36:644–7.

52. Merlob P, Mor N, Litwin A. Transient hepatic dysfunction in an infant of an epileptic mother treated with carbamazepine during pregnancy and breastfeading. Ann. Pharmacother. 1992;26:1563–5.

53. Bateson a N. Basic pharmacologic mechanisms involved in benzodiazepine tolerance and withdrawal. Curr. Pharm. Des. 2002;8:5–21.

54. Berlin a, Dahlström H. Pharmacokinetics of the anticonvulsant drug clonazepam evaluated from single oral and intravenous doses and by repeated oral administration. Eur. J. Clin. Pharmacol. 1975;9:155–9.

55. Khoo KC, Mendels J, Rothbart M, Garland W a, Colburn W a, Min BH, et al. Influence of phenytoin and phenobarbital on the disposition of a single oral dose of clonazepam. Clin. Pharmacol. Ther. 1980;28:368–75.

56. Yukawa E, Satou M, Nonaka T, Yukawa M, Ohdo S, Higuchi S, et al. Pharmacoepidemiologic investigation of clonazepam relative clearance by mixed-effect modeling using routine clinical pharmacokinetic data in Japanese patients. J. Clin. Pharmacol. 2002;42:81–8.

57. Yukawa E, Nonaka T, Yukawa M, Higuchi S, Kuroda T, Goto Y. Pharmacoepidemiologic investigation of a clonazepam-valproic acid interaction by mixed effect modeling using routine clinical pharmacokinetic data in Japanese patients. J. Clin. Pharm. Ther. 2003;28:497–504.

58. Yukawa E, Nonaka T, Yukawa M, Ohdo S, Higuchi S, Kuroda T, et al. Pharmacoepidemiologic investigation of a clonazepam-carbamazepine interaction by mixed effect modeling using routine clinical pharmacokinetic data in Japanese patients. J. Clin. Psychopharmacol. 2001;21:588–93.

59. Nanda RN, Johnson RH, Keogh HJ, Lambie DG, Melville ID. Treatment of epilepsy with clonazepam and its effect on other anticonvulsants. J. Neurol. Neurosurg. Psychiatry. 1977;40:538–43.

60. Tassinari CA, Michelucci R, Riguzzi P, Volpi L, Dravet C, Cano JP, et al. The Use of Diazepam and Clonazepam in Epilepsy. Epilepsia. 1998;39:S7–14.

61. Kadono K, Akabane T, Tabata K, Gato K, Terashita S, Teramura T. Quantitative Prediction of Intestinal Metabolism in Humans from a Scaling Factor. Drug Metab. Dispos. 2010;38:1230–7.

62. Dahlin M, Knutsson E, Amark P, Nergårdh a. Reduction of epileptiform activity in response to low-dose clonazepam in children with epilepsy: a randomized double-blind study. Epilepsia. 2000;41:308–15.

63. André M, Boutroy MJ, Dubruc C, Thenot JP, Bianchetti G, Sola L, et al. Clonazepam pharmacokinetics and therapeutic efficacy in neonatal seizures. Eur. J. Clin. Pharmacol. 1986;30:585–9.

64. Delattre M, Savic RM, Miller R, Karlsson MO, Lavielle M. Analysis of exposure-response of CI-945 in patients with epilepsy: application of novel mixed hidden Markov modeling methodology. J. Pharmacokinet. Pharmacodyn. 2012;39:263–71.

65. Lal R, Sukbuntherng J, Luo W, Tovera J, Lassauzet ML, Cundy KC. Population Pharmacokinetics and Pharmacodynamics of Gabapentin After Administration of Gabapentin Enacarbil. J. Clin. Pharmacol. 2012;

66. Fischer JH, Barr AN, Rogers SL, Fischer PA, Trudeau VL. Lack of serious toxicity following gabapentin overdose. Neurology. 1994;44:982–3.

67. Vollmer KO, van Hodenberg A, Kolle EU. Pharmacokinetics and metabolism of gabapentin in rat, dog and man. Arzneimittelforschung. 1986;36:830–9.

68. Carlsson KC, van de Schootbrugge M, Eriksen HO, Moberg ER, Karlsson MO, Hoem NO. A population pharmacokinetic model of gabapentin developed in nonparametric adaptive grid and nonlinear mixed effects modeling. Ther. Drug Monit. 2009;31:86–94.

69. Ouellet D, Bockbrader HN, Wesche DL, Shapiro DY, Garofalo E. Population pharmacokinetics of gabapentin in infants and children. Epilepsy Res. 2001;47:229–41.

70. Chen C. Meta-analyses of dose-exposure relationships for gabapentin following oral administration of gabapentin and gabapentin enacarbil. Eur. J. Clin. Pharmacol. 2013;69:1809–17.

71. Anderson GD, Hakimian S. Pharmacokinetic of Antiepileptic Drugs in Patients with Hepatic or Renal Impairment. :29–49.

72. Lal R, Sukbuntherng J, Luo W, Chen D, Blumenthal R, Ho J, et al. Clinical Pharmacokinetics of Gabapentin After Administration of Gabapentin Enacarbil Extended-Release Tablets in Patients With Varying Degrees of Renal Function Using Data From an Open-Label, Single-Dose Pharmacokinetic Study. Clin. Ther. 2012;34:201–13.

73. Tallian KB, Nahata MC, Lo W, Tsao C-Y. Pharmacokinetics of gabapentin in paediatric patients with uncontrolled seizures. J. Clin. Pharm. Ther. 2004;29:511–5.

74. Haig GM, Bockbrader HN, Wesche DL, Boellner SW, Ouellet D, Brown RR, et al. Single-dose gabapentin pharmacokinetics and safety in healthy infants and children. J. Clin. Pharmacol. 2001;41:507–14.

75. Behm MO, Kearns GL. Treatment of Pain with Gabapentin in a Neonate. Paediatrics. 2001;108:482–5.

76. Dixon R, Job S, Oliver R, Tompson D, Wright JG, Maltby K, et al. Lamotrigine does not prolong QTc in a thorough QT/QTc study in healthy subjects. Br. J. Clin. Pharmacol. 2008;66:396–404.

77. Jawad S, Yuen WC, Peck a W, Hamilton MJ, Oxley JR, Richens a. Lamotrigine: single-dose pharmacokinetics and initial 1 week experience in refractory epilepsy. Epilepsy Res. 1987;1:194–201.

78. Peck a W. Clinical pharmacology of lamotrigine. Epilepsia. 1991;32 Suppl 2:S9-12.

79. Brzaković B, Vučićević K, Kovačević SV, Miljković B, Prostran M, Martinović Ž, et al. Pharmacokinetics of lamotrigine in paediatric and young adult epileptic patients--nonlinear mixed effects modelling approach. Eur. J. Clin. Pharmacol. 2014;70:179–85.

80. Rivas N, Buelga DS, Elger CE, Santos-Borbujo J, Otero MJ, Domínguez-Gil A, et al. Population pharmacokinetics of lamotrigine with data from therapeutic drug monitoring in German and Spanish patients with epilepsy. Ther. Drug Monit. 2008;30:483–9.

81. Wegner I, Wilhelm a J, Lambrechts D a JE, Sander JW, Lindhout D. Effect of oral contraceptives on lamotrigine levels depends on comedication. Acta Neurol. Scand. 2014;129:393–8.

82. Singkham N, Towanabut S, Lertkachatarn S, Punyawudho B. Influence of the UGT2B7-161C-T polymorphism on the population pharmacokinetics of lamotrigine in Thai patients. Eur. J. Clin. Pharmacol. 2013;69:1285–91.

83. Mallaysamy S, Johnson MG, Rao PGM, Rajakannan T, Bathala L, Arumugam K, et al. Population pharmacokinetics of lamotrigine in Indian epileptic patients. Eur. J. Clin. Pharmacol. 2013;69:43–52.

84. Punyawudho B, Ramsay RE, Macias FM, Rowan a J, Collins JF, Brundage RC, et al. Population pharmacokinetics of lamotrigine in elderly patients. J. Clin. Pharmacol. 2008;48:455–63.

85. Chan V, Morris RG, Ilett KF, Tett SE. Population pharmacokinetics of lamotrigine. Ther. Drug Monit. 2001;23:630–5.

86. Hussein Z, Posner J. Population pharmacokinetics of lamotrigine monotherapy in patients with epilepsy: retrospective analysis of routine monitoring data. Br. J. Clin. Pharmacol. 1997;43:457–65.

87. He D, Wang L, Qin J, Zhang S, Lu W, Li L, et al. Population pharmacokinetics of lamotrigine in Chinese children with epilepsy. Acta Pharmacol. Sin. 2012;33:1417–23.

88. Reimers A, Skogvoll E, Sund JK, Spigset O. Lamotrigine in children and adolescents: the impact of age on its serum concentrations and on the extent of drug interactions. Eur. J. Clin. Pharmacol. 2007;63:687–92.

89. Almeida a. M, Falcão a. C, Sales F, Baldeiras I, Rocha MJ, Caramona MM. Lamotrigine pharmacokinetic evaluation in epileptic patients submitted to VEEG monitoring. Eur. J. Clin. Pharmacol. 2006;62:737–42.

90. Gidal BE, Anderson GD, Rutecki PR, Shaw R, Lanning a. Lack of an effect of valproate concentration on lamotrigine pharmacokinetics in developmentally disabled patients with epilepsy. Epilepsy Res. 2000;42:23–31.

91. Chen C. Validation of a population pharmacokinetic model for adjunctive lamotrigine therapy in children. Br. J. Clin. Pharmacol. 2000;50:135–45.

92. Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age. Clin. Pharmacokinet. 2006;45:351–63.

93. Franco V, Mazzucchelli I, Gatti G, Specchio LM, La Neve A, Papantonio A, et al. Changes in lamotrigine pharmacokinetics during pregnancy and the puerperium. Ther. Drug Monit. 2008;30:544–7.

94. Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch. Dis. Child. 2011;96:643–7.

95. Mikati MA, Fayad M, Koleilat M, Mounla N, Hussein R, Kazma A, et al. Efficacy, tolerability, and kinetics of lamotrigine in infants. J. Pediatr. 2002;141:31–5.

96. Ohman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. Epilepsia. 2000;41:709–13.

97. Liporace J, Kao A, D'Abreu A. Concerns regarding lamotrigine and breast-feeding. Epilepsy Behav. 2004;5:102–5.

98. Newport DJ, Pennell PB, Calamaras MR, Ritchie JC, Newman M, Knight B, et al. Lamotrigine in breast milk and nursing infants: determination of exposure. Pediatrics. 2008;122:e223-31.

99. Fotopoulou C, Kretz R, Bauer S, Schefold JC, Schmitz B, Dudenhausen JW, et al. Prospectively assessed changes in lamotrigine-concentration in women with epilepsy during pregnancy, lactation and the neonatal period. Epilepsy Res. 2009;85:60–4.

100. Rambeck B, Kurlemann G, Stodieck SR, May TW, Jürgens U. Concentrations of lamotrigine in a mother on lamotrigine treatment and her newborn child. Eur. J. Clin. Pharmacol. 1997;51:481–4.

101. Snoeck E, Stockis A. Dose-response population analysis of levetiracetam add-on treatment in refractory epileptic patients with partial onset seizures. Epilepsy Res. 2007;73:284–91.

102. Toublanc N, D Lacroix B, Yamamoto J, Lacroix BD, Yamamoto J. Development of an Integrated Population Pharmacokinetic Model for Oral Levetiracetam in Populations of Various Ages and Ethnicities. Drug Metab. Pharmacokinet. 2014;29:61–8.

103. Pigeolet E, Jacqmin P, Stockis A, Sargentini-Maier ML, Stockis A. Population pharmacokinetics of levetiracetam in Japanese and Western adults. Clin. Pharmacokinet. 2007;46:503–12.

104. Snoeck E, Jacqmin P, Sargentini-Maier ML, Stockis A. Modeling and simulation of intravenous levetiracetam pharmacokinetic profiles in children to evaluate dose adaptation rules. Epilepsy Res. 2007;76:140–7.

105. De Cock RFW, Allegaert K, Brussee JM, Sherwin CMT, Mulla H, De Hoog M, et al. Simultaneous pharmacokinetic modeling of gentamicin, tobramycin and vancomycin clearance from neonates to adults: Towards a semi-physiological function for maturation in glomerular filtration. Pharm. Res. 2014;31:2643–54.

106. Wang Y, Wang L, Lu W, Shang D, Wei M, Wu Y. Population pharmacokinetics modeling of levetiracetam in Chinese children with epilepsy. Acta Pharmacol. Sin. 2012;33:845–51.

107. Chhun S, Jullien V, Rey E, Dulac O, Chiron C, Pons G. Population pharmacokinetics of levetiracetam and dosing recommendation in children with epilepsy. Epilepsia. 2009;50:1150–7.

108. Toublanc N, Sargentini-Maier ML, Lacroix B, Jacqmin P, Stockis A. Retrospective Population Pharmacokinetic Analysis of Levetiracetam in Children and Adolescents with Epilepsy - Dosing Recommendations. Clin. Pharmacokinet. 2008;47:333–41.

109. Sharpe CM, Capparelli E V, Mower A, Farrell MJ, Soldin SJ, Haas RH. A seven-day study of the pharmacokinetics of intravenous levetiracetam in neonates: marked changes in pharmacokinetics occur during the first week of life. Pediatr. Res. 2012;72:43–9.

110. Merhar SL, Schibler KR, Sherwin CM, Meinzen-Derr J, Shi J, Balmakund T, et al. Pharmacokinetics of levetiracetam in neonates with seizures. J. Pediatr. Mosby, Inc.; 2011;159:152–154.e3.

111. Antunes NDJ, van Dijkman SC, Lanchote VL, Wichert-Ana L, Coelho EB, Alexandre Junior V, et al. Population pharmacokinetics of oxcarbazepine and its metabolite 10-hydroxycarbazepine in healthy subjects. Eur. J. Pharm. Sci. Elsevier; 2017;In press.

112. Park K-J, Kim J-R, Joo EY, Seo DW, Hong SB, Ko J-W, et al. Drug interaction and pharmacokinetic modeling of oxcarbazepine in korean patients with epilepsy. Clin. Neuropharmacol. 2012;35:40–4.

113. Wang Y, Zhang H, Niu C, Gao P, Chen Y, Peng J, et al. Population pharmacokinetics modeling of oxcarbazepine to characterize drug interactions in Chinese children with epilepsy. Acta Pharmacol. Sin. Nature Publishing Group; 2014;35:1342–50.

114. Sallas WM, Milosavljev S, D'Souza J, Hossain M. Pharmacokinetic drug interactions in children taking oxcarbazepine. Clin. Pharmacol. Ther. 2003;74:138–49.

115. Northam RS, Hernandez AW, Litzinger MJ, Minecan DN, Glauser TA, Mangat S, et al. Oxcarbazepine in Infants and Young Children With Partial Seizures. 2005;337–44.

116. Bülau P, Paar WD, von Unruh GE. Pharmacokinetics of oxcarbazepine and 10-hydroxy-carbazepine in the newborn child of an oxcarbazepine-treated mother. Eur. J. Clin. Pharmacol. 1988;34:311–3.

117. Marsot A, Brevaut-Malaty VV, Vialet R, Boulamery A, Bruguerolle B, Simon N. Pharmacokinetics and absolute bioavailability of phenobarbital in neonates and young infants, a population pharmacokinetic modelling approach. Fundam. Clin. Pharmacol. 2013;28:465–71.

118. Yukawa E, To H, Ohdo S, Higuchi S. Detection of a drug-drug interaction on population-based phenobarbitone clearance using nonlinear mixed-effects modeling. Eur. J. Clin. Pharmacol. 1998;54:69–74.

119. Goto S, Seo T, Murata T, Nakada N, Ueda N, Ishitsu T, et al. Population Estimation of the Effects of Cytochrome P450 2C9 and 2C19 Polymorphisms on Phenobarbital Clearance in Japanese. Ther. Drug Monit. 2007;29:118–21.

120. Vucićević K, Jovanović M, Golubović B, Kovačević SV, Miljković B, Martinović Ž, et al. Nonlinear mixed effects modelling approach in investigating phenobarbital pharmacokinetic interactions in epileptic patients. Eur. J. Clin. Pharmacol. 2015;71:183–90.

121. Yukawa E, Mamiya K. Effect of CYP2C19 genetic polymorphism on pharmacokinetics of phenytoin and phenobarbital in Japanese epileptic patients using Non-linear Mixed Effects Model approach. J. Clin. Pharm. Ther. 2006;31:275–82.

122. Mamiya K, Hadama A, Yukawa E, Ieiri I, Otsubo K, Ninomiya H, et al. CYP2C19 polymorphism effect on phenobarbitone Pharmacokineties in Japanese patients with epilepsy : analysis by population pharmacokinetics. Eur. J. Clin. Pharmacol. 2000;55:821–5.

123. Yukawa E, Suematsu F, Yukawa M, Minemoto M. Population pharmacokinetic investigation of phenobarbital by mixed effect modelling using routine clinical pharmacokinetic data in Japanese neonates and infants. J. Clin. Pharm. Ther. 2005;30:159–63.

124. Yukawa M, Yukawa E, Suematsu F, Takiguchi T, Ikeda H, Aki H, et al. Population pharmacokinetics of phenobarbital by mixed effect modelling using routine clinical pharmacokinetic data in Japanese neonates and infants: an update. J. Clin. Pharm. Ther. 2011;36:704–10.

125. Van Den Broek MPH, Groenendaal F, Toet MC, van Straaten HLM, Van Hasselt JGC, Huitema ADR, et al. Pharmacokinetics and Clinical Efficacy of Phenobarbital in Asphyxiated Newborns Treated with Hypothermia. Clin. Pharmacokinet. 2012;51:671–9.

126. Michaelis M, Menten ML. Die Kinetik der Invertinwirkung. Biochem. Z. 1913;49:333–69.

127. Johnson KA, Goody RS. The original Michaelis constant: Translation of the 1913 Michaelis-Menten Paper. Biochemistry. 2011;50:8264–9.

128. Stowe CD, Lee KR, Storgion SA, Phelps SJ. Altered phenytoin pharmacokinetics in children with severe, acute traumatic brain injury. J. Clin. Pharmacol. 2000;1452–61.

129. Ter Heine R, Maarseveen EM Van, Westerlaken MML Van Der, Braun KPJ, Koudijs SM, Berg MJ Ten, et al. The Quantitative Effect of Serum Albumin, Serum Urea, and Valproic Acid on Unbound Phenytoin Concentrations in Children. J. Child Neurol. 2013;29:803–10.

130. Kane SP, Bress AP, Tesoro EP. Characterization of Unbound Phenytoin Concentrations in Neurointensive Care Unit Patients Using a Revised Winter- ozer Equation methods : 2013;

131. Musteata FM. Calculation of Normalized Drug Concentrations in the Presence of Altered Plasma Protein Binding. Clin. Pharmacokinet. 2012;51:55–68.

132. Valodia P, Seymour MA, Miller R, McFadyen ML, Folb P. Factors Influencing the Population Pharmacokinetic Parameters of Phenytoin in Adult Epileptic Patients in South Africa. Ther. Drug Monit. 1999;21:57–62.

133. Odani A, Hashimoto Y, Takayanagi K, Otsuki Y, Koue T, Takano M, et al. Population Pharmacokinetics of Phenytoin in Japanese Patients with Epilepsy: Analysis with a Dose-Dependent Clearance Model. Biol. Pharm. Bull. 1996;19:444–8.

134. Yukawa E, Higuchi S, Aoyama T. Population Pharmacokinetics of Phenytoin from Routine Clinical Data in Japan: An Update. Chem. Pharm. Bull. 1990;38:1973–6.

135. Mamiya K, Ieiri I, Shimamoto J, Yukawa E, Imai J, Otsubo S, et al. The Effects of Genetic Polymorphisms of CYP2C9 and CYP2C 19 on Phenytoin Metabolism in Japanese Adult Patients with Epilepsy : Studies in Stereoselective Hydroxylation and Population Pharmacokinetics. Epilepsia. 1998;39:1317–23.

136. Al Za'abi M, Lanner A, Xiaonian X, Donovan T, Charles B. Application of routine monitoring data for determination of the population pharmacokinetics and enteral bioavailability of phenytoin in neonates and infants with seizures. Ther. Drug Monit. 2006;28:793–9.

137. Frey OR, von Brenndorff AI, Probst W. Comparison of phenytoin serum concentrations in premature neonates following intravenous and oral administration. Ann. Pharmacother. 1998;32:300–3.

138. Girgis IG, Nandy P, Nye JS, Ford L, Mohanty S, Wang S, et al. Pharmacokinetic-pharmacodynamic assessment of topiramate dosing regimens for children with epilepsy 2 to 10 years of age. Epilepsia. 2010;51:1954–62.

139. Ahmed GF, Marino SE, Brundage RC, Pakhomov SVS, Leppik IE, Cloyd JC, et al. Pharmacokinetic-pharmacodynamic modelling of intravenous and oral topiramate and its effect on phonemic fluency in adult healthy volunteers. Br. J. Clin. Pharmacol. 2015;79:820–30.

140. Doose DH, Walker SA, Gisclon LG. Single-Dose Pharmacokinetics Food on the Bioavailability A Novel Antiepileptic and Effect of Topiramate , Drug. 1996;884–91.

141. Bouillon-Pichault M, Jullien V, Bazzoli C, Pons G, Tod M. Pharmacokinetic design optimization in children and estimation of maturation parameters: example of cytochrome P450 3A4. J. Pharmacokinet. Pharmacodyn. 2011;38:25–40.

142. Silverstein FS, Ferriero DM. Off-label use of antiepileptic drugs for the treatment of neonatal seizures. Pediatr. Neurol. 2008;39:77–9.

143. Manitpisitkul P, Shalayda K, Todd M, Wang SS, Ness S, Ford L. Pharmacokinetics and safety of adjunctive topiramate in infants (1-24 months) with refractory partial-onset seizures: A randomized, multicenter, open-label phase 1 study. Epilepsia. 2013;54:156–64.

144. Filippi L, Poggi C, la Marca G, Furlanetto S, Fiorini P, Cavallaro G, et al. Oral topiramate in neonates with hypoxic ischemic encephalopathy treated with hypothermia: a safety study. J. Pediatr. Mosby, Inc.; 2010;157:361–6.

145. Ohman I, Vitols S, Luef G, Söderfeldt B, Tomson T. Topiramate kinetics during delivery, lactation, and in the neonate: preliminary observations. Epilepsia. 2002;43:1157–60.

146. Nakashima H, Oniki K, Nishimura M, Ogusu N, Shimomasuda M, Ono T, et al. Determination of the Optimal Concentration of Valproic Acid in Patients with Epilepsy: A Population Pharmacokinetic-Pharmacodynamic Analysis. PLoS One. 2015;10:e0141266.

147. Ogusu N, Saruwatari J, Nakashima H, Noai M, Nishimura M, Deguchi M, et al. Impact of the superoxide dismutase 2 Val16Ala polymorphism on the relationship between valproic acid exposure and elevation of gamma-glutamyltransferase in patients with epilepsy: a population pharmacokinetic-pharmacodynamic analysis. PLoS One. 2014;9:e111066.

148. Ahmad AM, Boudinot FD, Barr WH, Reed RC, Garnett WR. The use of Monte Carlo simulations to study the effect of poor compliance on the steady state concentrations of valproic acid following administration of enteric-coated and extended release divalproex sodium formulations. Biopharm. Drug Dispos. 2005;26:417–25.

149. Bondareva IB, Jelliffe RW, Sokolov a V, Tischenkova IF. Nonparametric population modeling of valproate pharmacokinetics in epileptic patients using routine serum monitoring data: implications for dosage. J. Clin. Pharm. Ther. 2004;29:105–20.

150. Lin W, Jiao Z, Wang C, Wang H, Ma C, Huang P, et al. Population Pharmacokinetics of Valproic Acid in Adult Chinese Epileptic Patients and its Application in an Individualized Dosage Regimen. Ther. Drug Monit. 2015;37:76–83.

151. Ding J, Wang Y, Lin W, Wang C, Zhao L, Li X, et al. A Population Pharmacokinetic Model of Valproic Acid in Pediatric Patients with Epilepsy: A Non-Linear Pharmacokinetic Model Based on Protein-Binding Saturation. Clin. Pharmacokinet. 2015;54:305–17.

152. Correa T, Rodriguez I, Romano S. Population Pharmacokinetics of Valproate in Mexican Children with Epilepsy. Biopharm. Drug Dispos. 2008;29:511–20.

153. Vucićević K, Miljković B, Pokrajac M, Prostran M, Martinović Z, Grabnar I. The influence of drug-drug interaction and patients' characteristics on valproic acid's clearance in adults with epilepsy using nonlinear mixed effects modeling. Eur. J. Pharm. Sci. 2009;38:512–8.

154. Jiang D, Bai X, Zhang Q, Lu W, Wang Y, Li L, et al. Effects of CYP2C19 and CYP2C9 genotypes on pharmacokinetic variability of valproic acid in Chinese epileptic patients: nonlinear mixed-effect modeling. Eur. J. Clin. Pharmacol. 2009;65:1187–93.

155. Jiang D, Wang L, Wang Y-Q, Li L, Lu W, Bai X-R. Population pharmacokinetics of valproate in Chinese children with epilepsy. Acta Pharmacol. Sin. 2007;28:1677–84.

156. Jiang D, Wang L. Population pharmacokinetic model of valproate and prediction of valproate serum concentrations in children with epilepsy. Acta Pharmacol. Sin. 2004;25:1576–83.

157. Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, et al. Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations. N. Engl. J. Med. 2010;362:2185–93.

158. Lindhout D, Schmidt D. In-Utero Exposure to Valproate and Neural Tube Defects. Lancet. 1986;14:1392–3.

159. Irvine-Meek JM, Hall KW, Otten NH, Leroux M, Budnik D, Seshia SS. Pharmacokinetic study of valproic acid in a neonate. Pediatr. Pharmacol. 1982;2:317–21.

160. Alfonso I, Alvarez L a., Gilman J, Dunoyer C, Yelin K, Papazian O. Intravenous Valproate Dosing in Neonates. J. Child Neurol. 2000;15:827–9.

161. Gal P, Oles KS, Gilman JT, Weaver R. Valproic acid efficacy, toxicity, and pharmacokinetics in neonates with intractable seizures. Neurology. 1988;38:467–71.

162. Gutierrez Garcia M, Garcia Benavas E, Perez Iglesias F, Garcia Diaz B. Treatment with intravenous valproic acid in a newborn. Farm. Hosp. 2010;34:259–61.

163. Gugler R, von Unruh GE. Clinical pharmacokinetics of Valproic Acid. Clin. Pharmacokinet. 1980;5:67–83.

164. Oommen KJ, Mathews S. Zonisamide: a new antiepileptic drug. Clin. Neuropharmacol. 1999;22:192–200.

165. Levy RH, Ragueneau-Majlessi I, Garnett WR, Schmerler M, Rosenfeld W, Shah J, et al. Lack of a clinically significant effect of zonisamide on phenytoin steady-state pharmacokinetics in patients with epilepsy. J. Clin. Pharmacol. 2004;44:1230–4.

166. Ragueneau-Majlessi I, Levy RH, Brodie M, Smith D, Shah J, Grundy JS. Lack of pharmacokinetic interactions between steady-state zonisamide and valproic acid in patients with epilepsy. Clin. Pharmacokinet. 2005;44:517–23.

167. Levy RH, Ragueneau-Majlessi I, Brodie MJ, Smith DF, Shah J, Pan W-J. Lack of clinically significant pharmacokinetic interactions between zonisamide and lamotrigine at steady state in patients with epilepsy. Ther. Drug Monit. 2005;27:193–8.

168. Kochak M, Page G, Padgett S. Steady-state pharmacokinetics of Zonisamide, an antiepileptic agent for treatment of refractory complex partial seizures. J. Clin. Pharmacol. 1998;38:166–71.

169. Hashimoto Y, Odani A, Tanigawara Y, Yasuhara M, Okuno T, Hori R. Population Analysis of the Dose-Dependent Pharmacokinetics of Zonisamide in Epileptic Patients. Biol. Pharm. Bull. 1994;17:323–6.

170. Kawada K, Itoh S, Kusaka T, Isobe K, Ishii M. Pharmacokinetics of zonisamide in perinatal period. Brain Dev. 2002;24:95–7.

171. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. Clin. Pharmacokinet. 2013;52:627–45.

172. Gomez-ramirez J, Sanz R. On the limitations of standard statistical modeling in biological systems : A full Bayesian approach for biology. Prog. Biophys. Mol. Biol. Elsevier Ltd; 2013;113:80–91.

173. Marshall EMWS, Burghaus R, Cosson V, Cheung SYA, Chenel M, DellaPasqua O, et al. Good Practices in Model-Informed Drug Discovery and Development : Practice, Application, and Documentation. CPT Pharmacometrics Syst. Pharmacol. 2016;5:93–122.

174. Danhof M, de Jongh J, De Lange ECM, Della Pasqua O, Ploeger B a, Voskuyl R a. Mechanism-based pharmacokinetic-pharmacodynamic modeling: biophase distribution, receptor theory, and dynamical systems analysis. Annu. Rev. Pharmacol. Toxicol. 2007;47:357–400.

175. Harnisch L, Shepard T, Pons G, Della Pasqua O. Modeling and Simulation as a Tool to Bridge Efficacy and Safety Data in Special Populations. CPT Pharmacometrics Syst. Pharmacol. 2013;2:e28.

176. Mould DR. Models for Disease Progression : New Approaches and Uses. Clin. Pharmacol. Ther. Nature Publishing Group; 2009;92:125–31.

177. Piana C, de Jesus Antunes N, Della Pasqua O. Implications of pharmacogenetics for the therapeutic use of antiepileptic drugs. Expert Opin. Drug Metab. Toxicol. 2014;10:341–58.

178. Piana C, Danhof M, Pasqua O Della. Influence of covariate distribution on the predictive performance of pharmacokinetic models in paediatric research. :145–57.

179. Bonate PL, Ahamadi M, Budha N, Ruiz-garcia A, Struemper H, Wade JR. Methods and strategies for assessing uncontrolled drug – drug interactions in population pharmacokinetic analyses : results from the International Society of Pharmacometrics (ISOP) Working Group. :123–35.

180. Yasuda SU, Zhang L, Huang S. The Role of Ethnicity in Variability in Response to Drugs : Focus on Clinical Pharmacology Studies. 2008;417–23.

181. Phan VH, Moore MM, Mclachlan AJ, Piquette-Miller M, Xu H, Clarke SJ. Ethnic differences in drug metabolism and toxicity from chemotherapy Ethnic differences in drug metabolism and toxicity from chemotherapy. Expert Opin. Drug Metab. Toxicol. 2009;5:243–57.

182. Engel J, Pitkänen A, Loeb JA, Dudek FE, Bertram EH, Cole AJ, et al. Epilepsy biomarkers. Epilepsia. 2013;54 Suppl 4:61–9.

183. van Dijkman SC, Voskuyl RA, de Lange EC. Biomarkers in epilepsy–A modelling perspective. Eur. J. Pharm. Sci. Elsevier; 2017;In press.

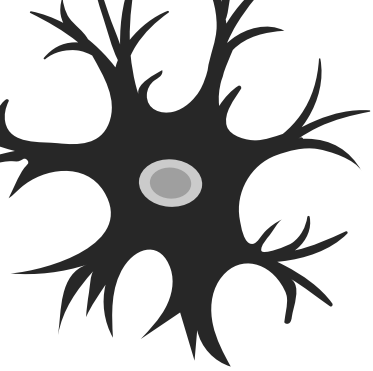
184. van Dijkman SC, Rauwé WM, Danhof M, Della Pasqua O. Pharmacokinetic interactions and dosing rationale for antiepileptic drugs in adults and children. Br. J. Clin. Pharmacol. 2017;In press.

185. van Dijkman SC, Wicha SG, Danhof M, Della Pasqua OE. Individualised dosing algorithms and therapeutic monitoring for antiepileptic drugs. Clin. Pharmacol. Ther. 2017;In press.

186. Faught E. Adherence to antiepilepsy drug therapy. Epilepsy Behav. Elsevier Inc.; 2012;25:297–302.

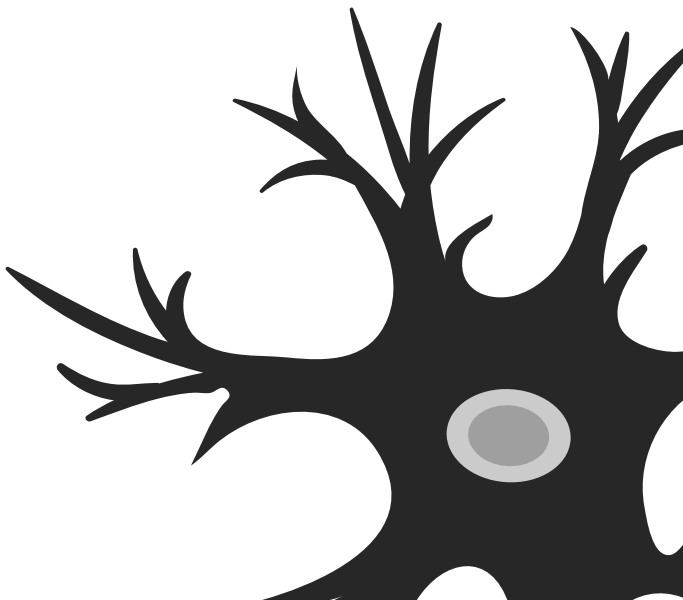
187. Kwan P, Brodie MJ. Epilepsy after the first drug fails: substitution or add-on? Seizure. 2000;9:464–8.

188. St Louis EK, Rosenfeld WE, Bramley T. Antiepileptic drug monotherapy: the initial approach in epilepsy management. Curr. Neuropharmacol. 2009;7:77–82.



SECTION III

MODEL-BASED DOSING ALGORITHMS



CHAPTER 4

PHARMACOKINETIC INTERACTIONS AND DOSING RATIONALE FOR ANTIEPILEPTIC DRUGS IN ADULTS AND CHILDREN

Pharmacokinetic interactions and dosing rationale for antiepileptic drugs in adults and children

Sven C. van Dijkman, Willem M. Rauwé, Meindert Danhof, Oscar Della Pasqua

British Journal of Clinical Pharmacology, 2017

SUMMARY

Aim: Population pharmacokinetic modelling has been widely used across many therapeutic areas to identify sources of variability, which are incorporated into models as covariate factors. Despite numerous publications on pharmacokinetic (PK) drug-drug interactions (DDIs) between antiepileptic drugs (AEDs), such data are not used to support the dose rationale for polytherapy in the treatment of epileptic seizures. Here we assess the impact of DDIs on plasma concentrations and evaluate the need for AED dose adjustment.

Methods: Models describing the pharmacokinetics of carbamazepine, clobazam, clonazepam, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide in adult and paediatric patients were collected from the published literature and implemented in NONMEM v7.2. Taking current clinical practice into account, we explore simulation scenarios to characterise AED exposure in virtual patients receiving mono-, and polytherapy. Css, Cmax and Cmin were selected as parameters of interest for the purpose of this analysis.

Results: Our simulations show that DDIs can cause major changes in AED concentrations both in adults and children. When more than one AED is used, even larger changes are observed in the concentrations of the primary drug, leading to significant differences in Css between mono- and polytherapy for most AEDs. These results suggest that currently recommended dosing algorithms and titration procedures do not ensure attainment of appropriate therapeutic concentrations.

Conclusions: The effect of DDIs on AED exposure cannot be overlooked. Clinical guidelines must take into account such covariate effects and ensure appropriate dosing recommendations for adult and paediatric patients who require combination therapy.

WHAT IS KNOWN ABOUT THIS SUBJECT

- First-line and alternative first line anti-epileptic drugs (AEDs) are often used in combination with second-line line drugs (i.e., add-on).
- Many AED combinations lead to pharmacokinetic (PK) drug-drug interactions (DDIs), which may result in large changes in drug exposure.
- The implications of such DDIs have not been characterised in existing clinical guidelines.

WHAT THIS STUDY ADDS

- We evaluate how demographic and clinical factors, including co-medications (polytherapy), affect systemic exposure to AEDs in the target patient population. In addition, we demonstrate that AED dosing regimens can be optimised to ensure drug concentrations are maintained within a reference therapeutic range.
- DDIs can lead to significant changes in AED exposure and potentially alter the efficacy and safety profile of AEDs in adult and paediatric patients.
- These results form the basis for a comprehensive review of clinical guidelines for the use of first and second line AEDs, including novel algorithms for dose adjustment.

1. INTRODUCTION

Epilepsy is a collection of syndromes characterised by the occurrence of paroxysmal seizures. Many patients require prolonged and often life-long treatment with anti-epileptic drugs (AEDs), which are developed and approved based primarily on the evidence of efficacy in specific seizure types. From a clinical perspective, this has led to treatment choices based on a classification system that discriminates AEDs into first and second-line treatment. A first-line treatment is tried first and usually used on its own. If first-line treatment does not work, then another drug (i.e., an alternative first-line treatment) may be tried on its own. First-line treatment drugs may also be used as combinations (i.e., add-on treatment) if seizure control is not achieved or a given regimen is not tolerated [1].

At the moment approximately 20 AEDs are available including first and second line treatment options. Different guidelines have been proposed to guide health care professionals and prescribing physicians on the use of AEDs, with special focus on the criteria for selection of newer drugs. In addition to providing recommendations for the treatment of specific populations such as women and HIV patients, attention is also given to the importance of dose titration and tapering procedures. Nevertheless, it has been shown that 10-20% of the patients whose target dose has been achieved, still show unresolved seizures and can benefit from dose-adjustments [2,3]. Despite evidence on the role of pharmacoresistance and progression of the underlying pathological processes, the lack of response can be partly explained by inter-individual variability in the pharmacokinetics (PK) [4]. The impact of such variability is particularly important in the paediatric population, where maturation processes and developmental growth are known to affect drug disposition [5–7]. In addition, children who do not adequately respond to first-line treatment are given multiple AEDs in combination, which can incur PK (and pharmacodynamic (PD)) drug-drug interactions (DDIs).

Population PK modelling has been widely used across many therapeutic areas to describe drug exposure and identify sources of variability, which are then incorporated into models as covariate factors [8,9]. Consequently,

differences in drug exposure due to explanatory factors such as DDIs or demographic and clinical parameters can be predicted before treatment is initiated. The availability of such models also allows us to perform clinical trial simulations (CTS) and not-in-trial simulations (NITS) and explore the potential implication of covariate effects on individual patients or subgroups of the target patient population [3,10]. When performed in a systematic manner, the use of simulation scenarios becomes a powerful tool for the evaluation of the impact of multiple, concurrent factors on drug exposure, providing the rationale for dose adjustment purposes [11,12]. Here, we show how clinical trial simulations can be used to characterise pharmacokinetic DDIs for the most widely used AEDs at clinically relevant doses and regimens. Scenarios are evaluated which reflect the impact of titration steps, different maintenance doses and add-on treatments. Bearing in mind current clinical practice, we aim to assess the impact of DDIs on the exposure to AEDs and establish the need for further dose adjustment. We anticipate that our analysis will assist the review of clinical guidelines, taking into account the role of covariate factors in future dosing recommendations. Most importantly, it will provide clinicians further insight into the role of PK variability in the overall efficacy and safety profile of AEDs.

2. METHODS

Pharmacokinetic models and virtual patient demographics

Models describing the PK of carbamazepine (CBZ) [13], clobazam (CLBZ) [14], clonazepam (CLNZ) [15], lamotrigine (LMT) [16,17], levetiracetam (LVT) [18], oxcarbazepine (OXC) [19], phenobarbital (PHB) [20], phenytoin (PHT) [21], topiramate (TPM) [22], valproic acid (VPA) [23,24], and zonisamide (ZNS) [25] were collected from the published literature. Given the primary objective of our analysis, models were selected if covariate effects were identified for one or more AEDs and study population included > 50 patients. In addition, whenever possible, preference was given to models based on PK data from both adult and paediatric patients. Furthermore, parameterisation of the covariate effect (i.e., DDI) should be based on changes in clearance to allow easier differentiation between treatment conditions, i.e., the presence of the co-medication. An overview of the model structure, including details on the parameterisation of the covariate effects for each AED is presented in tables 1A and 1B.

Further information on the clinical protocols used to develop the pharmacokinetic models and identify the covariate effects is provided in the **supplemental material** (downloadable from the online version of this article). As modelling codes were not available in the original publications, models were transcribed manually into standard control-stream file format in NONMEM v7.2 [26]. For the sake of accuracy and quality, model transcription was assessed one by one before the implementation of the simulation scenarios by comparing model-predicted concentrations for the original patient population to the reported results in the corresponding publications (see **supplemental material**). If no deviations were observed during this initial quality check, the PK model code was subsequently transcribed into the appropriate format for simulation purposes in R v3.1.1 [27]. Simulation scenarios, comprising treatment conditions at different dose levels and DDIs were selected for both adult and paediatric patients. For each scenario, a population of 1000 virtual patients was simulated using the demographic baseline characteristics listed in table 2. It was anticipated that spurious correlations between covariates would be negligible using random sampling for such a large number of patients. One exception was

the correlation (colinearity) between weight and age in children, which is highly relevant for the characterisation of pharmacokinetics in this population. This was particularly important for TPM, which had both weight and age as covariate factors in the model. In addition to demographic factors, other influential covariate factors such as genetic polymorphisms were also simulated if included in the original publication. To ensure accurate characterization of the covariate effects, demographic and other relevant clinical variables were sampled according to a uniform distribution.

Table 1A Overview of the population pharmacokinetic models used for the evaluation of drug-drug interactions for carbamazepine, clobazam, clonazepam, lamotrigine, levetiracetam, and oxcarbazepine

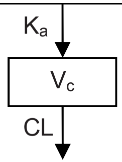
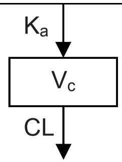
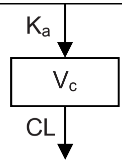
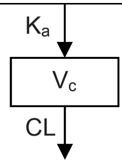
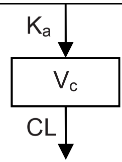
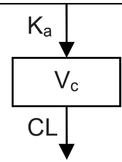
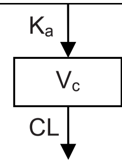
Model	Carbamazepine	Clobazam	Clonazepam	Lamotrigine Adults	Lamotrigine Children	Levetiracetam	Oxcarbazepine
First author	Jiao[13]	Saruwatari[14]	Yukawa[15]	Rivas[16]	He[17]	Toublanc[18]	Park[19]
Population	Chinese	Japanese	Japanese	German/ Spanish	Chinese	Japanese (model building), US (validation)	Korean
Sample size (No.of patients)	585	85	137	284	600	259	199
Sample size (No.of patients)	687	128	259	404	1699	1833	254
Age (years)	1.2-85.1	1-52	0.3-32.6	26.8-51.3	0.5-17	4-55	3-80
Weight (kg)	5-115	8-102	5-90	61.8-85	6-98	14-107	10-95
Samples at	Trough	0-10h post-dose	2-6h post-dose	TDM	TDM	Random	TDM
Graphical representation							
Parameters	K_a, V_c ,CL	K_a, V_c ,CL	K_a, V_c ,CL	K_a, V_c ,CL	K_a, V_c ,CL	K_a, V_c ,CL	K_a, V_c ,CL
Between-subject variability	V_c, CL	K_a, V_c ,CL	V_c, CL	CL	CL	K_a, V_c ,CL	CL
Covariates CL	WT, Dose, PHB, PHT, VPA, Elderly (>65)	WT, PHB, PHT, ZNS, CYP2C19 & POR*28 genotypes	WT, CBZ, VPA	WT, CBZ, PHB, VPA	WT, CBZ, PHB, VPA	WT, Clearance Comedication (CBZ, PHB, PHT, VPA)	WT, EIAED (comedication CBZ/PHB/PHT)
Covariates V	WT	WT	WT	WT	WT	WT	WT

Table 1B Overview of the population pharmacokinetic models used for the evaluation of drug-drug interactions for phenobarbital, phenytoin, topiramate, valproic acid, and zonisamide

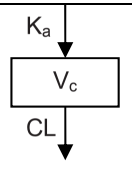
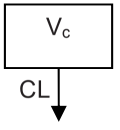
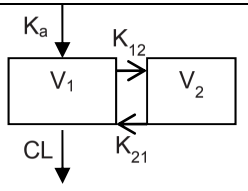
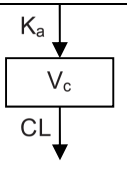
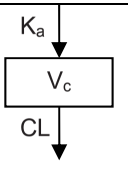
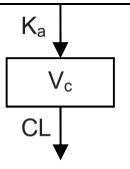
Model	Phenobarbital	Phenytoin	Topiramate	Valproate Adults	Valproate Children	Zonisamide
First author	Goto[20]	Odani[21]	Girgis[22]	Blanco-Serrano[23]	Blanco-Serrano[24]	Okada[25]
Population	Japanese	Japanese	NA (Caucasian presumably)	Spanish	Spanish	Japanese
Sample size (No.of patients)	79	116	1217	255	208	99
Sample size (No.of patients)	260	531	4640	770	534	282
Age	0.8-44	1-37	2-85	14-95	0.1-14	1.36-39.24
Weight	8-80	42.4±16.5	NA	4-74	27-100	10-117
Samples at	TDM	Peak/Trough	NA	TDM	TDM	4.3±2.8h post-dose
Graphical representation						
Parameters	K_a, V_c ,CL	V_c ,CL (V_{max}, K_m)	K_a, V_{ss} (V_1 +V_2), K_{12}, K_{21}, CL	K_a, V_c ,CL	K_a, V_c ,CL	K_a, V_c ,CL
Between-subject variability	V_c, CL	V_c, V_{max}, K_m	K_a, V_c ,CL	CL	CL	CL
Covariates CL	WT, PHT, VPA	WT, Daily PHT Dose, ZNS	Age, WT, Inducers (CBZ/PHB/PHT), VPA, NEMD (ZNS)	WT, Dose, CBZ, PHT, PHB	WT, Dose, CBZ	WT, Dose, CYP2C19 genotype, CBZ, PHB, PHT
Covariates V	-	WT	WT	WT	WT	WT

Table 2 Patient baseline demographic characteristics used for the simulation scenarios, in which a virtual cohort of patients was treated with one or more AEDs.

Population	adults	children
Age (years)	18-65, uniformly distributed	4-14, uniformly distributed
Mean weight (kg)	75 (male) 65 (female)	(Age·3)+7[†]
Coefficient of variance on weight	16 %	10 %
Dose interval (hr)	12	12
Dose	mg/day	mg/kg/day

†Based on the weight-by-age formula proposed by Luscombe & Owens[28]

Table 3 Simulated doses, co-medications, and corresponding reference therapeutic range for each AED Reference AED concentration ranges were taken from Patsalos et al 2008 [31]. See main text for further details on the abbreviations and supporting references.

Drug	**Doses adults (mg/day, * µg/day)**	**Doses children (mg/kg/day, * µg/kg/day)**	**Add-on medication simulated**	**Therapeutic window [31] (mg/L, * µg/L)**
CBZ	400, 800, 1200	10, 15, 20	PHB ∨ PHT ∨ VPA	4-12
CLBZ	10, 20, 30 *	0.2, 0.3, 0.4 *	PHB ∨ PHT ∨ ZNS	30-300 *
CLNZ	2, 5, 8 *	0.05, 0.075, 0.1 *	VPA	20-70 *
LMT	200, 300, 400	4, 6, 8	((CBZ ⊕ PHB ⊕ PHT) ⊕ IND[a]) ∨ VPA	2.5-15
LVT	1000, 2000, 3000	20, 30, 40	Inducers[b]	12-46
OXC	600, 1200, 1800	15, 20, 25	CBZ ⊕ PHB ⊕ PHT	3-35
PHB	60, 150, 240	2, 4, 6	PHT ∨ VPA	10-40
PHT	200, 300, 400	5, 7.5, 10	ZNS	10-20
TPM	200, 300, 400	5, 7.5, 10	Inducers[c] ∨ VPA	5-20
VPA	400, 800, 1200	10, 20, 30	CBZ ∨ PHB ∨ PHT	50-100
ZNS	200, 300, 400	5, 7.5, 10	CBZ ∨ PHB ∨ PHT	10-40

∨ all combinations are possible, ⊕ only one combination is possible

[a] For LMT, if more than 1 of CBZ, PHB, or PHT is added, only the effect indicated by IND (and/or VPA) affects LMT clearance

[b] For LVT the original paper[17] mentions inducers "such as carbamazepine"

[c] For TPM, clearance is induced by adding any of the following: CBZ, PHB and PHT, no distinction is made between adding one or more of these

Simulation scenarios

One and two compartment models were implemented in R according to equations 1 and 2.1-2.5, as described in the PFIM optimal design tool documentation [29]. The concentration *versus* time profiles of each AED were simulated at steady state for the typical adult and paediatric populations (table 2), following the administration of a range of clinically relevant doses (table 3). Given the objectives of the current investigation, we have decided not apply bridging and extrapolation concepts to scale pharmacokinetic parameters from adults to children as basis for the paediatric dose selection [30]. Instead, paediatric doses were scaled by body weight on a mg/kg basis, as typically done by prescribing physicians in clinical practice. Secondary PK parameters were then derived, including average steady-state (C_{ss}), peak (C_{max}) and trough (C_{min}) concentrations.

A key premise for the evaluation of the different simulation scenarios is the set of assumptions used, which include the following points:

1. Attainment and maintenance of AED exposure within a target range is desirable for optimal treatment response, irrespective of drug use as a single agent (monotherapy) or as combinations. The reference target concentration ranges published by Patsalos et al [31] were considered as relevant for the adult and paediatric populations.
2. In addition, it was assumed that interindividual variability in pharmacodynamics, i.e., different individual sensitivity to individual drug effects are captured by the proposed target range, whereas resistance to treatment would impose exposure to higher drug concentrations, which are likely to be associated with poor tolerability.
3. Model misspecification was deemed to be minimal and parameter distributions to be precise and accurate to a sufficiently high degree to allow realistic simulations.
4. Covariate effects are reasonably well captured by the models, despite the limited number of patients included for the development of the models (table 1A/B).
5. Bias in the estimates of the covariate effects is minimal even if DDIs are treated as discrete covariates in the model. It is acknowledged, however, that discrete covariate effects may impair one's ability to adjust the dose, as variability in exposure or the use of different dose levels of the add-on

drug may alter the magnitude of the interaction. This is particularly important in the case of multiple DDIs.
6. Whereas discrete parameterisation of DDIs may not fully capture the range of conditions or variation in clinical practice, it does provide a stronger basis for the dose rationale, as compared to scenarios where DDIs are completely overlooked.

Simulations were performed in two steps. First, we aimed to identify the dose or dose levels that maximised the fraction of virtual patients whose C_{ss} values remained within the target exposure range for each drug. Subsequently, the impact of DDIs on the systemic exposure of the first-line or alternative first-line AED was simulated (table 3). In total 76 scenarios were considered, taking into account the most clinically relevant dosing regimens and combinations. This resulted in a total of 33 scenarios for monotherapy and 43 scenarios for different AED combination. As scenario included 1000 virtual patients, our analysis comprises a population of 76000 patients.

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

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

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

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

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

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

$$C_{ss} = \frac{1}{24}\frac{DD}{CL} \quad (3)$$

Equations 1-3. C_t: concentration at time t. τ: dosing interval. D: Dose of dose interval τ. DD: Daily dose. V or V_1: central volume of distribution. k_a: absorption rate constant. CL: clearance. t: time. t_D: time of dose. Q: inter-compartmental clearance. V_2: peripheral volume of distribution. As none of the models included intravenous data, bioavailability estimates were not available; clearance and volume values used in the analysis were therefore based on apparent estimates.

Assessment of the impact of covariate effects on drug exposure

The target C_{ss} value used for optimisation purposes was set to the drug concentration half-way between the minimum and maximum values of the therapeutic window for each AED (table 3). Details of the rationale for this approach are described in a previous publication by our group, where different dosing algorithms have been assessed for personalisation of AED therapy [3]. In brief, the ratio between predicted C_{ss} and target C_{ss} was calculated (ratio=predicted/target) and results were subsequently summarised in tabular and graphical format. Whisker-box plots were generated separately for adults and children to describe the dispersion in drug exposure across the population, including the median and 95% prediction interval for each dose and DDI scenario. To facilitate the interpretation of the findings and visualise the impact of dosing titration and/or optimisation procedures, the percentage of the population with concentrations outside the therapeutic range was also summarised numerically along with the whisker-box plots. In addition, the percentage adjustment needed to bring the median C_{ss} values back to the target concentration was calculated and provided for each AED.

3. RESULTS

A preliminary analysis of the pharmacokinetic models showed acceptable performance for the purposes of our investigation. Different dose and dosing regimens were simulated for each AED according to the scenarios shown in table 3. For the sake completeness, an overview of the concentration vs. time profiles for each AED in adult and paediatric patients is presented in the **supplemental material** (see online version of this article). These results are complemented by a summary of the procedures used for evaluation of model performance, including the results relative to the secondary PK parameters (Cmax, Cmin).

Monotherapy: impact of standard dose regimens on systemic drug exposure

For most drugs the simulated average steady-state concentrations (C_{ss}) fall within the reference values for a large fraction of the adult and paediatric populations. Notable exceptions were PHT and VPA, where significant proportion of patients is at risk of achieving sub- or supra-therapeutic drug concentrations (**figures 1 and 2**). In fact, the deviations from the reference range are evident when considering the median estimates. Likewise, despite the use of dosing regimens in mg/kg, PHT concentrations in children fall outside the therapeutic window in at least 50% of the patients. For VPA the situation is somewhat more favourable, with roughly 20% of the simulated population falling outside the reference therapeutic range. In the case of PHT, the deviation in exposure is compounded by the known nonlinearity and large inter-individual variability in pharmacokinetics. There are important clinical implications for patients on PHT when plasma concentrations are > 20 mg/L. In reality, the evidence that a significant proportion of the population is exposed to drug concentrations above the therapeutic range may explain the incidence of adverse events.

Polytherapy: impact of DDIs on systemic drug exposure

The use of simulations reveals that DDIs can cause major changes to AED concentrations both in adults and children (**figures 3 and 4**). When more than one AED is added to the combination therapy, changes in the concentrations of the primary drug may be even larger. This contrasts with the results observed for monotherapy, where drug concentrations for the majority of the AEDs remained within the reference therapeutic range. In many cases, AED interaction results in median C_{ss} values which lie outside the reference therapeutic window. On the other hand, in certain cases the interaction of multiple co-medications may partially or completely counteract each other, resulting in a 0% net change in the exposure to the first line drug. An example of the latter is the interaction of LMT with combination therapy including PHT and VPA. A preliminary evaluation of the effect of DDIs suggests that the doses of the first line and possibly second line drugs used as add-on treatment need to be adjusted, sometimes by even more than 200% (table 4).

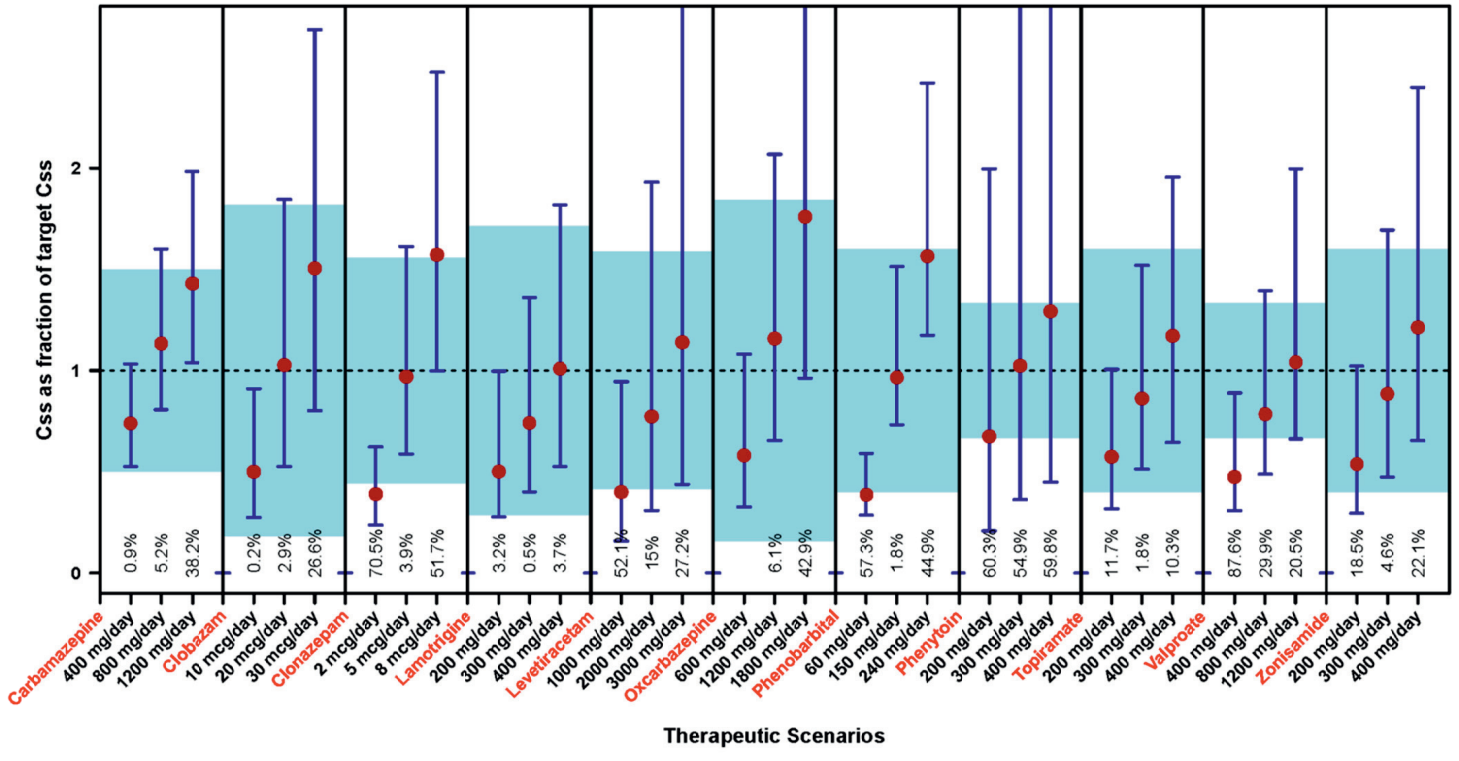


Figure 1 Median (circles) and 95% prediction interval (bars) for the steady-state concentrations (C_{ss}) achieved in adults for different AEDs and dosing scenarios. Shaded area represents the reference therapeutic range; numbers shown below each bar are percentages of the population with C_{ss} values outside the reference therapeutic range.

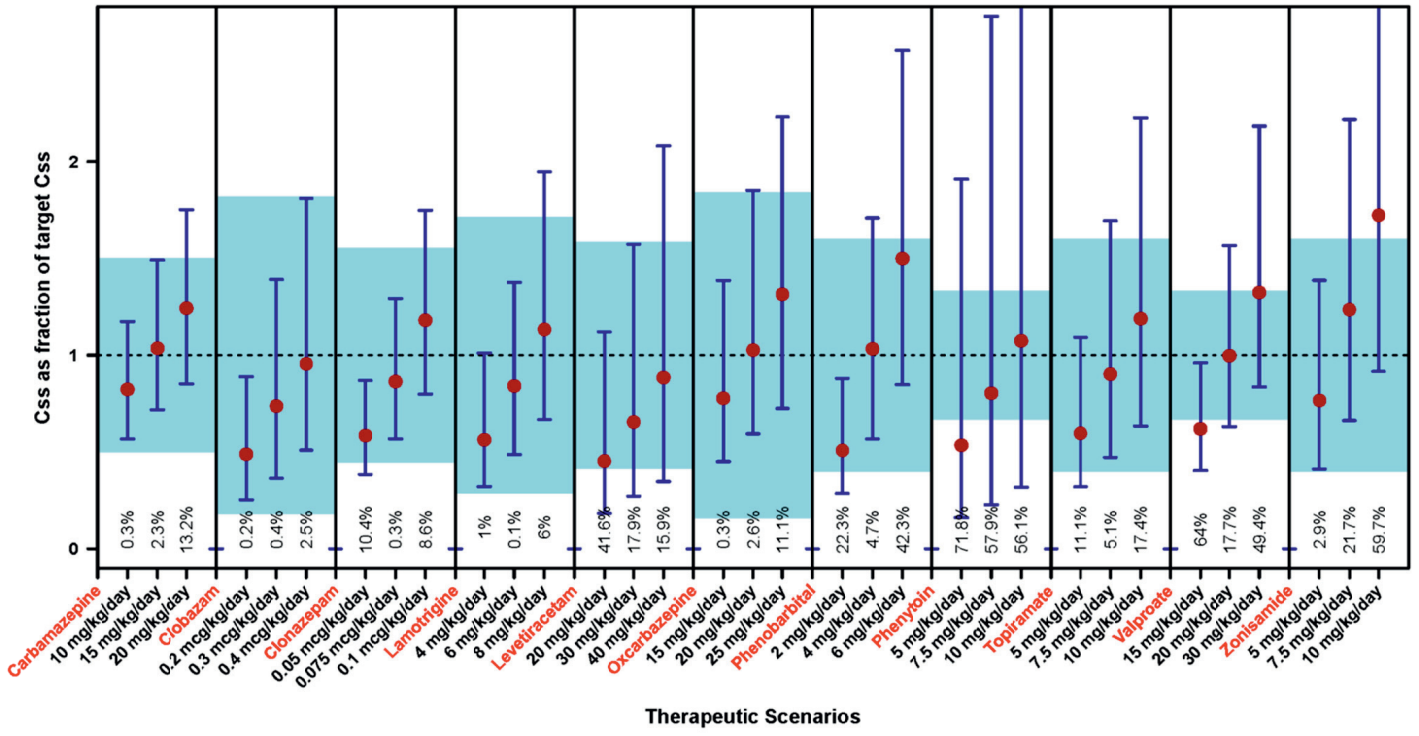


Figure 2 Median (circles) and 95% prediction interval (bars) for the steady-state concentrations (C_{ss}) achieved in children for different AEDs and dosing scenarios. Shaded area represents the reference therapeutic range; numbers shown below the bars are percentages of the population with C_{ss} values outside the reference therapeutic range.

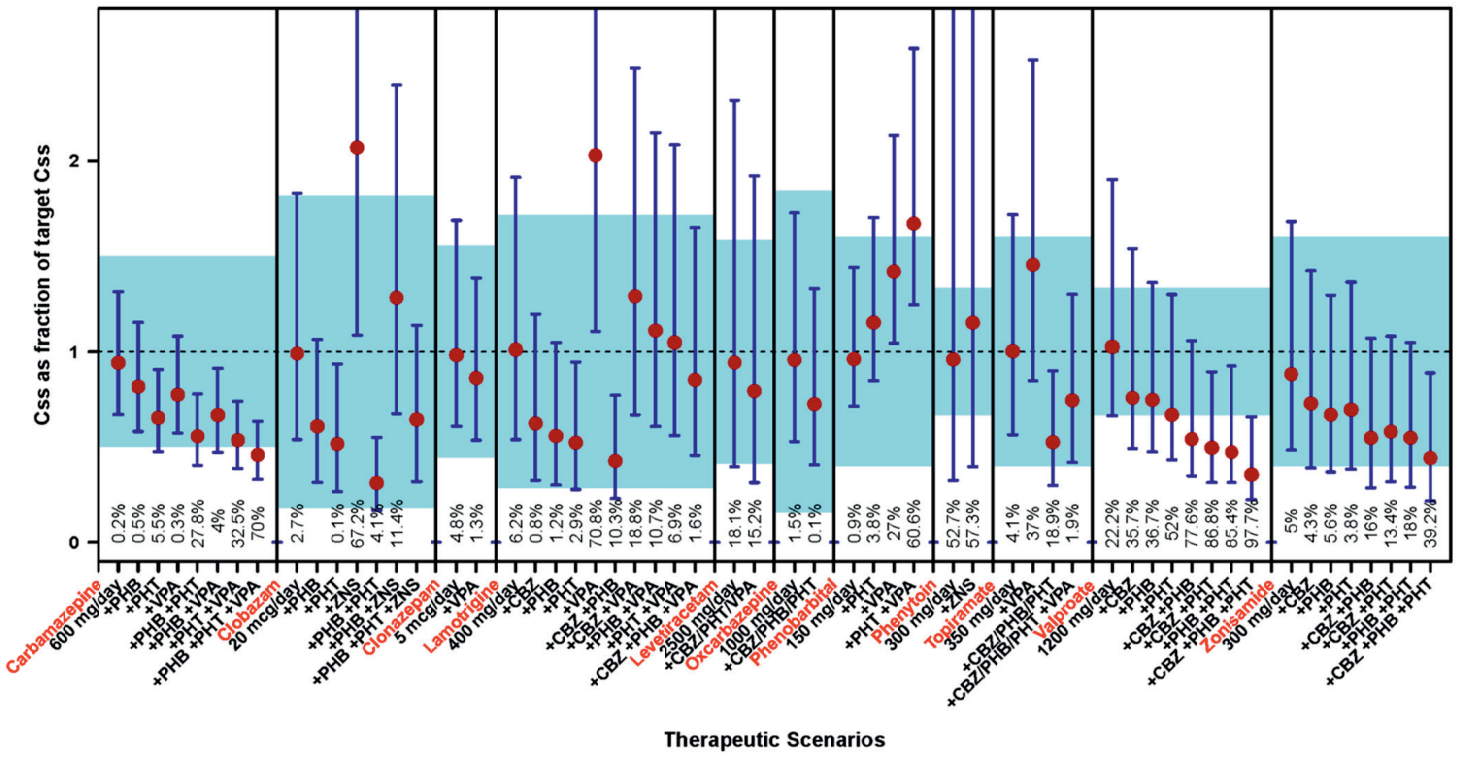


Figure 3 Median (circles) and 95% prediction interval (bars) for the steady-state concentrations (C_{ss}) achieved in adults for different AEDs and DDI scenarios. Shaded area represents the reference therapeutic range; numbers shown below the bars are percentages of the population with C_{ss} values outside the reference therapeutic range.

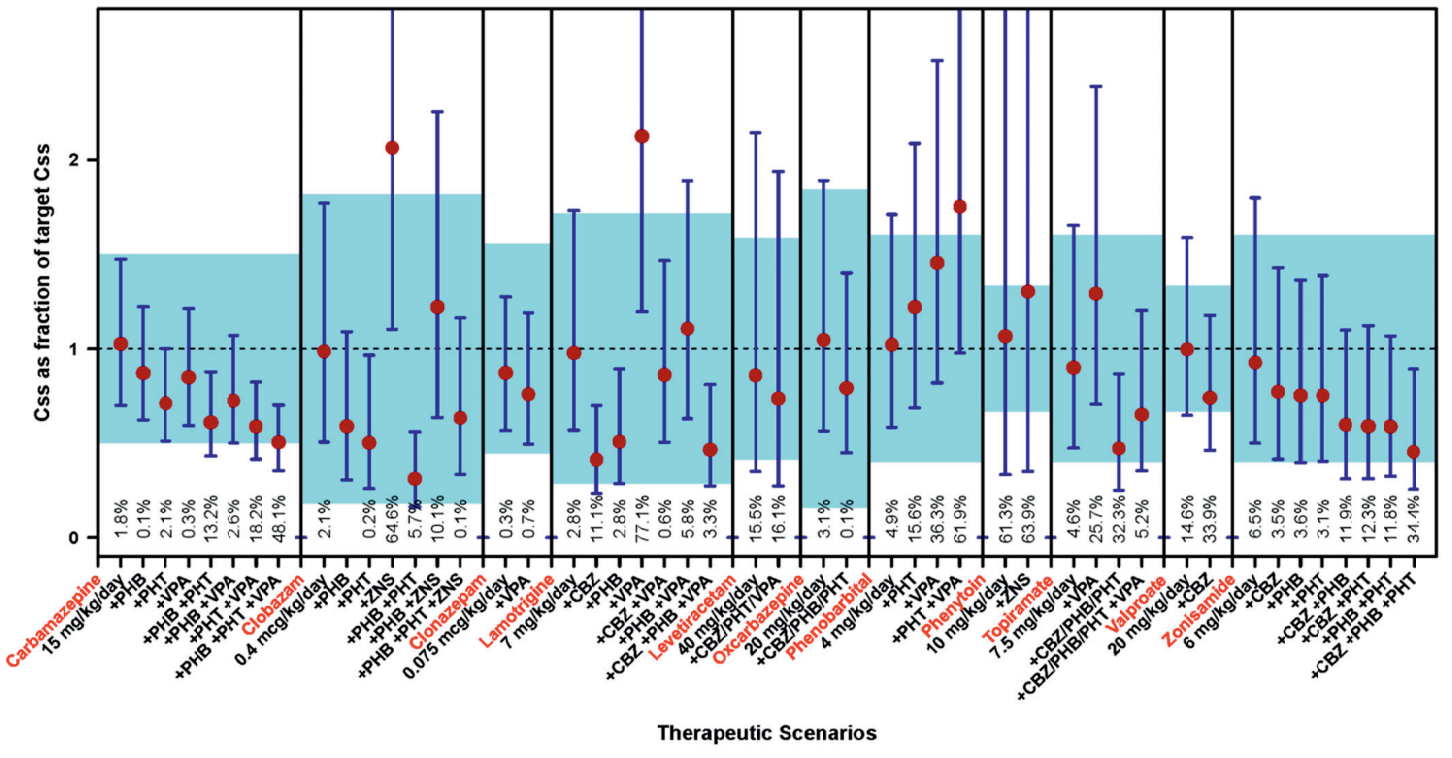


Figure 4 Median (circles) and 95% prediction interval (bars) for the steady-state concentrations (C_{ss}) achieved in children for different AEDs and DDI scenarios. Shaded area represents the reference therapeutic range; numbers shown below the bars are percentages of the population with C_{ss} values outside the reference therapeutic range.

4. DISCUSSION

Given the incidence of epileptic seizures across a wide age range in the patient population, rational prescribing of AEDs requires not only an understanding of the drugs' pharmacodynamic properties, but also careful consideration of the factors known to affect drug disposition [6]. Despite numerous publications in which demographic, clinical and genetic covariate factors have been identified, limited attention has been given to the magnitude and variability of such effects and their clinical implication. In most cases, covariate effects are assessed as part of a population PK analysis, where the main objective is the characterization of overall drug disposition properties, rather than the optimisation of therapeutic interventions in a wider patient population [32,33].

In a recent publication we have shown how model-based approaches can be used in conjunction with therapeutic drug monitoring to personalise AED therapy [3]. The current investigation was aimed at exploring the implications of covariate effects on systemic exposure, with special focus on drug-drug interactions (DDIs), i.e., when patients transition from monotherapy to combination treatment with alternative first line or second line therapy (polytherapy). We found that covariate effects on the disposition of levetiracetam, phenytoin, and valproic acid leads to considerable variation in drug exposure and consequently to a large proportion of patients reaching average steady-state concentrations outside the therapeutic window (15%, 54%, and 21% respectively). The impact of covariate effects on the disposition of the other 8 drugs included in the analysis appears to be less strong, resulting in a smaller proportion of patients outside the therapeutic window. By contrast, when DDIs come into play, exposure to most AEDs deviates from the reference therapeutic window (up to 98% for valproic acid), most notably when more than one co-medication was added. Moreover, there was no clear correlation between the mechanism of interactions and their effect size [34].

Whilst the analysis and interpretation of the simulation results rely on a set of important assumptions regarding covariate effects, it is clear that the relevance of DDIs should not be overlooked in clinical practice, as first-line

treatments are often accompanied by second-line drugs, which are combined as add-on therapy in patients who fail to show acceptable clinical response on monotherapy. We have assumed that the models described the DDIs to a sufficiently accurate degree to learn about their impact on exposure in the population. However, it should be highlighted that DDIs have been implemented as discrete covariates on clearance, i.e., clearance estimates change depending on whether a co-medication was given or not. We cannot exclude the possibility that despite steady-state concentrations the magnitude of such interactions may be dose-dependent [35]. To take into account the multiple inter-dependencies in the case of AED poly-therapy, the application of more physiology-based pharmacokinetic (PBPK) models may more accurately predict complex DDIs. On the other hand, if metabolic interactions (e.g., CYP enzymes) reflect high or maximum induction or inhibition when the co-medication exposure is at therapeutically relevant concentrations, further variation in dose or concentration may not affect the magnitude of the interaction any more. In this light, the predicted dose changes of first line drugs in table 4 should be seen as typical values, based on commonly used dose levels of first-line and co-medication AEDs. These results do not exclude the fact that there may be additional variability, which is unaccounted for, depending on the dose of the co-medication(s).

Currently, clinical guidelines do not consider the need to assess in a quantitative manner the contribution of covariate factors on drug exposure and consequently on the rationale for dose selection or titration algorithms [3]. Whereas some product labels provide dosing recommendations for individuals with renal and hepatic impairment, no specific dose adjustment is proposed to account for other relevant factors. Often DDIs are mentioned but no formal dosing recommendation is provided, taking into account AED disposition and other relevant patient characteristics. This is particularly important in infants older than 2-3 months and children, in whom systemic clearance is higher than adults after normalization for differences in body weight. This general pattern has been shown for various AEDs [36,37]. At the other extreme of age, in the elderly, systemic clearance is generally reduced compared with younger adults because of less efficient metabolism, reduced renal function, or both [36]. Likewise, patient

demographic characteristics, such as obesity, also lead differences in drug disposition, with significant changes in hepatic blood flow and/or metabolic activity (e.g. increased CYP enzyme expression), which have not been taken into account in our analysis, as weight range simulated did not include obese patients [38]. It should also be noted that despite known polymorphism in drug metabolism, there may be an interaction between genotype and degree of DDI that was not captured in the models that included CYP genotypes (table 4). We have assumed that such a CYP genotype – DDI interaction may have a limited role in the overall shift from the target exposure when compared to the degree of DDI itself. Additional data from *in silico* systems, such as SIMCYP™ would be required to explore phenotypical and genotypical differences in a systematic manner [39]. Another potential factor leading to variability in systemic exposure, which has not been included in the current analysis, is plasma protein binding. In the presence of competing moieties, changes in unbound fraction may affect drug disposition and eventually treatment response, as has been described for VPA and PHT.

It should be highlighted that the lack of guidance regarding DDIs may be partly explained by the lack of consensus on the benefit of therapeutic drug monitoring, especially when performed in an empirical manner [7,40–42]. Another point to consider is that clinicians tend to focus on age as the explanatory factor influencing the PK profile of AEDs. However, systemic exposure at any age may depend on different covariate factors, such as body weight, genetics, co-morbidities, organ function and metabolic capacity. Clearly, in the presence of these multiple interacting factors, it may not be possible to disentangle the contribution of each one independently. Often unless quantitative clinical pharmacology methods are implemented, such a situation prevents us from proposing dosing adjustment algorithms that correctly account for the effect of DDIs. This concept has been illustrated by the integration of therapeutic drug monitoring with Bayesian algorithms to support dose adjustment for carbamazepine (CBZ) and/or valproate (VPA) [42], resulting in with increased seizure control, better safety profile and reduced treatment costs.

Our investigation does not focus on the advantages of any specific approach. Rather, it draws attention to the fact that the characterisation of covariate effects and variability in drug exposure is essential for dose optimisation [43–45]. However, we acknowledge that not all clinically relevant DDIs have been evaluated or parameterised (e.g. the effect of VPA co-administration on PHT pharmacokinetics) [46,47]. We also recognise that even though many of the published models have been derived from limited clinical data and often lack a rigorous validation procedure in terms of parameter precision and predictive performance, some interesting lessons can be learnt from the simulation scenarios presented here. First, thanks to the identification of interindividual parameter variability, it is possible to select target (monotherapy) doses for most AEDs, which yield plasma concentrations that are within a reference therapeutic range, which is applicable to the majority of the population. This does not exclude the possibility that each patient may have an optimal target concentration and benefit from dose individualisation [3]. Second, DDIs can cause significant changes in the systemic exposure to first line drugs, and this also applies for many add-on drugs in a combination [48,49]. In theory, this implies that the observed treatment response, or lack thereof, when adding one or more drugs to the backbone first line AED cannot be directly attributed to the add-on drug. Instead, it may simply be the result of changes in exposure to the first drug in the combination. From a therapeutic perspective, one should envisage a scenario in which systemic concentrations of the primary drug are comparable when patients are switched from monotherapy to combinations. Such a scenario provides the appropriate basis for titration of the add-on drug.

In conclusion, we have explored the effects of DDIs on the systemic exposure to AEDs when used in combination therapy. Whereas numerous factors may contribute to lack of efficacy and poor tolerability, the effect of interindividual pharmacokinetic variability and covariate factors on drug disposition cannot be ignored in clinical practice. Our analysis offers a strong basis for the review of clinical guidelines for the treatment of epileptic seizures with AEDs, taking into account the impact of DDIs on the dose rationale.

REFERENCES

1. National Institute for Health and Care Excellence. Epilepsies: diagnosis and management (CG137) [Internet]. Available from: http://www.nice.org.uk/guidance/cg137

2. Kwan P, Brodie MJ. Epilepsy after the first drug fails: substitution or add-on? Seizure. 2000; 9:464–8.

3. van Dijkman SC, Wicha SG, Danhof M, Della Pasqua O. Individualised dosing algorithms and therapeutic monitoring for antiepileptic drugs. Clin Pharmacol Ther. 2017; doi: 10.1002/cpt.777.

4. Piana C, de Jesus Antunes N, Della Pasqua O. Implications of pharmacogenetics for the therapeutic use of antiepileptic drugs. Expert Opin Drug Metab Toxicol. 2014; 10:341–58.

5. Thomson AH, Brodie MJ. Pharmacokinetic optimisation of anticonvulsant therapy. Clin Pharmacokinet. 1992; 23:216–30.

6. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. Clin Pharmacokinet. 2013; 52:627–45.

7. van Dijkman SC, Alvarez-Jimenez R, Danhof M, Della Pasqua O. Pharmacotherapy in pediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go. Expert Opin Drug Metab Toxicol. 2016; 12:1143–56.

8. Piana C, Zhao W, Adkison K, Burger D, Jacqz-Aigrain E, Danhof M, Della Pasqua O. Covariate effects and population pharmacokinetics of lamivudine in HIV-infected children. Br J Clin Pharmacol. 2014; 77:861–72.

9. Castro FA De, Piana C, Simões BP, Lanchote VL, Pasqua O Della. Busulfan dosing algorithm and sampling strategy in stem cell transplantation patients. Br J Clin Pharmacol. 2015; 80:618–29.

10. Chain AS, Dieleman JP, van Noord C, Hofman A, Stricker BH, Danhof M, Sturkenboom MC, Della Pasqua O. Not-in-trial simulation I: Bridging cardiovascular risk from clinical trials to real-life conditions. Br J Clin Pharmacol. 2013; 76:964-72.

11. Musuamba FT, Teutonico D, Maas HJ, Facius A, Yang S, Danhof M, Della Pasqua O. Prediction of disease progression, treatment response and dropout in chronic obstructive pulmonary disease (COPD). Pharm Res. 2015; 32:617–27.

12. Vegvari C, Cauët E, Hadjichrysanthou C, Lawrence E, Weverling GJ, De Wolf F, Anderson RM. Using clinical trial simulators to analyse the sources of variance in clinical trials of novel therapies for acute viral infections. PLoS One. 2016; 11:1–18.

13. Jiao Z, Shi X-J, Zhao Z-G, Zhong M-K. Population pharmacokinetic modeling of steady state clearance of carbamazepine and its epoxide metabolite from sparse routine clinical data. J Clin Pharm Ther. 2004; 29:247–56.

14. Saruwatari J, Ogusu N, Shimomasuda M, Nakashima H, Seo T, Tanikawa K, Tsuda Y, Nishimura M, Nagata R. Effects of CYP2C19 and P450 oxidoreductase polymorphisms on the population pharmacokinetics of clobazam and N-desmethylclobazam in Japanese patients with epilepsy. 2014; 450:302–9.

15. Yukawa E, Satou M, Nonaka T, Yukawa M, Ohdo S, Higuchi S, Kuroda T, Goto Y. Influence of age and comedication on steady-state clonazepam serum level-dose ratios in Japanese epileptic patients. J Clin Pharm Ther. 2001; 26:375–9.

16. Rivas N, Buelga DS, Elger CE, Santos-Borbujo J, Otero MJ, Domínguez-Gil A, García MJ. Population pharmacokinetics of lamotrigine with data from therapeutic drug monitoring in German and Spanish patients with epilepsy. Ther Drug Monit. 2008; 30:483–9.

17. He D, Wang L, Qin J, Zhang S, Lu W, Li L, Zhang J, Bao W, Song X, Liu H. Population pharmacokinetics of lamotrigine in Chinese children with epilepsy. Acta Pharmacol Sin. 2012; 33:1417–23.

18. Toublanc N, Sargentini-Maier ML, Lacroix B, Jacqmin P, Stockis A. Retrospective population pharmacokinetic analysis of levetiracetam in children and adolescents with epilepsy - Dosing recommendations. Clin Pharmacokinet. 2008; 47:333–41.

19. Park K-J, Kim J-R, Joo EY, Seo DW, Hong SB, Ko J-W, Kim S-R, Huh W, Lee S-Y. Drug interaction and pharmacokinetic modeling of oxcarbazepine in korean patients with epilepsy. Clin Neuropharmacol. 2012; 35:40–4.

20. Goto S, Seo T, Murata T, Nakada N, Ueda N, Ishitsu T, Nakagawa K. Population Estimation of the effects of cytochrome P450 2C9 and 2C19 polymorphisms on phenobarbital clearance in Japanese. Ther Drug Monit. 2007; 29:118–21.

21. Odani A, Hashimoto Y, Takayanagi K, Otsuki Y, Koue T, Takano M, Yasuhara M, Hattori H, Furusho K, Inui K. Population pharmacokinetics of phenytoin in Japanese patients with epilepsy: Analysis with a dose-dependent clearance model. Biol Pharm Bull. 1996; 19:444–8.

22. Girgis IG, Nandy P, Nye JS, Ford L, Mohanty S, Wang S, Ochalski S, Eerdekens M, Cox EE. Pharmacokinetic-pharmacodynamic assessment of topiramate dosing regimens for children with epilepsy 2 to 10 years of age. Epilepsia. 2010; 51:1954–62.

23. Blanco-serrano B, Otero MJ, Santos-buelga D, Garcı MJ, García-Sánchez MJ, Serrano J, Domínguez-Gil A. Population estimation of valproic acid clearance in adult patients using routine clinical pharmacokinetic data. Biopharm Drug Dispos. 1999; 20:233–40.

24. Blanco-Serrano B, García Sánchez MJ, Otero MJ, Buelga DS, Serrano J, Domínguez-Gil A. Valproate population pharmacokinetics in children. J Clin Pharm Ther. 1999; 24:73–80.

25. Okada Y, Seo T, Ishitsu T, Wanibuchi A, Hashimoto N, Higa Y, Nakagawa K. Population estimation regarding the effects of cytochrome P450 2C19 and 3A5 polymorphisms on zonisamide clearance. Ther Drug Monit. 2008; 30:540–3.

26. Beal SL, Sheiner LB, Boeckmann A, Bauer RJ. NONMEM user's guide. Icon Development Solutions, Ellicott City;

27. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2014.

28. Luscombe M, Owens B. Weight estimation in resuscitation: is the current formula still valid? Arch Dis Child. 2007; 92: 412-5.

29. Bazzoli C, Retout S, Mentré F. Design evaluation and optimisation in multiple response nonlinear mixed effect models: PFIM 3.0. Comput Methods Programs Biomed. 2010; 98:55–65.

30. Harnisch L, Sheparp T, Pons G, Della Pasqua O. Modelling and simulation as a tool to bridge efficacy and safety data in special populations. CPT Pharmacometrics Syst Pharmacol 2:e28, 2013

31. Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser TA, Johannessen SI, Leppik IE, Tomson T, Perucca E. Antiepileptic drugs - best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008; 49:1239–76.

32. Nielsen JC, Kowalski KG, Karim A, Patel M, Wesche DL, Tolbert D. Population pharmacokinetics analysis of vigabatrin in adults and children with epilepsy and children with infantile spasms. Clin Pharmacokinet. 2014; 53:1019–31.

33. Sugiyama I, Bouillon T, Yamaguchi M, Suzuki H, Hirota T. Population pharmacokinetic analysis for 10-monohydroxy derivative of oxcarbazepine in pediatric epileptic patients shows no difference between Japanese and other ethnicities. Drug Metab Pharmacokinet. 2014; 30:160–7.

34. Riva R, Albani F, Contin M, Baruzzi A. Pharmacokinetic interactions between antiepileptic drugs - Clinical considerations. Clin Pharmacokinet. 1996; 31:470–93.

35. Prostran M, Jovanović M, Sokić D, Grabnar I, Vovk T, Prostran M, Vučićević K, Miljković B. Population pharmacokinetics of topiramate in adult patients with epilepsy using nonlinear mixed effects modelling. Eur J Pharm Sci. 2013; 50:282–9.

36. Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age. Clin Pharmacokinet. 2006; 45:351–63.

37. Landmark CJ, Baftiu A, Tysse I, Valsø B, Larsson PG, Rytter E, Johannessen SI. Pharmacokinetic variability of four newer antiepileptic drugs, lamotrigine, levetiracetam, oxcarbazepine, and topiramate. Ther Drug Monit. 2012;34:1.

38. Ghobadi C, Johnson TN, Aarabi M, Almond LM, Allabi AC, Rowland-Yeo K, Jamei M, Rostami-Hodjegan A. Application of a systems approach to the bottom-up assessment of pharmacokinetics in obese patients: expected variations in clearance. Clin Pharmacokinet. 2011; 50:809-22.

39. Djebli N, Fabre D, Boulenc X, Fabre G, Sultan E, Hurbin F. Physiologically based pharmacokinetic modeling for sequential metabolism: effect of CYP2C19 genetic polymorphism on clopidogrel and clopidogrel active metabolite pharmacokinetics. Drug Metab Dispos. 2015; 43:510-22.

40. Jacob S, Nair AB. An updated overview on therapeutic drug monitoring of recent antiepileptic drugs. Drugs 2016; 16:303–16.

41. Patsalos PN. Drug interactions with the newer antiepileptic drugs (AEDs) - Part 1: pharmacokinetic and pharmacodynamic interactions between AEDs. Clin Pharmacokinet. 2013; 52:927–66.

42. Patsalos PN. Drug interactions with the newer antiepileptic drugs (AEDs) - Part 2: pharmacokinetic and pharmacodynamic interactions between AEDs and drugs used to treat non-epilepsy disorders. Clin Pharmacokinet. 2013; 52:1045–61.

43. Bondareva IB, Jelliffe RW, Andreeva O V, Bondareva KI. Predictability of individualized dosage regimens of carbamazepine and valproate mono- and combination therapy. J Clin Pharm Ther. 2011; 36:625–36.

44. Bondareva IB, Sokolov a V, Tischenkova IF, Jelliffe RW. Population pharmacokinetic modelling of carbamazepine by using the iterative Bayesian (IT2B) and the nonparametric EM (NPEM) algorithms: implications for dosage. J Clin Pharm Ther. 2001; 26:213–23.

45. Zhao W, Lopez E, Biran V, Durrmeyer X, Fakhoury M, Jacqz-Aigrain E. Vancomycin continuous infusion in neonates: dosing optimisation and therapeutic drug monitoring. Arch Dis Child. 2013; 98:449–53.

46. Yuen G, Taylor J. Predicting phenytoin dosages using Bayesian feedback: a comparison with other methods. Ther Drug Monitoring. 1983; 5:437–41.

47. Tobler A, Mühlebach S. Intravenous phenytoin: a retrospective analysis of Bayesian forecasting versus conventional dosing in patients. Int J Clin Pharm. 2013; 35:790–7.

48. Ohara M, Takahashi H, Lee MTM, Wen MS, Lee TH, Chuang HP, Luo CH, Arima A, Onozuka A, Nagai R, Shiomi M, Mihara K, Morita T, Chen YT. Determinants of the over-anticoagulation response during warfarin initiation therapy in Asian patients based on population pharmacokinetic- pharmacodynamic analyses. PLoS One. 2014; 9:1–11.

49. Siasos G, Oikonomou E, Zaromitidou M, Kioufis S, Kokkou E, Mourouzis K, Vlasis K, Vavuranakis M, Stone PH, Papavassiliou AG, Tousoulis D. Clopidogrel response variability is associated with endothelial dysfunction in coronary artery disease patients receiving dual antiplatelet therapy. Atherosclerosis. 2015; 242:102–8.

CHAPTER 5

INDIVIDUALISED DOSING ALGORITHMS AND THERAPEUTIC DRUG MONITORING FOR ANTIEPILEPTIC DRUGS

Individualised dosing algorithms and therapeutic monitoring for antiepileptic drugs

Sven C. van Dijkman, Sebastian G. Wicha, Meindert Danhof, Oscar E. Della Pasqua

Clinical Pharmacology & Therapeutics, 2017

SUMMARY

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

Study Highlights

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

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

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

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

1. Introduction

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

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

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

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

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

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

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

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

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

2. Methods

Pharmacokinetic models and virtual patient demographics

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Personalised dosing algorithms

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

Individualised dosing algorithms

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

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

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

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

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

Optimised blood sampling for TDM

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

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

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

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

Graphical and statistical summaries of the simulated scenarios

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

3. Results

Implications of dosing algorithms for systemic exposure to AEDs

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

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

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

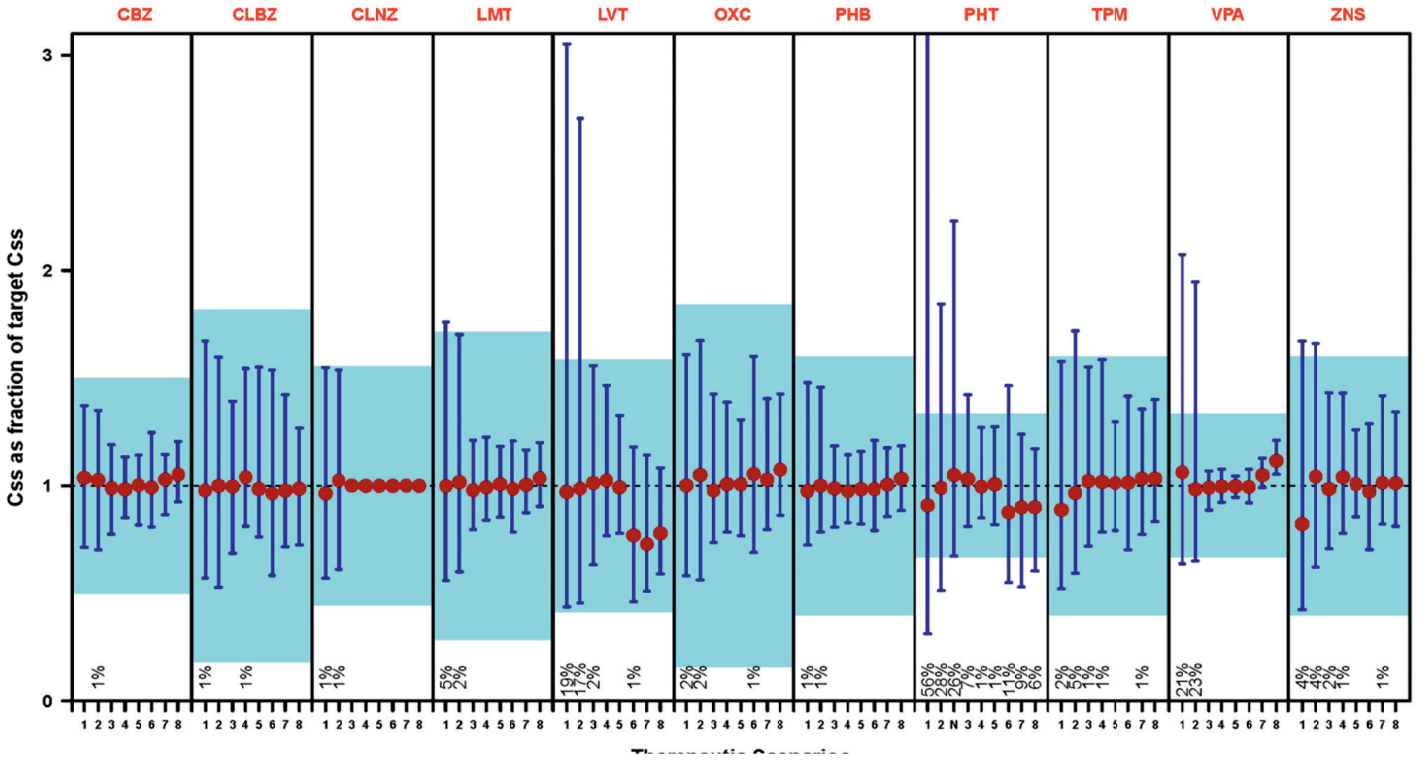


Figure 1 Overview of median (circles) and 95% prediction interval (bars) of drug exposures (C_{ss} as the fraction of target C_{ss}) in adults for different drugs and dosing scenarios, therapeutic window shown as a shaded area, numbers listed below the bars are percentages of the population with C_{ss}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

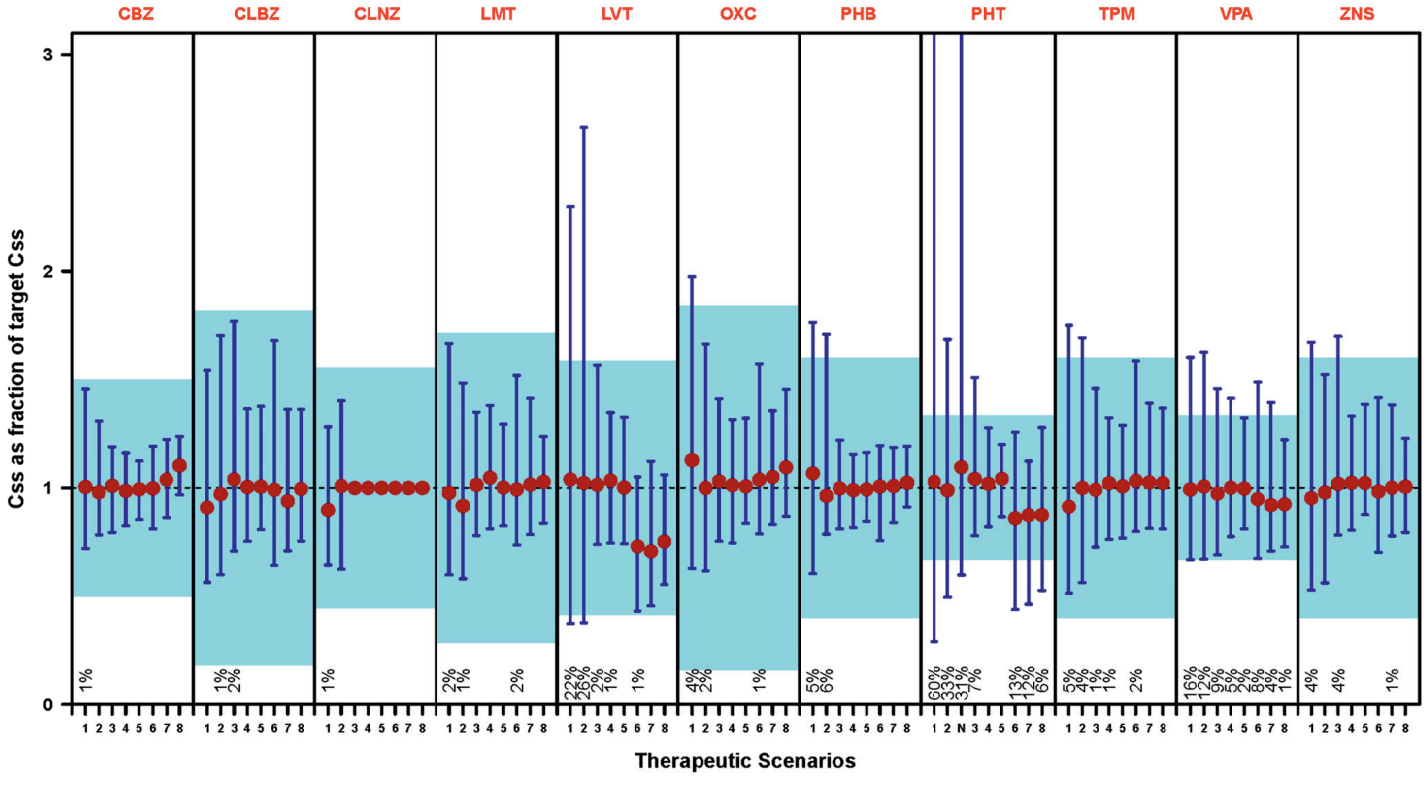


Figure 2 Overview of median (circles) and 95% prediction interval (bars) of drug exposures (C_{ss} as the fraction of target C_{ss}) in children for different drugs and dosing scenarios, therapeutic window shown as a shaded area, numbers listed below the bars are percentages of the population with C_{ss}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

Implications of optimised sampling times for TDM

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

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

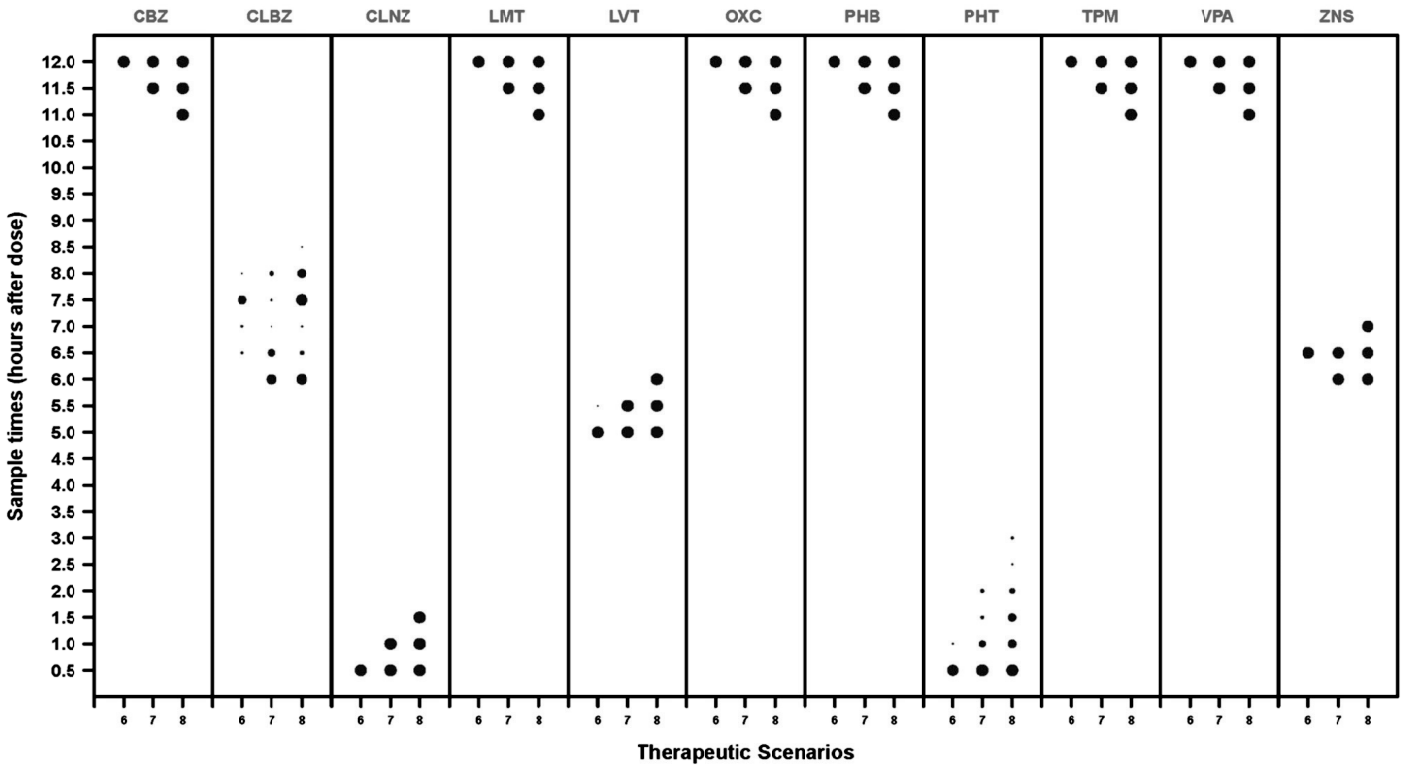


Figure 3 Overview of optimised samples in hours after dose (circles) for each drug and number of samples per individual. The relative size of the circle represents the relative frequency of sampling at each specific time point, i.e. if more patients were sampled at the time point, a larger circle is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

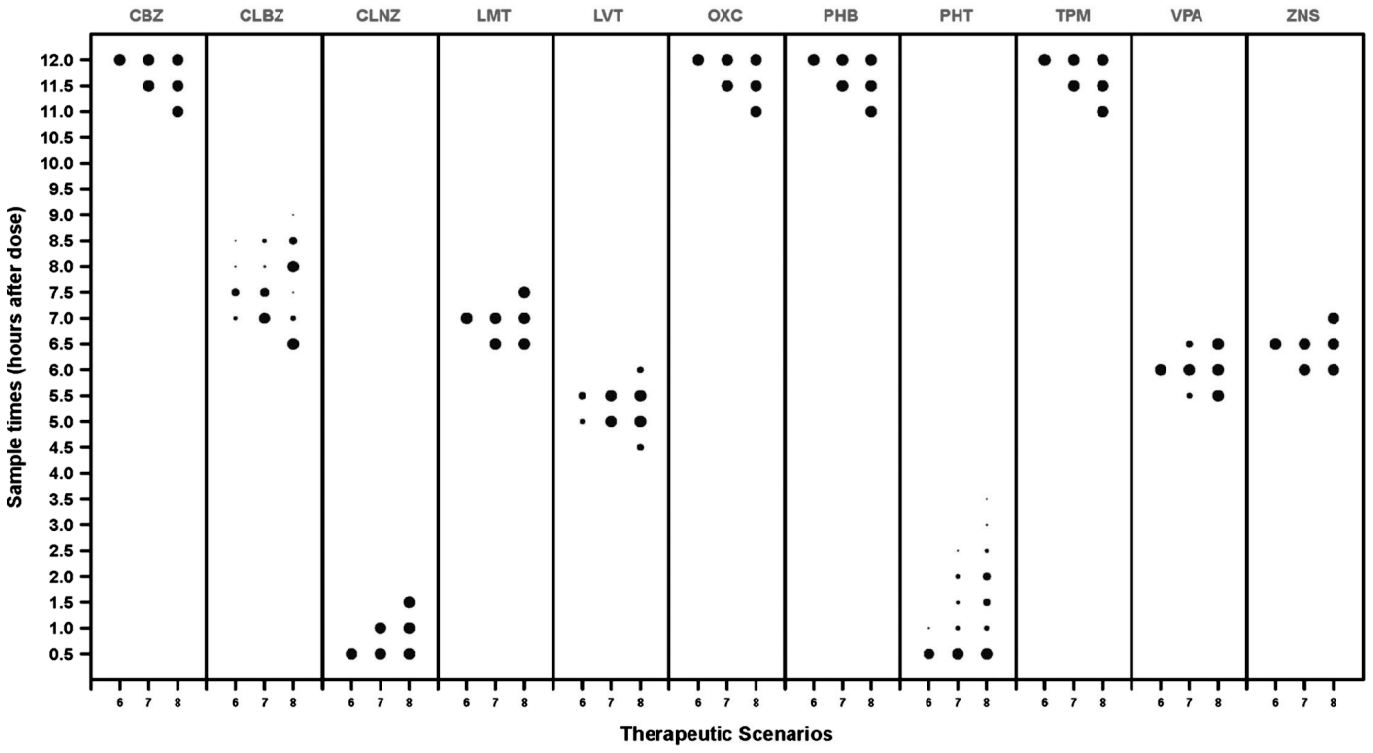


Figure 4 Overview of optimised samples in hours after dose (circles) for each drug, and number of samples per individual. The relative size of the circle represents the relative frequency of sampling at each specific time point, i.e. if more patients were sampled at the time point, a larger circle is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

4. Discussion

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

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

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

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

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

Potential limitations

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

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

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

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

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

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

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

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

References

1. van Dijkman SC, Alvarez-Jimenez R, Danhof M, Della Pasqua O. Pharmacotherapy in pediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go. Expert Opin Drug Metab Toxicol. 2016;12(10):1143–56.

2. Piana C, de Jesus Antunes N, Della Pasqua O. Implications of pharmacogenetics for the therapeutic use of antiepileptic drugs. Expert Opin Drug Metab Toxicol. 2014;10(3):341–58.

3. Kwan P, Brodie MJ. Epilepsy after the first drug fails: substitution or add-on? Seizure. 2000 Oct;9(7):464–8.

4. Dalic L, Cook MJ. Managing drug-resistant epilepsy: Challenges and solutions. Neuropsychiatr Dis Treat. 2016;12:2605–16.

5. van Dijkman SC, Rauwé WM, Danhof M, Della Pasqua O. Pharmacokinetic interactions and dosing rationale for antiepileptic drugs in adults and children (companion paper - under review).

6. Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age. Clin Pharmacokinet. 2006 Aug;45(4):351–63.

7. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. Clin Pharmacokinet. 2013 Aug;52(8):627–45.

8. Nielsen JC, Kowalski KG, Karim A, Patel M, Wesche DL, Tolbert D. Population Pharmacokinetics Analysis of Vigabatrin in Adults and Children with Epilepsy and Children with Infantile Spasms. Clin Pharmacokinet. 2014;53(11):1019–31.

9. Sugiyama I, Bouillon T, Yamaguchi M, Suzuki H, Hirota T. Population pharmacokinetic analysis for 10-monohydroxy derivative of oxcarbazepine in pediatric epileptic patients shows no difference between Japanese and other ethnicities. Drug Metab Pharmacokinet. 2014;30(2):160–7.

10. Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser T a., Johannessen SI, et al. Antiepileptic drugs - best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008 Jul;49(7):1239–76.

11. Neels HM, Sierens AC, Naelaerts K, Scharpé SL, Hatfield GM, Lambert WE. Therapeutic drug monitoring of old and newer anti-epileptic drugs. Clin Chem Lab Med. 2004 Jan;42(11):1228–55.

12. Hudson SAA, Farquhar DLL, Thompson D, Smith RGG. Phenytoin Dosage Individualisation - Five Methods Compared in The Elderly. J Clin Pharm Ther. 1990;15(1):25–34.

13. Lee FXL, Kong ST, Chan DWS, Chan E, Tan WW, Ho PC. Developing a Nomogram for Dose Individualization of Phenytoin in Asian Pediatric Patients Derived From Population Pharmacokinetic Modeling of Saturable Pharmacokinetic Profiles of the Drug. 2013;117543:54–62.

14. Croes S, Koop AH, Van Gils SA, Neef C. Efficacy, nephrotoxicity and ototoxicity of aminoglycosides, mathematically modelled for modelling-supported therapeutic drug monitoring. Eur J Pharm Sci. 2012;45(1–2):90–100.

15. Vinks AA. The application of population pharmacokinetic modeling to individualized antibiotic therapy. Int J Antimicrob Agents. 2002;19:313–22.

16. Gotta V, Widmer N, Montemurro M, Leyvraz S, Haouala A, Decosterd LA, et al. Therapeutic drug monitoring of imatinib: Bayesian and alternative methods to predict trough levels. Clin Pharmacokinet. 2012;51(3):187–201.

17. Padulles Caldes A, Colom H, Caldes A, Cerezo G, Torras J, Grinyo JM, et al. Optimal sparse sampling for estimating ganciclovir/valganciclovir AUC in solid organ transplant patients using NONMEN. Ther Drug Monit. 2014;36(3):371–7.

18. Brooks E, Tett SE, Isbel NM, Staatz CE. Population Pharmacokinetic Modelling and Bayesian Estimation of Tacrolimus Exposure: Is this Clinically Useful for Dosage Prediction Yet? Clin Pharmacokinet. 2016;55(11):1295–335.

19. Cortese DA. A vision of individualized medicine in the context of global health. Clin Pharmacol Ther. 2007;82(5):491–3.

20. Yukawa E, Satou M, Nonaka T, Yukawa M, Ohdo S, Higuchi S, et al. Influence of age and comedication on steady-state clonazepam serum level-dose ratios in Japanese epileptic patients. J Clin Pharm Ther. 2001 Oct;26(5):375–9.

21. Academy of Medical Sciences. Stratified, Personalised or P4 medicine: a new direction for placing the patient at the centre of healthcare and health education (Technical report). May 2015 [Internet]. [cited 2016 Oct 6]. Available from: http://www.phgfoundation.org/file/13380

22. Borgelt LM, Hart FM, Bainbridge JL. Epilepsy during pregnancy: Focus on management strategies. Int J Womens Health. 2016;8:505–17.

23. Perucca E, Dulac O, Shorvon S, Tomson T. Harnessing the clinical potential of antiepileptic drug therapy: dosage optimisation. CNS Drugs. 2001;15(8):609–21.

24. Jacob S, Nair AB. An Updated Overview on Therapeutic Drug Monitoring of Recent Antiepileptic Drugs. Drugs R D. 2016;16(4):303–16.

25. Jayachandran D, Laínez-Aguirre J, Rundell A, Vik T, Hannemann R, Reklaitis G, et al. Model-based individualized treatment of chemotherapeutics: Bayesian population modeling and dose optimization. PLoS One. 2015;10(7):1–24.

26. Van Den Broek MPH, Groenendaal F, Toet MC, van Straaten HLM, Van Hasselt JGC, Huitema ADR, et al. Pharmacokinetics and Clinical Efficacy of Phenobarbital in Asphyxiated Newborns Treated with Hypothermia. Clin Pharmacokinet. 2012;51(10):671–9.

27. Nakashima H, Oniki K, Nishimura M, Ogusu N, Shimomasuda M, Ono T, et al. Determination of the Optimal Concentration of Valproic Acid in Patients with Epilepsy: A Population Pharmacokinetic-Pharmacodynamic Analysis. PLoS One. 2015;10(10):e0141266.

28. Ogusu N, Saruwatari J, Nakashima H, Noai M, Nishimura M, Deguchi M, et al. Impact of the superoxide dismutase 2 Val16Ala polymorphism on the relationship between valproic acid exposure and elevation of gamma-glutamyltransferase in patients with epilepsy: a population pharmacokinetic-pharmacodynamic analysis. PLoS One. 2014;9(11):e111066.

29. Delattre M, Savic RM, Miller R, Karlsson MO, Lavielle M. Analysis of exposure-response of CI-945 in patients with epilepsy: application of novel mixed hidden Markov modeling methodology. J Pharmacokinet Pharmacodyn. 2012 Jun;39(3):263–71.

30. Girgis IG, Nandy P, Nye JS, Ford L, Mohanty S, Wang S, et al. Pharmacokinetic-pharmacodynamic assessment of topiramate dosing regimens for children with epilepsy 2 to 10 years of age. Epilepsia. 2010 Oct;51(10):1954–62.

31. Darwich AS, Ogungbenro K, Vinks AA, Powell JR, Reny J-L, Marsousi N, et al. Why has model-informed precision dosing not yet become common clinical reality? Lessons from the past and a roadmap for the future. Clin Pharmacol Ther. 2017;Feb 9.

32. Wojciechowski J, Hopkins AM, Upton RN. Interactive pharmacometric applications using R and the Shiny package. CPT pharmacometrics Syst Pharmacol. 2015;4(3):146–59.

33. Wicha SG, Kees MG, Solms A, Minichmayr IK, Kratzer A, Kloft C. TDMx: A novel web-based open-access support tool for optimising antimicrobial dosing regimens in clinical routine. Int J Antimicrob Agents. 2015;45(4):442–4.

34. Milosheska D, Grabnar I, Vovk T. Dried blood spots for monitoring and individualization of antiepileptic drug treatment. Eur J Pharm Sci. 2015;75:25–39.

35. Patsalos PN, Berry DJ. Therapeutic drug monitoring of antiepileptic drugs by use of saliva. Ther Drug Monit. 2013;35(1):5–29.

36. Beal SL, Sheiner LB, Boeckmann A, Bauer RJJ. NONMEM 7.2.0 User's Guides. Ellicott City, MD, USA: Icon Development Solutions; 2011.

37. Jiao Z, Shi X-J, Zhao Z-G, Zhong M-K. Population pharmacokinetic modeling of steady state clearance of carbamazepine and its epoxide metabolite from sparse routine clinical data. J Clin Pharm Ther. 2004 Jun;29(3):247–56.

38. Saruwatari J, Ogusu N, Shimomasuda M, Nakashima H, Seo T, Tanikawa K, et al. Effects of CYP2C19 and P450 Oxidoreductase Polymorphisms on the Population Pharmacokinetics of Clobazam and N -Desmethylclobazam in Japanese Patients With Epilepsy. 2014;450(June):302–9.

39. Rivas N, Buelga DS, Elger CE, Santos-Borbujo J, Otero MJ, Domínguez-Gil A, et al. Population pharmacokinetics of lamotrigine with data from therapeutic drug monitoring in German and Spanish patients with epilepsy. Ther Drug Monit. 2008 Aug;30(4):483–9.

40. He D, Wang L, Qin J, Zhang S, Lu W, Li L, et al. Population pharmacokinetics of lamotrigine in Chinese children with epilepsy. Acta Pharmacol Sin. 2012 Nov;33(11):1417–23.

41. Toublanc N, Sargentini-Maier ML, Lacroix B, Jacqmin P, Stockis A. Retrospective Population Pharmacokinetic Analysis of Levetiracetam in Children and Adolescents with Epilepsy - Dosing Recommendations. Clin Pharmacokinet. 2008;47(5):333–41.

42. Park K-J, Kim J-R, Joo EY, Seo DW, Hong SB, Ko J-W, et al. Drug interaction and pharmacokinetic modeling of oxcarbazepine in korean patients with epilepsy. Clin Neuropharmacol. 2012;35(1):40–4.

43. Goto S, Seo T, Murata T, Nakada N, Ueda N, Ishitsu T, et al. Population Estimation of the Effects of Cytochrome P450 2C9 and 2C19 Polymorphisms on Phenobarbital Clearance in Japanese. Ther Drug Monit. 2007 Feb;29(1):118–21.

44. Odani A, Hashimoto Y, Takayanagi K, Otsuki Y, Koue T, Takano M, et al. Population Pharmacokinetics of Phenytoin in Japanese Patients with Epilepsy: Analysis with a Dose-Dependent Clearance Model. Biol Pharm Bull. 1996;19(3):444–8.

45. Blanco-serrano B, Otero MJ, Santos-buelga D, Garcı MJ, García-Sánchez MJ, Serrano J, et al. Population Estimation of Valproic Acid Clearance in Adult Patients using Routine Clinical Pharmacokinetic Data. Biopharm Drug Dispos. 1999 Jul;20(5):233–40.

46. Blanco-Serrano B, García Sánchez MJ, Otero MJ, Buelga DS, Serrano J, Domínguez-Gil A. Valproate population pharmacokinetics in children. J Clin Pharm Ther. 1999 Feb;24(1):73–80.

47. Okada Y, Seo T, Ishitsu T, Wanibuchi A, Hashimoto N, Higa Y, et al. Population estimation regarding the effects of cytochrome P450 2C19 and 3A5 polymorphisms on zonisamide clearance. Ther Drug Monit. 2008 Aug;30(4):540–3.

48. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2014.

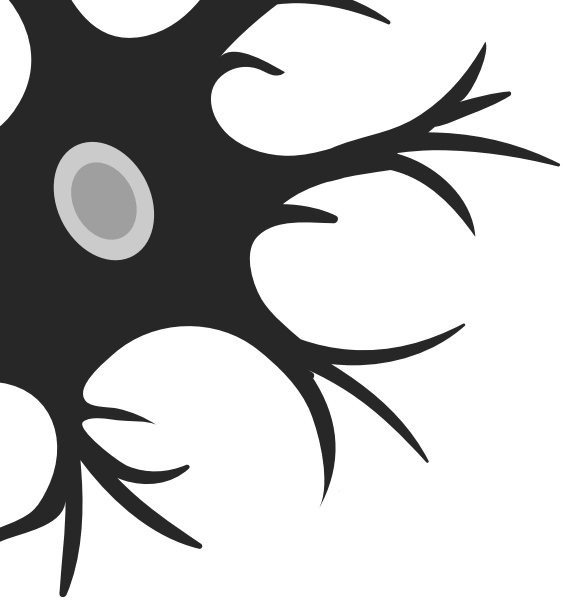
49. Bazzoli C, Retout S, Mentré F. Design evaluation and optimisation in multiple response nonlinear mixed effect models: PFIM 3.0. Comput Methods Programs Biomed. 2010;98(1):55–65.

50. Dubois A, Bertrand J, Mentré F. Mathematical Expressions of the Pharmacokinetic and Pharmacodynamic Models implemented in the PFIM software. (March 2011).

51. Ludden TM, Allen JP, Valutsky WA, Vicuna A V, Nappi JM, Hoffman SF, et al. Individualization of phenytoin dosage regimens. Clin Pharmacol Ther. 1977;21(3):287–93.

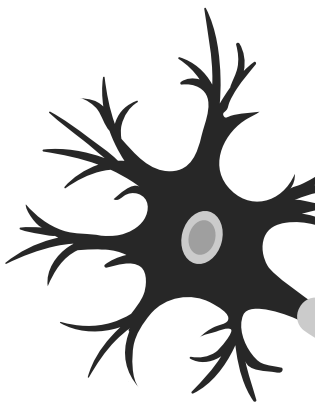
52. Kang D, Bae KS, Houk BE, Savic RM, Karlsson MO. Standard error of empirical bayes estimate in NONMEM VI. Korean J Physiol Pharmacol. 2012;16(2):97–106.

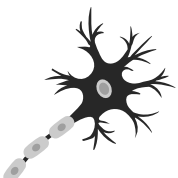
53. Bondareva IB, Sokolov a V, Tischenkova IF, Jelliffe RW. Population pharmacokinetic modelling of carbamazepine by using the iterative Bayesian (IT2B) and the nonparametric EM (NPEM) algorithms: implications for dosage. J Clin Pharm Ther. 2001 Jun;26(3):213–23.



SECTION IV

EVIDENCE GENERATION & SYNTHESIS IN EPILEPSY TRIALS





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

Accepted for publication in Clinical Pharmacokinetics

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**.

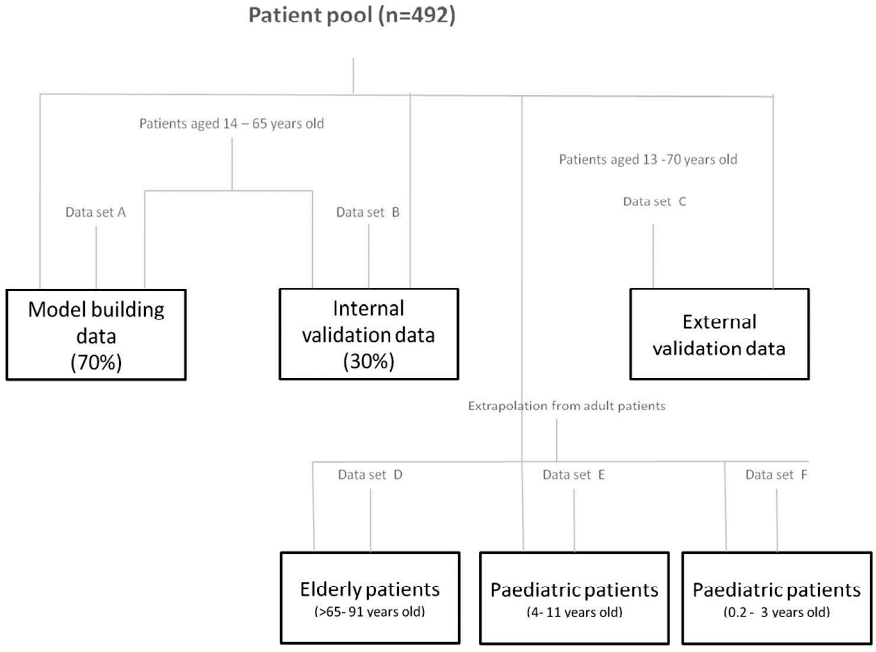


Figure 1. Data sets and population characteristics for the development of a population pharmacokinetic model in adult, paediatric and elderly patients.

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**.

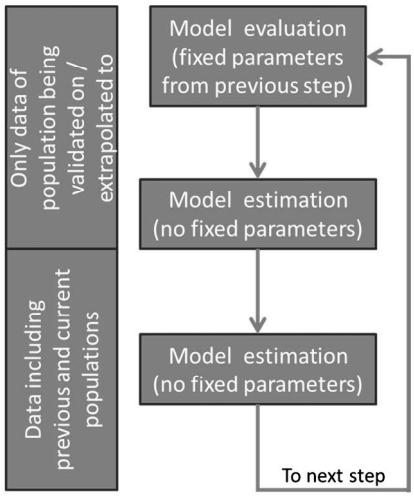


Figure 2. Schematic overview of validation and extrapolation steps.

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**).

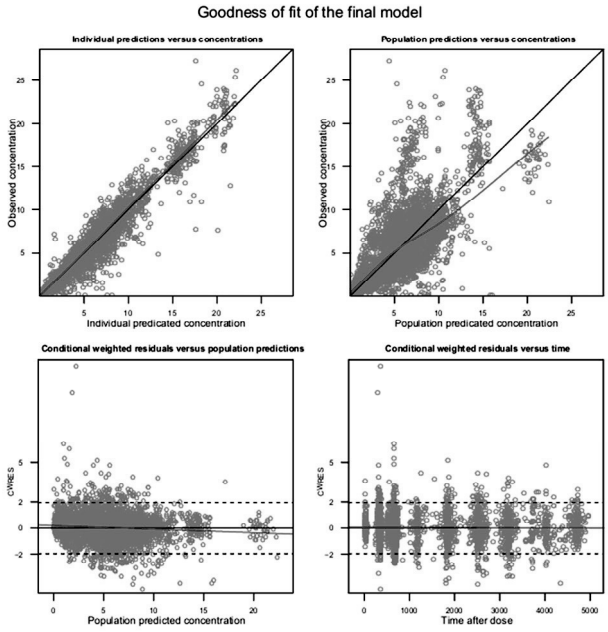


Figure 3. Goodness of fit plots of the final model. Individual- (IPRED) and population (PRED) model predictions are compared to the observations (DV). Conditional weighted residuals (CWRES), are compared to the PRED and time after dose. Black solid lines: identity line. Red solid lines: trend line. Blue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

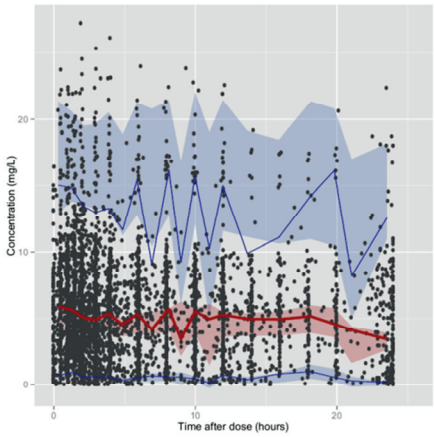


Figure 4. Visual predictive check (VPC) of the final model. The median (red line) and 95% CI (blue lines) of the observed data are plotted against the simulated data of 1000 subjects (highlighted areas; median in red, 95% prediction interval in blue). Individual observations in the data are shown as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

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

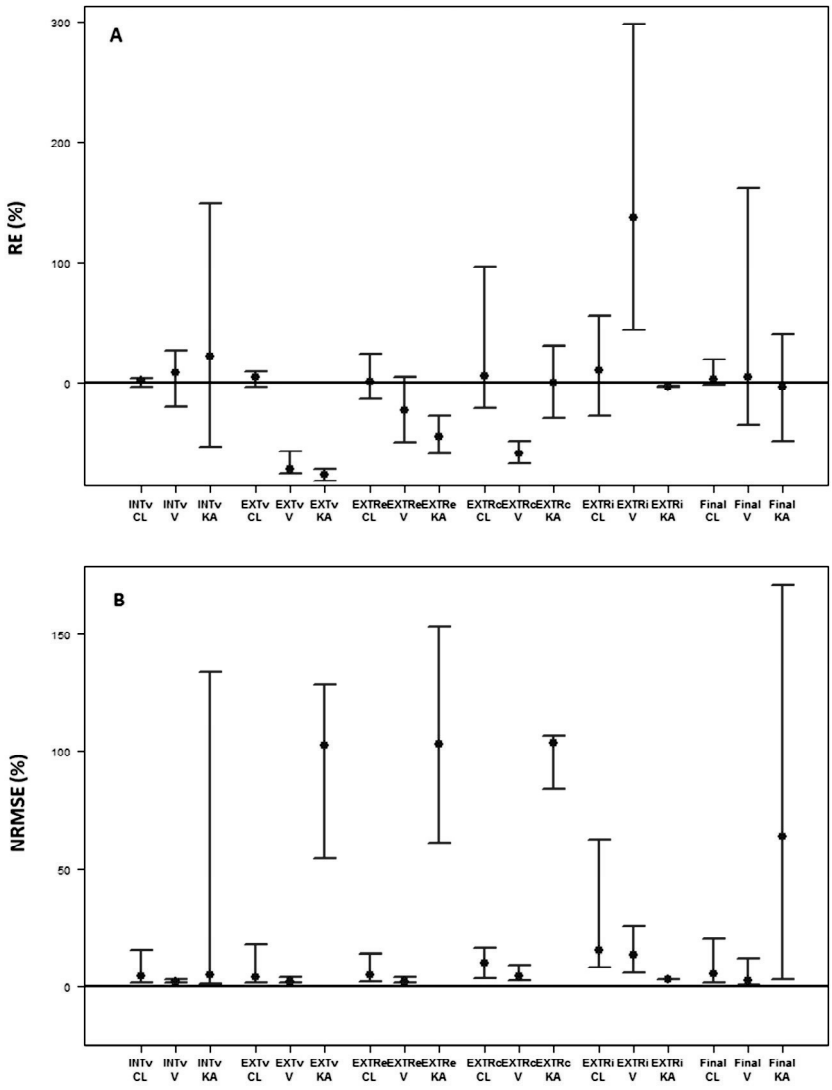


Figure 5. Evaluation of parameter predictions during validation and extrapolation steps; internal validation (INTv), external validation (EXTv), extrapolation to adults 65-91 years (EXTRe), extrapolation to children 4-11 years (EXTRc), extrapolation to infants and toddlers <2 years (EXTRi), evaluation 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).

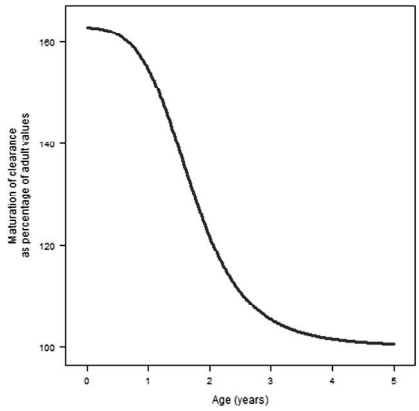


Figure 6. Sigmoidal function describing changes in clearance associated with age and metabolic maturation processes.

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

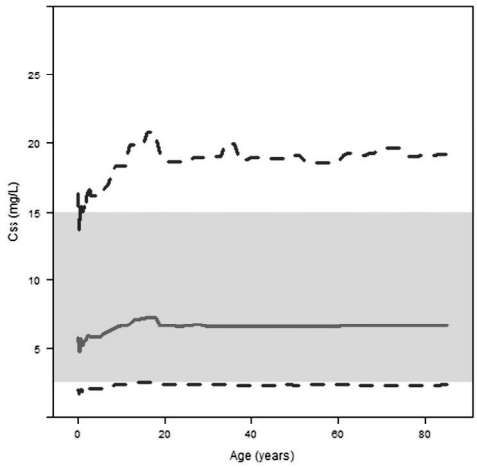


Figure 7. C_{ss} ranges resulting from optimised dosing regimens over age, as listed in table 5. Shown are the median (red line) and 95% prediction interval (blue dashed lines) of the simulated C_{ss} values. The blue shaded area is the putative target therapeutic range.

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.

References

1. Steiner TJ, Dellaportas CI, Findley LJ, Gross M, Gibberd FB, Perkin GD, Park DM, Abbott R. Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin. Epilepsia. 1999;40(5):601–7.

2 Mullens EL. Clinical experience with lamotrigine monotherapy in adults with newly diagnosed epilepsy: A review of published randomised clinical trials. Clin Drug Investig. 1998;16(2):125–33.

3. Fitton A, Goa KL. Lamotrigine in Epilepsy. 1995;50(4):691–713.

4. Brodie MJ, Richens a, Yuen a W. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. Lancet. 1995;345(8948):476–9.

5. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. Clin Pharmacokinet. 2013 Aug;52(8):627–45.

6. Anderson GD, Saneto RP. Modified-Release Formulations of Second-Generation Antiepileptic Drugs: Pharmacokinetic and Clinical Aspects. CNS Drugs. 2015; 29(8):669-81.

7. Lovrić M, Božina N, Hajnšek S, Kuzman MR, Sporiš D, Lalić Z, Božina T, Granić P. Association between lamotrigine concentrations and ABCB1 polymorphisms in patients with epilepsy. Ther Drug Monit. 2012; 34(5):518-25.

8. Johannessen Landmark C, Baftiu A, Tysse I, Valsø B, Larsson PG, Rytter E, Johannessen SI. Pharmacokinetic variability of four newer antiepileptic drugs, lamotrigine, levetiracetam, oxcarbazepine, and topiramate: a comparison of the impact of age and comedication. Ther Drug Monit. 2012; 34(4):440-5.

9. Lott RS. Lamotrigine: treatment of epilepsy in the elderly. Consult Pharm. 2003; 18(11):979-92.

10. Tomson T. Gender aspects of pharmacokinetics of new and old AEDs: pregnancy and breast-feeding. Ther Drug Monit. 2005; 27(6):718-21.

11. Reimers A, Skogvoll E, Sund JK, Spigset O. Lamotrigine in children and adolescents: the impact of age on its serum concentrations and on the extent of drug interactions. Eur J Clin Pharmacol. 2007; 63(7):687-92.

12. Wegner I, Wilhelm AJ, Lambrechts DA, Sander JW, Lindhout D. Effect of oral contraceptives on lamotrigine levels depends on comedication. Acta Neurol Scand. 2014;129(6):393–8.

13. Chen C. Validation of a population pharmacokinetic model for adjunctive lamotrigine therapy in children. Br J Clin Pharmacol. 2000; 50(2):135–45.

14. Punyawudho B, Ramsay RE, Macias FM, Rowan AJ, Collins JF, Brundage RC, Birnbaum AK, Richard C, Birnbaum AK, Brundage RC, Birnbaum AK. Population pharmacokinetics of lamotrigine in elderly patients. J Clin Pharmacol. 2008; 48(4):455–63.

15. Wegner I, Wilhelm AJ, Sander JW, Lindhout D. The impact of age on lamotrigine and oxcarbazepine kinetics: a historical cohort study. Epilepsy Behav. 2013; 29(1):217–21.

16. Mallaysamy S, Johnson MG, Rao PGM, Rajakannan T, Bathala L, Arumugam K, van Hasselt JGC, Ramakrishna D. Population pharmacokinetics of lamotrigine in Indian epileptic patients. Eur J Clin Pharmacol. 2013; 69(1):43–52.

17. Hussein Z, Posner J. Population pharmacokinetics of lamotrigine monotherapy in patients with epilepsy: retrospective analysis of routine monitoring data. Br J Clin Pharmacol. 1997; 43(5):457–65.

18. He D, Wang L, Qin J, Zhang S, Lu W, Li L, Zhang J, Bao W, Song X, Liu H. Population pharmacokinetics of lamotrigine in Chinese children with epilepsy. Acta Pharmacol Sin. 2012; 33(11):1417–23.

19. Chan V, Morris RG, Ilett KF, Tett SE. Population pharmacokinetics of lamotrigine. Ther Drug Monit. 2001; 23(6):630–5.

20. Singkham N, Towanabut S, Lertkachatarn S, Punyawudho B. Influence of the UGT2B7-161C-T polymorphism on the population pharmacokinetics of lamotrigine in Thai patients. Eur J Clin Pharmacol. 2013; 69(6):1285–91.

21. Brzaković B, Vučićević K, Kovačević SV, Miljković B, Prostran M, Martinović Ž, Pokrajac M. Pharmacokinetics of lamotrigine in paediatric and young adult epileptic patients--nonlinear mixed effects modelling approach. Eur J Clin Pharmacol. 2014; 70(2):179–85.

22. Holford N, Heo Y, Anderson B. A Pharmacokinetic Standard for Babies and Adults. J Pharm Sci. 2013;102(9):2941–52.

23. Wolf P. Lamotrigine: preliminary clinical observations on pharmacokinetics and interactions with traditional antiepileptic drugs. J Epilepsy. 1992;5:73–79.

24. Piña-Garza JE1, Levisohn P, Gucuyener K, Mikati MA, Warnock CR, Conklin HS, Messenheimer J. Adjunctive lamotrigine for partial seizures in patients aged 1 to 24 months. Neurology. 2008; 70(22 Pt 2):2099-108.

25. Pellock JM, Carman WJ, Thyagarajan V, Daniels T, Morris DL, D'Cruz O. Efficacy of antiepileptic drugs in adults predicts efficacy in children: a systematic review. Neurology. 2012; 79(14):1482-9.

26. Bauer RJ. NONMEM user guide introduction to NONMEM 7.3.0. 2014;

27. Lindbom L, Pihlgren P, Jonsson N. PsN-Toolkit - A collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed. 2005;79:241–57.

28. Keizer RJ, van Benten M, Beijnen JH, Schellens JHM, Huitema ADR. Piraña and PCluster: A modeling environment and cluster infrastructure for NONMEM. Comput Methods Programs Biomed. Elsevier Ireland Ltd; 2011;101(1):72–9.

29. Keizer RJ, Karlsson MO, Hooker A. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT pharmacometrics Syst Pharmacol. 2013;2:e50.

30. R Development CoreTeam. R: A Language and Environment for Statistical Computing. Vienna, Austria : the R Foundation for Statistical Computing. 2015;

31. de Onis M. The WHO Child Growth Standards. World Rev Nutr Diet. 2015;113:278–94.

32. Luscombe M, Owens B. Weight estimation in resuscitation: is the current formula still valid? Arch Dis Child. 2007;92(5):412–5.

33. Rivas N, Buelga DS, Elger CE, Santos-Borbujo J, Otero MJ, Domínguez-Gil A, García MJ. Population pharmacokinetics of lamotrigine with data from therapeutic drug monitoring in German and Spanish patients with epilepsy. Ther Drug Monit. 2008; 30(4):483–9.

34. Almeida AM, Falcão AC, Sales F, Baldeiras I, Rocha MJ, Caramona MM. Lamotrigine pharmacokinetic evaluation in epileptic patients submitted to VEEG monitoring. Eur J Clin Pharmacol. 2006;62:737–42.

35. Lardizabal D V, Morris HH, Hovinga CA, Del Mar Carreño M. Tolerability and pharmacokinetics of oral loading with lamotrigine in epilepsy monitoring units. Epilepsia. 2003;44(4):536–9.

36. Grasela THTH, Fiedler-Kelly J, Cox E, Womble GPGP, Risner MEME, Chen C. Population Pharmacokinetics of Lamotrigine Adjunctive Therapy in Adults with Epilepsy. Pharmacokinet Pharmacodyn. 1999;39(4):373–84.

37. Ramsay RE, Pellock JM, Garnett WR, Sanchez RM, Valakas a M, Wargin W a, Lai a a, Hubbell J, Chern WH, Allsup T. Pharmacokinetics and safety of lamotrigine (Lamictal) in patients with epilepsy. Epilepsy Res. 1991;10:191–200.

38. Reimers A, Skogvoll E, Sund JK, Spigset O. Drug interactions between lamotrigine and psychoactive drugs: evidence from a therapeutic drug monitoring service. J Clin Psychopharmacol. 2005; 25:342–8.

39. Gidal BE, Anderson GD, Rutecki PR, Shaw R, Lanning a. Lack of an effect of valproate concentration on lamotrigine pharmacokinetics in developmentally disabled patients with epilepsy. Epilepsy Res. 2000; 42(1):23–31.

40. Anderson BJ, Holford NHG. Mechanistic Basis of Using Body Size and Maturation to Predict Clearance in Humans. Drug Metab Pharmacokinet. 2009; 24(1):25–36.

41. Cella M, Knibbe C, de Wildt SN, Van Gerven J, Danhof M, Della Pasqua O. Scaling of pharmacokinetics across paediatric populations: the lack of interpolative power of allometric models. Br J Clin Pharmacol. 2012; 74(3):525-35.

42. Piana C, Danhof M, Della Pasqua O. Influence of covariate distribution on the predictive performance of pharmacokinetic models in paediatric research. Br J Clin Pharmacol. 2014;78(1):145-57

43. Reimers A. Trends and changes in the clinical use of lamotrigine. Pharmacoepidemiol Drug Saf. 2009;18(12):132–9.

44. Franco V, Canevini MP, Capovilla G, De Sarro G, Galimberti CA, Gatti G, Guerrini R, La Neve A, Rosati E, Specchio LM, Striano S, Tinuper P, Perucca E. Off-Label Prescribing of Antiepileptic Drugs in Pharmacoresistant Epilepsy: A Cross-Sectional Drug Utilization Study of Tertiary Care Centers in Italy. CNS Drugs. 2014;28(10):939–49..

45. Kim H-J, Kim T-E, Joo EY, Seo D-W, Lee S-Y, Hong SB. Effect of comedication on lamotrigine clearance in Korean epilepsy patients. Clin Chim Acta. 2014; 438:269–73.

46. Miyagi SJ, Collier AC. Pediatric Development of Glucuronidation : The Ontogeny of Hepatic UGT1A4. Drug Metab Dispos. 2007;35(9):1587–92.

47. Strassburg CP, Strassburg A, Kneip S, Barut A, Tukey RH, Rodeck B, Manns MP. Developmental aspects of human hepatic drug glucuronidation in young children and adults. Gut. 2002;50:259–65.

48. Krekels EHJ, Johnson TN, den Hoedt SM, Rostami-Hodjegan A, Danhof M, Tibboel D, Knibbe CAJ. From Pediatric Covariate Model to Semiphysiological Function for Maturation: Part II—Sensitivity to Physiological and Physicochemical Properties. CPT Pharmacometrics Syst Pharmacol. 2012;1(10):e10.

49. Edginton AN, Schmitt W, Voith B, Willmann S. A mechanistic approach for the scaling of clearance in children. Clin Pharmacokinet. 2006;45(7):683–704.

50. Anderson GD. Children versus adults: pharmacokinetic and adverse-effect differences. Epilepsia. 2002; 43 Suppl 3(5):53–9.

51. van Dijkman SC, Wicha SG, Danhof M, Della Pasqua O. Individualised dosing algorithms and therapeutic monitoring for antiepileptic drugs. Clin Pharmacol Ther. 2017 doi: 10.1002/cpt.777

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

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

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

To be submitted

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.

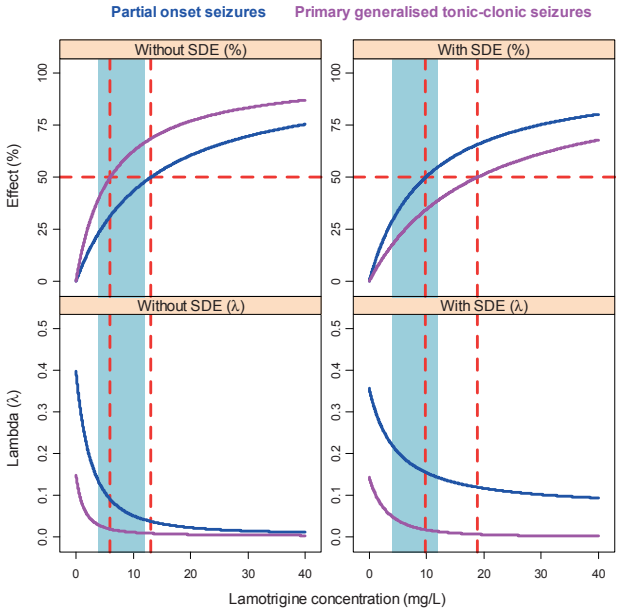


Figure 1. Effect as a percentage of maximum effect (upper panels) and change in lambda (lower panels) versus lamotrigine concentration (in mg/L) for patients with partial onset seizures (blue lines) and primary generalised tonic-clonic seizures (magenta lines) based on the estimates of baseline lambda (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.

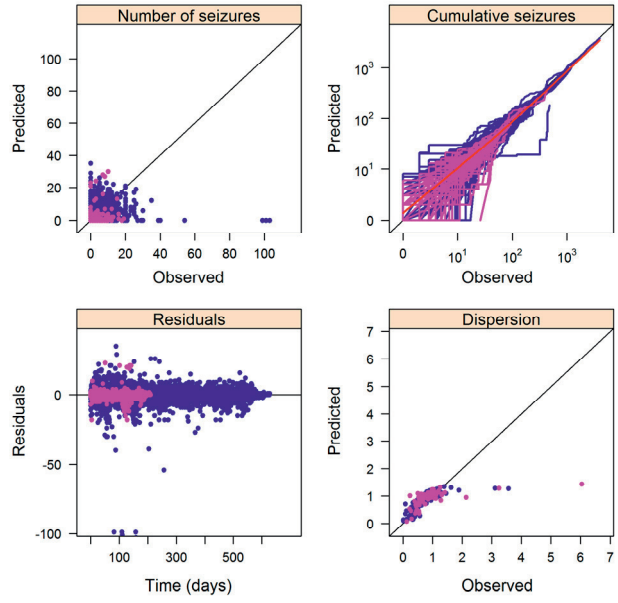


Figure 2. Goodness-of-fit plots for the final model not using stochastic differential equations for patients with PO (blue) and PGTC (magenta) seizure types. The red line in the upper right panel shows a loess fit of the cumulative observed versus predicted seizures.

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.

REFERENCES

1. Meyer J, Fardo D, Fleming ST, Hopenhayn C, Gokun Y, Ryan M. Generic antiepileptic drug prescribing: a cross-sectional study. Epilepsy Behav. 2013 Jan;26(1):1–6.

2. Kwan P, Sills GJ, Brodie MJ. The mechanisms of action of commonly used antiepileptic drugs. Pharmacol Ther. 2001;90:21–34.

3. Naritoku DK, Warnock CR, Messenheimer JA, Borgohain R, Evers S, Guekht AB, et al. Lamotrigine extended-release as adjunctive therapy for partial seizures. Neurology. 2007;69(16):1610–8.

4. Girgis IG, Nandy P, Nye JS, Ford L, Mohanty S, Wang S, et al. Pharmacokinetic-pharmacodynamic assessment of topiramate dosing regimens for children with epilepsy 2 to 10 years of age. Epilepsia. 2010 Oct;51(10):1954–62.

5. Van Den Broek MPH, Groenendaal F, Toet MC, van Straaten HLM, Van Hasselt JGC, Huitema ADR, et al. Pharmacokinetics and Clinical Efficacy of Phenobarbital in Asphyxiated Newborns Treated with Hypothermia. Clin Pharmacokinet. 2012;51(10):671–9.

6. Nakashima H, Oniki K, Nishimura M, Ogusu N, Shimomasuda M, Ono T, et al. Determination of the Optimal Concentration of Valproic Acid in Patients with Epilepsy: A Population Pharmacokinetic-Pharmacodynamic Analysis. PLoS One. 2015;10(10):e0141266.

7. Ogusu N, Saruwatari J, Nakashima H, Noai M, Nishimura M, Deguchi M, et al. Impact of the superoxide dismutase 2 Val16Ala polymorphism on the relationship between valproic acid exposure and elevation of gamma-glutamyltransferase in patients with epilepsy: a population pharmacokinetic-pharmacodynamic analysis. PLoS One. 2014;9(11):e111066.

8. Delattre M, Savic RM, Miller R, Karlsson MO, Lavielle M. Analysis of exposure-response of CI-945 in patients with epilepsy: application of novel mixed hidden Markov modeling methodology. J Pharmacokinet Pharmacodyn. 2012 Jun;39(3):263–71.

9. van Dijkman SC, Alvarez-Jimenez R, Danhof M, Della Pasqua O. Pharmacotherapy in pediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go. Expert Opin Drug Metab Toxicol. 2016;12(10):1143–56.

10. Plan EL. Modeling and simulation of count data. CPT pharmacometrics Syst Pharmacol. 2014;3(August 13):e129.

11. Trocóniz IF, Plan EL, Miller R, Karlsson MO. Modelling overdispersion and Markovian features in count data. J Pharmacokinet Pharmacodyn. 2009 Oct;36(5):461–77.

12. Beal SL, Sheiner LB, Boeckmann A, Bauer RJJ. NONMEM 7.2.0 User's Guides. Ellicott City, MD, USA: Icon Development Solutions; 2011.

13. Keizer RJ, Karlsson MO, Hooker a. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT pharmacometrics Syst Pharmacol. 2013;2(November 2012):e50.

14. Lindbom L, Pihlgren P, Jonsson N. PsN-Toolkit - A collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed. 2005;79:241–57.

15. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2014.

16. Tornøe CW, Overgaard R V., Agersø H, Nielsen H a., Madsen H, Jonsson EN. Stochastic differential equations in NONMEM®: Implementation, application, and comparison with ordinary differential equations. Pharm Res. 2005;22(8):1247–58.

17. Deng C, Plan EL, Karlsson MO. Approaches for modeling within subject variability in pharmacometric count data analysis: dynamic inter-occasion variability and stochastic differential equations. J Pharmacokinet Pharmacodyn. 2016;43(3):305–14.

18. Petersson KJF, Hanze E, Savic RM, Karlsson MO. Semiparametric distributions with estimated shape parameters. Pharm Res. 2009;26(9):2174–85.

CHAPTER 8

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

Exposure-response relationship and dose rationale for lamotrigine in children aged 1-24 months

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

To be submitted

SUMMARY

Objective: The anti-epileptic drug (AED) lamotrigine (LMT) is approved for treatment of partial-onset type seizures in adults and adolescents. Given the known differences in pharmacokinetics in this age group, we aim to investigate the dose rationale for lamotrigine using a model-based approach that has been developed for older patients. **Methods:** Data of children aged 1-24 months with partial type seizures receiving LMT as adjuvant therapy were retrieved from the clinical database of GlaxoSmithKline. A PKPD Poisson model with Markovian features was used to describe seizure counts over time, along with the drug effect. The dose rationale was evaluated taking into account differences in pharmacokinetics and the PKPD model parameter estimates. The analysis was complemented by the simulation of a clinical trial in which paediatric patients are treated with doses that yield exposures comparable to the efficacious range observed in the age range > 24 months. **Results:** The use of a drug-disease model provided insight into the exposure-response relationship of lamotrigine in infants and toddlers. Model parameter estimates were comparable to those in adults with partial seizures. The main difference was in the placebo effect, which was significantly larger. Maximum efficacy was enough to suppress disease activity, while potency (EC_{50}) was slightly higher than in adults. Clinical trial simulations showed that statistically significant differences can be detected and efficacy demonstrated when differences in pharmacokinetics and placebo effect are taken into account. **Conclusions:** The use of a drug-disease model allows for the characterisation of exposure-response relationship of lamotrigine in children younger than 2 years of age. It appears that lamotrigine is efficacious in patients younger than 2 years with partial onset seizure and that efficacy can be extrapolated from adults and older paediatric patients

1. Introduction

Roughly 68 million people worldwide suffer from epilepsy, with up to 25% of those patients belonging to the paediatric subpopulation [1,2]. Poor and rural areas contribute to a disproportionate degree to that number, leading to a need for anti-epileptic drugs (AEDs) that are efficacious and safe for children, yet affordable. Most of the popular AEDs have been thoroughly investigated in adults, but due to ethical and practical constraints, little is known about their pharmacokinetics (PK) and pharmacodynamics (PD) in very young children[3,4]. Given the lack of data, many AEDs have not been approved for use in subset of the paediatric population, but are nevertheless used off-label[5] by clinicians. Consequently, many paediatric patients receive unproven medical treatment daily, possibly with the inappropriate drug and dosing regimen, possibly exposing patients unnecessarily drug levels and long titration times [6,7].

Lamotrigine (LMT)[8] an AED with predictable PK and a favourable efficacy and safety profile in adults and adolescents [9,10]. Recently, we have described the development of a population-wide pharmacokinetic model for LMT in patients aged 0.2 – 91 years of age. The analysis showed that body weight-adjusted clearance in the younger (1-24 months) population is higher compared to that in older patients. In fact, a maturation function is required to account for the differences observed in this age group [11]. This model was subsequently used as basis for another investigation, in which we have attempted to characterise the exposure-response relationship of lamotrigine in adults with partial-onset (PO) and primary generalised tonic-clonic (PGTC) seizures using a Poisson model with Markovian features [12]. LMT has been approved for the treatment of partial- and primary generalized seizures in patients with epilepsy aged 2 years and older, but failed to show adequate efficacy compared to placebo in a small sample of subjects 1-24 months old (N=38) [13]. A possible cause of this lack of efficacy may have been the lower exposure that was reached in this population due to the higher drug clearance relative to body-weight. However, in paediatric epilepsy, epileptologists suggest that differences in the epilepsy in adults and young children are the likely cause of lack of efficacy. Here we attempt to explore whether the underlying exposure-

response relationship of lamotrigine truly differs between populations and most importantly whether failure in detecting efficacy can be assigned to inaccurate dose selection and sample size. While a new trial may be required to ultimately prove this hypothesis, we show how these questions can be addressed using clinical trial simulations (CTS) [14]. A secondary objective is to establish the feasibility of bridging concepts in paediatric epilepsy.

2. Methods

2.1 Subjects & original study design

Data from a clinical efficacy and safety study of LMT in children was used (clinicaltrials.gov ID NCT00043875). Included were male and female subjects between the age of 1-24 months at study entry, with a confident diagnosis of epilepsy and a history of at least four reliably detectable recurrent partial seizures per month. Seizures were required to be uncontrolled by at least one other AED with plasma concentrations within the acceptable therapeutic ranges. Subjects were included if they had a diagnosis of severe, progressive myoclonus, had seizures not related to epilepsy or as the result of drug withdrawal. Subjects were not allowed to suffer from clinically relevant chronic conditions which may affect the LMT PK.

Subjects were required to submit at least two weeks of historical baseline daily seizure counts at inclusion. Once included, they were up-titrated with LMT to a dose of 5.1 mg/kg/d (when combined with VPA or non-enzyme inducing AEDs) or 15.6 mg/kg/d (given in combination with enzyme inducing AEDs). After titration, patients were further optimised according to clinical efficacy and safety according to the treating physician. These titration and optimisation phases occurred during the open-label phase (OLP). At the end of the OLP, those patients with a reduction in seizure frequency of at least 40% compared to baseline were allowed to continue to the double blind phase (DBP), with a maximum of 38 subjects. In the DBP, subjects were randomised in a 1:1 ratio to either LMT continuation or

LMT down-titration and subsequent conversion to placebo. During the DBP, escape criteria were used to determine treatment failure. These criteria were at least 50% increase in monthly seizure frequency, having double the amount of consecutive 2-day seizure counts compared to the optimisation phase, onset of a new and more severe seizure type, clinically significant worsening of non-partial seizures, the need to therapeutically intervene to control seizures, or status epilepticus. An overview of the trial phases can be found in **Figure 1**.

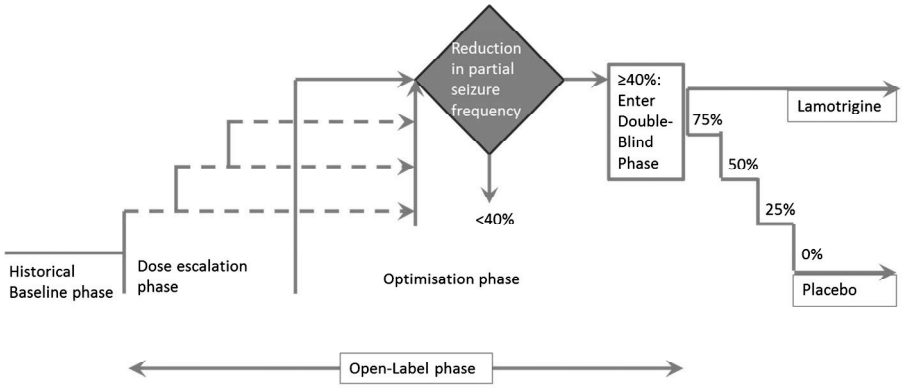


Figure 1. Schematic overview of the trial phases involved in the original study.

An overview of the demographics is shown in **Table 1**. The previously developed PK model [11] in combination with the available concentration and covariate data was used to predict individual values of peak, mean and trough concentrations (Cmax, Cavg, and Cmin respectively) for every day of the study duration in the dataset. Data manipulation, and statistical and graphical analysis were performed using R v3.1.1 [15]. Model building was performed using an environment consisting of NONMEM v7.3[16], Piraña v2.9.0 [17], and PsN v4.2.0 [18].

Table 1. Subject demographics for the data used in this study. Numbers of subjects receiving co-medications are listed, with the dose range given in parentheses.

Variable	Mean (SD)
Number of subjects	170
Weight (kg)	11 (2.2)
Age (y)	1.3 (0.4)
Seizure freq (day^{-1})	5.576 (10.8)
Comedications:	N (dose range)
Carbamazepine	56 (1-800)
Clobazam	10 (1-15)
Clonazepam	27 (0.05-25)
Diazepam	6 (0.9-30)
Gabapentin	1 (400-400)
Levetiracetam	2 (62.5-500)
Lorazepam	3 (0.20-0.75)
Oxcarbazepine	5 (90-540)
Phenobarbital	66 (8-300)
Primidone	2 (62-125)
Phenytoin	16 (14-300)
Topiramate	33 (12.5-400)
Valproic acid	18 (150-600)
Zonisamide	5 (50-200)

2.2 Pharmacodynamic analysis

The seizure count data was described with a Poisson distribution, consisting of a single parameter lambda (λ), which describes both the number and variance of the distribution of events (seizures per day). If k is the number of events, the probability of observing k is given by equation 1. Given the difficulties of estimating factorials, k! was approximated using the Stirling formula (equation 2). Differences in lambda were identified between baseline, placebo effect and treatment effect. Separate lambdas were estimated for the case when seizures or no seizures occurred on the previous day, which is the Markov element in this model. Over- or under-dispersion were taken into account by estimating an overdispersion factor. In the current application of the model, stochastic differential equations were not included. A more technical discussion of the model may be found elsewhere [12,19].

$$P(x = k) = \frac{\lambda^k}{k!} * e^{-\lambda} \quad (1)$$

$$k! \sim \sqrt{(2\pi k)} * \left(\frac{k}{e}\right)^k \quad (2)$$

Baseline seizure rate was separated from placebo and treatment effect, with treatment effect either as a constant factor or resulting from LMT exposure as measured by average, peak or trough daily concentration. After the introduction of each covariate, the change in objective function value (OFV) was determined, with a decrease of 3.84 points or more considered an improvement with $p<0.05$. Followed by this forward inclusion, backwards exclusion was applied to determine if the data was as well described after elimination of the model element. PD models were evaluated using observed (DV) versus predicted seizure amounts per day (IPRED), cumulative observed versus individually predicted seizures per day, difference (residual) between cumulative observed and individually predicted seizures per day over time, and predicted versus observed overdispersion.

2.3 Clinical trial simulations

To determine the impact of the choice of number of subjects on the ability to estimate statistically significant difference between lamotrigine and placebo trial arms, seven scenarios were created, ranging in number of subjects from 40 to 500. Parameters for baseline disease severity, OVDP, EC_{50} and Emax were sampled from distributions estimated from the original thirty-eight subjects included in the original trial. Exposure to lamotrigine was varied from levels as those found in the original trial to levels adjusted for the increased clearance in the population at levels of 25%, 50% and 75%. For each of the scenarios, the last four weeks of the optimization phase and four weeks of double blind phase were simulated. Statistical significance of differences in changes in seizure frequency between optimisation and double blind phase were estimated using a one-sided mid-p test.

3. Results

3.1 Clinical trial results

Steady-state concentrations as predicted by the PK model were relatively low (mean: 4.05, sd: 7.89, range: 0.23-10.7 mg/L) compared to the therapeutic range as defined for adults (4-12 mg/L). In previous studies in adults with PO-type seizures, average steady-state concentrations were around 6 mg/L. The primary endpoint, i.e. reaching escape criteria, occurred in 58% of LMT-treated patients and 84% PBO-treated patients, at a p-value of 0.07 this was not found statistically significant. Secondary endpoints such as time to escape also showed differences between LMT and PBO that approached statistical significance. Large variability was observed in seizure frequency both between and within individuals. The use of LMT did not result in statistically significant increases in side-effects compared to PBO. The overall lack of statistical significance in clinical endpoints based on the responder-enriched study design pointed to an underpowered study design.

3.2 Pharmacodynamic Model

A pharmacodynamic model was built based on a Poisson distribution with an overdispersion factor and Markovian features, as described previously by others [19]. Baseline lambda was dependent on the previous day and was modified by either a placebo or treatment effect. Treatment effect was dependent on average daily concentrations as predicted by the PK model. Estimated parameter values can be found in **Table 2**. The PD model was able to describe the data reasonably well with only moderate over- or under predictions of seizure counts per day and it followed the general trend in seizure counts over time well (**Figure 2**). Overdispersion was highly similar between observed and predicted seizures. While many variants of the model and many covariates were investigated, no improvements could be made on the base model.

Table 2. Parameter values of the final model, all parameters but EC_{50} are on the log scale.

Parameters	Parameter value (%RSE)	Parameter value in adults	Variance as Ω^2 [%RSE] (Shrinkage %)
Lambda (PDV>0)	-0.879 (6%)	-0.992	8 [26.6%] (28.4%)
Lamdba (PDV=0)	0.181 (93.9%)	-1.22	3.53 [16.3%] (3.4%)
OVDP	-2.45 (10%)	-1.26	9.31 [24.3%] (15.3%)
EPB	-1.82 (28%)	-0.247	1.41 [56.2%] (71%)
Emax	-5.11 (5.1%)	-4.70	63 [26.8%] (26.5%)
EC_{50}	6.17 (11.3%)†	13.06†	12.3 [21.2%] (18.6%)

OVDP: overdispersion factor; EPB: placebo effect; Emax: maximum LMT effect; EC_{50}: average daily concentration of LMT at which 50% of the maximum effect is reached, on normal scale.

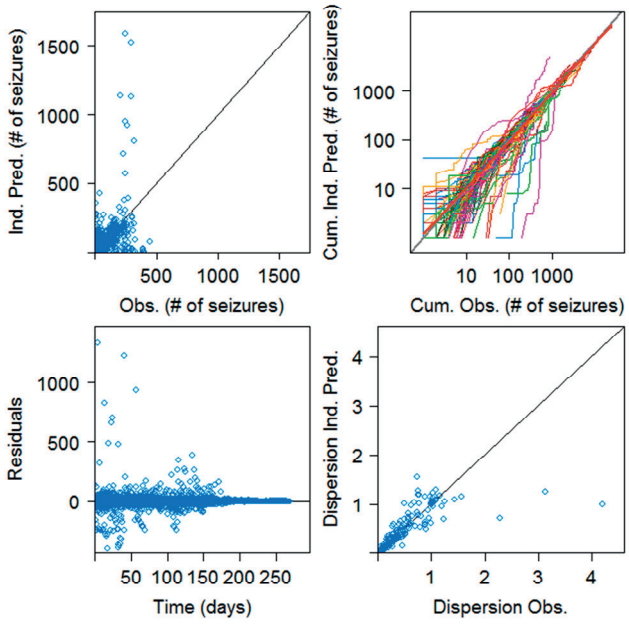


Figure 2. Goodness-of-fit for the final model. Top left panel: Individual observed versus predicted seizure counts. Top right panel: cumulative individual observed versus predicted seizure counts. Bottom left panel: residuals () of seizure counts. Bottom right panel: observed versus predicted dispersion.

3.3 Clinical trial simulations

Clinical trial simulations were performed based on several levels of subject inclusion. The model predicted subjects reaching escape criteria based on the actual trial data well. Simulations showed that increasing numbers of subjects would increase the power of the trial and reduce the p-value accordingly. A minimum of 200 subjects was required to achieve a p value of 0.05 or less at a power of 80% in simulated trials (**Figure 3**).

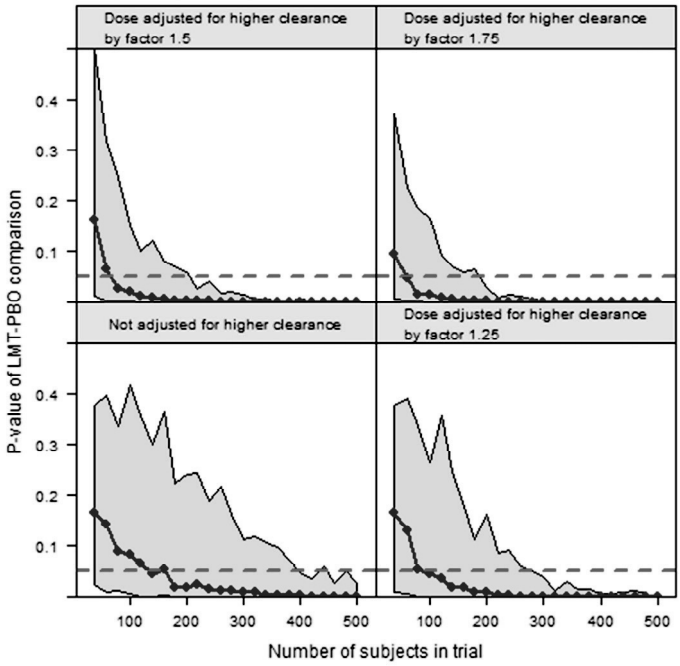


Figure 3. Median p-values (blue lines & dots), depending on the number of subjects in the virtual clinical trial and the level of exposure compared to the original trial. The shaded area represents the 80% prediction interval for each scenario, based on 100 simulated runs. At the number of subjects where the shaded area dips below the red dotted line, the trial design has reached a predicted p-value of below 0.05 at a power of 80%. LMT: lamotrigine; PBO: placebo

4. Discussion

In this work we set out to determine the exposure-response relationship of lamotrigine in children aged 1-24 months and establish the dose rationale for prospective clinical trials using modelling and simulations. Thanks to the availability of historical data, including studies in which seizure counts were collected in individual patients, we have shown that treatment response to LMT can be characterised by the same Poisson model with Markovian features used for adults and older paediatric patients. Most importantly, model parameter estimates describing disease specific properties were found to be of the same order of magnitude across age groups. The actual difference in this population is the placebo effect, which is significantly larger in young children. Based on clinical trial simulations, it appears that statistically significant differences can be detected and efficacy demonstrated if exposure is adjusted to account for differences in pharmacokinetics and in placebo effect.

As previously shown in adults with PO seizures, a drug-disease model can be used to describe seizure counts over time. Given our interest in the role of bridging and extrapolation principles in paediatric research and the somewhat limited patient pool, we have decided to apply the same model used for adults and older paediatric patients, despite conflicting views regarding the differences in the underlying pathology in this group of patients. We have assumed that structurally, the differences may be in parameters estimates, not in the way seizure frequency is parameterised in this model. In fact, the data was well described.

Since LMT has been used off label in this population, it remains unclear whether dose and dosing regimens are appropriate. Thus, in **Error! Reference source not found.** we provide dosing recommendations stratified for baseline seizure frequency. To achieve a 50% seizure reduction in a typical patient from our trial data, a LMT average daily concentration of only 1 mg/L is required, resulting in a dose of only 18 mg/day in a typical 1-year old patient. However, doses provided per stratified baseline seizure frequency show that, as the baseline seizure frequency increases, doses approach levels that may be high enough to lead to toxic effects. Doses to

achieve the same result in our previous study in adults with PO seizures are provided for comparison.

Table 3. Seizure frequency at the start of treatment is used as covariate for dose selection, based on the PK and PD of a typical adult weighing 70 kg derived from the earlier adult PD model, and a typical 1-year old patient weighing 10 kg derived from the current PD model. The earlier-presented PK model may be used for further dose personalisation, especially in toddlers and infants. Total doses may be rounded to 5 mg, as more accurate dosing differences may not easily be achieved using dosing tools based on lamotrigine oral suspension formulations currently available. 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. Care should be taken not to go over the maximum total daily dose.

Seizure frequency (day^{-1})	Dose for adult PO seizures (mg/kg/day)	Dose for paediatric PO seizures (mg/day)
0.1	3	4
0.2	6	8
0.3	9	13
0.4-0.6	11-16	17-26
0.7-0.9	18-24	32-45

Our parameter results in **Table 2** clearly show that in addition to striking differences in pharmacokinetics, placebo effect is significantly different in young children. In addition, apparent differences were observed for EC_{50}, which was found to be lower than that in adults, showing that these young patients are possibly more sensitive to the effect of LMT. However, given that both values are within the same order of magnitude, it is not possible to establish the clinical relevance of such differences. On the other hand, it should be noted that the larger placebo effect in children has been previously reported in literature [20]. These similarities seem to suggest that estimates from adult patients may be used to support the dose rationale in young children, which has recently been taken up by the FDA, although this does not necessarily extend to patients younger than 4 years [21,22]. The fact that differences were found between adults and these young children show that overall response profiles may not necessarily arise from exactly the same parameter distributions. Whilst we have to

acknowledge the limited number of patients and the absence of further details on the companion drugs, these findings highlight the advantages of a parametric approach; empirical extrapolation may not be as effective. A comparison of parameters from adults with PO seizures to those in the current population is provided in **Table 2**.

Based on the aforementioned findings, it became evident that previously failed clinical trials may simply be a consequence of poorly designed studies. Clinical trial simulations showed that the original trial of LMT in patients aged 1-24 months old was statistically underpowered. Indeed, while statistically treatment response did not separate from placebo, the predicted effect size was found to be comparable to adults and quite clinically relevant, after correcting for the differences in pharmacokinetics. Statistical significance was shown to be reached by inclusion of at least 200 subjects in a study, assuming that dosing will be adjusted for the increased clearance in the population of interest. At the same time, our analysis suggests that paediatric doses may be derived based on bridging and extrapolation principles. These results also shed light into the requirements for the development of a model-based dosing algorithm, as similar principles should be applied to both populations.

We acknowledge that our investigation has some important limitations. First, it should be noted that the clinical trial simulations are based on a model built to describe seizure counts. We could not evaluate the impact of prior treatment or increase in severity. We also have account for the potential bias in estimates due to inclusion and exclusion criteria. Second, the limited number of patients on placebo (19 out of 177), may not have allowed sufficient precision and accuracy in estimation of the placebo effect. Third, our simulations were based on the parameters found in the only 38 subjects included in the double blind phase of the trial. Many more subjects were included during the open-label phase, although the results of the primary endpoint of the trial were not based on these other subjects.

Whereas a larger body of evidence may be required to confirm our findings, they provide an indication that LMT may be efficacious in this population, if patients are treated with the appropriate dose. As such, our methods may

provide a framework for the implementation of a common dosing algorithm across the overall population of patients with PO seizures. It also highlights the importance of endpoint selection and trial design requirements for establishing efficacy. In the field of epilepsy such issues are often undervalued and it is suspected that the use of suboptimal trial designs has led to many failures in showing superiority to placebo. As has been pointed out elsewhere, not only the choice of endpoint but also its statistical analysis has great implications for the validity of the outcome of a trial [6].

In conclusion, despite some limitations, the use of a drug-disease model allowed the characterisation of the exposure-response relationship of lamotrigine in patients younger than 2 years of age. Estimates suggest comparable disease-specific parameters between adults and young children, which provides the basis for further review of the role of bridging and extrapolation in this patient group. The doses and dosing regimens proposed here should be considered in future studies aimed at the evaluation of the efficacy and safety of lamotrigine in this subgroup of patients.

References

1. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia. 2010 May;51(5):883–902. Cardarelli WJ, Smith BJ. The Burden of Epilepsy to Patients and Payers. Am J Manag Care. 2010;16(12):331–6.

2. Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age. Clin Pharmacokinet. 2006 Aug;45(4):351–63.

3. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. Clin Pharmacokinet. 2013 Aug;52(8):627–45.

4. de Sá Borges AP, De Almeida Campos MS, Pereira LRL. Evaluation of unlicensed and off-label antiepileptic drugs prescribed to children: Brazilian Regulatory Agency versus FDA. Int J Clin Pharm. 2013;35(3):425–31.

5. van Dijkman SC, Alvarez-Jimenez R, Danhof M, Della Pasqua O. Pharmacotherapy in pediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go. Expert Opin Drug Metab Toxicol. 2016;12(10):1143–56.

6. van Dijkman SC, Wicha SG, Danhof M, Della Pasqua OE. Individualised dosing algorithms and therapeutic monitoring for antiepileptic drugs. Clin Pharmacol Ther. 2017;In press(June).

7. Meyer J, Fardo D, Fleming ST, Hopenhayn C, Gokun Y, Ryan M. Generic antiepileptic drug prescribing: a cross-sectional study. Epilepsy Behav. 2013 Jan;26(1):1–6.

8. Matsuo F, Bergen D, Faught E, Messenheimer J a, Dren a T, Rudd GD, et al. Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. U.S. Lamotrigine Protocol 0.5 Clinical Trial Group. Neurology. 1993;43(November):2284–91.

9. Schachter SC, Leppik IE, Matsuo F, Messenheimer J a., Faught E, Moore EL, et al. Lamotrigine: A six-month, placebo-controlled, safety and tolerance study. J Epilepsy. 1995;8(95):201–9.

10. van Dijkman SC, de Jager NCB, Rauwé WM, Danhof M, Della Pasqua O. Predictability of lamotrigine pharmacokinetics across ages using allometric scaling; suggestions for targeted dosing. Under Rev.

11. van Dijkman SC, de Jager NCB, Rauwé WM, Danhof M, Della Pasqua O. Differences in the exposure-response of adjunctive lamotrigine therapy between partial onset and primary generalised tonic-clonic seizures in adults. Under Rev.

12. GSK trial database - LAM20006 [Internet]. Available from: https://www.gsk-clinicalstudyregister.com/study/LAM20006

13. Jadhav PR, Kern SE. The need for modeling and simulation to design clinical investigations in children. J Clin Pharmacol. 2010 Sep;50(9 Suppl):121S–129S.

14. R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2014.

15. Bauer RJ. NONMEM user guide introduction to NONMEM 7.3.0. 2014;

16. Keizer RJ, Karlsson MO, Hooker a. Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose. CPT pharmacometrics Syst Pharmacol. 2013;2(November 2012):e50.

17. Lindbom L, Pihlgren P, Jonsson N. PsN-Toolkit - A collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed. 2005;79:241–57.

18. Plan EL. Modeling and simulation of count data. CPT pharmacometrics Syst Pharmacol. 2014;3(August 13):e129.

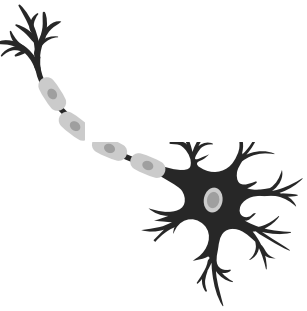
19. Rheims S, Cucherat M, Arzimanoglou A, Ryvlin P. Greater response to placebo in children than in adults: a systematic review and meta-analysis in drug-resistant partial epilepsy. PLoS Med. 2008 Aug 12;5(8):e166.

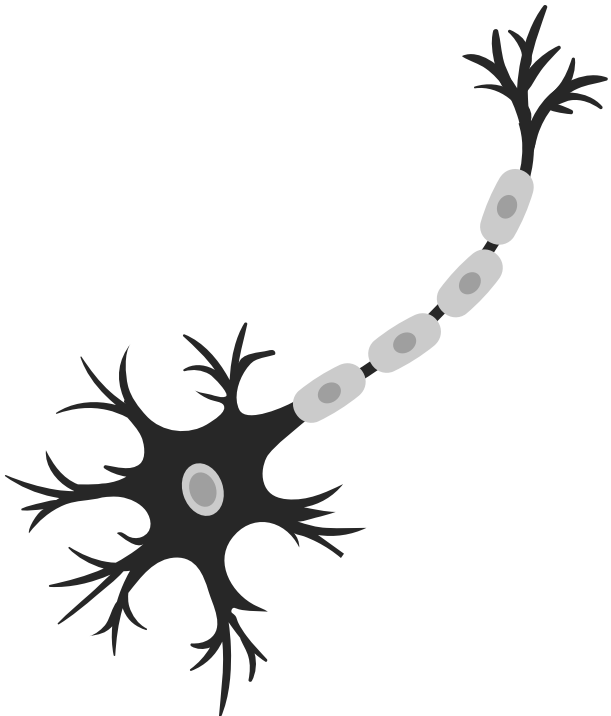
20. Pellock JM, Carman WJ, Thyagarajan V, Daniels T, Morris DL, D'Cruz O. Efficacy of antiepileptic drugs in adults predicts efficacy in children: a systematic review. Neurology. 2012 Oct 2;79(14):1482–9.

21. Nordli D, Bagiella E, Arzimanoglou A, Wang J, Kumar D, Laurenza A, et al. Extrapolation of efficacy data from adults with primary generalized tonic-clonic seizures (PGTC) to pediatric patients: a meta-analysis of published clinical trials (S37.004). Neurology. 2017;88(16):Supplement S37.004; 1526-532X.

SECTION V

CONCLUSIONS & PERSPECTIVES





CHAPTER 9

CONCLUSIONS AND FUTURE PERSPECTIVES

Conclusions and Future Perspectives

1. Conclusions

The objective of modern clinical pharmacology is to improve the effectiveness of current treatments and to provide new medicines to treat as many diseases and conditions as possible. In addition, its goal encompasses the development of methods and tools that allow for optimisation of evidence generation and evidence synthesis, ensuring appropriate prescription, delivery and use of medicines. Since the 1960s, with the Kefauver-Harris amendment to the Food Drug and Cosmetic Act in the USA in 1962 [1] and, with the European Directive harmonising requirements for marketing authorisations in 1965 [2], the action of national and supranational governments has established the need for appropriate scientific evidence on efficacy and safety of all new drugs before their approval for clinical use. These principles already take into account the concept of interindividual variability and recognise the fact the requirements to treat vulnerable patients may differ from the general population. Indeed, the recognition that therapeutic response is affected by intrinsic and extrinsic determinants of variability sets the foundations for personalised treatment, separating patients into different groups—with medical decisions, practices, interventions and/or products being tailored to the individual patient based on their predicted response or risk of disease. While the tailoring of treatment to patients goes back to the time of Hippocrates [1], the development of new diagnostic, mathematical and statistical approaches along with computer and informatics allows the implementation of dosing algorithms based on detailed understanding of disease and underlying exposure-response relationship.

In this thesis, we set out to show how understanding of pharmacokinetics, pharmacodynamics and exposure-response relationships may be used in conjunction with modelling and simulation to personalise antiepileptic drug treatment in paediatric epilepsy. In the first section we reflect on the key issues in the diagnosis and treatment of epileptic seizures. An extensive

review of current practices in paediatric epilepsy is presented together with the implications of different sources of variability for treatment outcome. A clear picture emerges regarding the consequences of empirical experimental evidence and the opportunities for the characterisation of exposure-response relationships using quantitative clinical pharmacology. It also becomes evident that knowledge regarding pharmacokinetics and pharmacodynamics is not being used to support clinical decisions, with titration, tapering and switching of drugs and dosing regimens as the method of choice to tackle inter-individual differences in treatment response. In the second section, we review the use of pharmacokinetic and pharmacokinetic-pharmacodynamic modelling for the most commonly used antiepileptic drugs. These data provides a baseline for the development and implementation of personalised treatment using model-based dosing algorithms, where we show that parameterisation of the impact of intrinsic and extrinsic factors (i.e., covariate effects) can already be used to guide dose selection and/or stratify patients. Focus was given to the role of demographic differences and drug-drug interactions, as they represent common causes of variability in drug exposure. These analyses have shed light into the gaps in knowledge, and in particular the lack of data regarding the exposure-response relationships of anti-epileptic drugs. In the third section, we make use of a paradigm compound, lamotrigine, to illustrate the requirements for the development of model-based dosing algorithms and their application in drug development and in clinical practice. We show how insight into covariate effects in pharmacokinetics and pharmacodynamics, along with the underlying exposure-response relationship allows further optimisation of treatment in children. We take the opportunity to highlight the experimental challenges associated with current research and propose possible solutions to overcome these issues. In this concluding chapter, we re-iterate the questions posed at the onset of this thesis, reflect on the results obtained, including some of the main limitations, and future steps required to implement personalised pharmacotherapy in paediatric epilepsy.

1.1 Knowledge integration

Neurologists have around 20 anti-epileptic drugs (AEDs) in their armament against epileptic seizures. Regardless, up to 30-40% of patients do not respond sufficiently to pharmacotherapy [2,3]. With the alternatives being invasive treatment such as vagus nerve stimulation or epileptic focus resection, there is a need for the optimal utilisation of existing AEDs as well as better experimental protocols for the evaluation of new compounds. Modelling and simulation techniques offer an opportunity for personalisation of treatment due to its ability to identify relevant sources of variability and integrate existing knowledge regarding the contribution of multiple factors to variation in exposure, pharmacological effect and clinical response. Of note is the possibility of using prior information, i.e. evidence synthesis, and exploration of hypothetical scenarios *in silico*, i.e., clinical trial simulations (CTS).

In other fields such as oncology, infectious diseases, and diabetes, modelling and simulation has advanced to a stage where models are starting to approximate the relevant physiology and pathology to a significant degree, leading up to systems pharmacology. In epilepsy, however, the complexity of the disease, the lack of biomarkers along with the use of the discrete measures of the clinical symptoms have resulted in a status quo, in which there appears to be no alternative to treatment optimisation through trial and error, as defined by titration, tapering and treatment switch guidelines [4]. Evidence exists for the selection of some AEDs over others in specific seizure types, syndromes, or in few cases known aetiologies. Yet, these guidelines only provide very rough guidance in terms of first-, second- and sometimes third-line AED choices. There appears to be no need for insight into the underlying exposure-response relationships, as it is assumed that variability in response to treatment cannot be, at least in part, assigned to specific factors. Once an AED is selected, information regarding dose titration across a predefined range of doses is considered as sufficient to establish whether a patient will respond to treatment or not. Again, no quantitative guidance is linked to these procedures other than therapeutic drug monitoring, which is often used to

determine treatment adherence as opposed to its use for dose personalisation.

In chapter 1, we argued that PKPD and disease modelling are essential to cope with this complexity and to eventually achieve rational epilepsy pharmacotherapy. In this context, paediatric epilepsy stands out from adult epilepsy and other disease areas due to the existence of specific paediatric types of epilepsy, even larger lacunas in paediatric evidence, and the fact that some paediatric epilepsy phenotypes exhibit more severe disease progression than that typically observed in adults. These factors are often used to justify the choice for polytherapy in paediatric cases. As such, prescribing physicians need to make careful assessment of combinations and dose adjustments, but these are often based on adult doses expressed in mg/kg body weight. It is now common knowledge that drug clearance scales non-linearly with weight [5]. Moreover, doses in children younger than 2 years of age need to account for ontogeny processes and other developmental changes, which are not characterised by the effect of body weight. Likewise the role of drug-drug interactions cannot be overlooked. In Chapter I, we reviewed different sources of variability in treatment outcome in epilepsy.

One of the questions we aimed to answer in this thesis was whether ***inter-individual differences in exposure to AEDs and inadequate response in some patients can be explained by size and age-related covariate factors.*** To address this question, in **Chapter 3** we have summarised all available PK and PKPD models in the published literature for AEDs. By doing so, an overview was created of the different model parameterisations and covariate effects, such as drug-drug interactions (DDIs), effect of body weight and age, genotype, and other covariates. While size and age-related covariate factors explained differences in exposure to some degree, a considerable proportion of the overall variability in pharmacokinetics remains after adjusting for these factors. Typically, the variability in clearance, expressed as coefficient of variance (CV%), is roughly 50% for most models for most AEDs. The review in chapter 3 also showed that most AED PK models were in the form of one-compartment model with first-order absorption and elimination. Notable exceptions were models for the

correlation between bound and unbound concentrations of valproic acid and phenytoin, and the physiology-based PK (PBPK) models for valproic acid [6]. Not many PD models were found in literature, and those that are available model the correlation between exposure and parametrically secondary outcome measures such as the time to first seizure analysis for topiramate efficacy. A database of predictive models was created, which allows looking up possible approaches to model pharmacological data in epilepsy, it aids in identifying the most relevant covariates to screen for in an analysis, and it reveals the models that are currently available for clinical personalisation of treatment and dose.

1.2 Model-based dosing algorithms

In **Chapters 4 and 5** we address three other important questions proposed at the start of this thesis, namely whether evidence of ***drug-drug interaction studies in adults can be used to assume similar effects in the paediatric population*** and evaluate ***the implications of commonly recommended empirical dosing in mg/kg*** in children. Using simulations and a selection of literature models from chapter III, we show the impact of DDIs on clinically relevant measures of drug exposure. Through these simulations, we also demonstrate the implications of adding one or more other AEDs onto the existing therapy, i.e., dose adjustments are typically required to ensure maintenance of comparable exposure levels to the primary AED. Furthermore, under the assumption of similar exposure-response, our results show important differences in terms of the magnitude of the effect of DDIs in children. This evidence reinforced the relevance of model-based dosing algorithms as a tool for dose personalisation. In chapter V, we use simulations to explore the impact of integrating therapeutic drug monitoring (TDM) with model-based concepts to define the dose rationale for individual paediatric patients. Variability in the time to achieve a predefined target AED exposure, as well as the variability in exposure during the maintenance phase were significantly reduced by an approach based on a combination of models and TDM, when compared to other approaches. These findings provided the basis for an answer to the

fourth question included in the objectives of this thesis, namely that ***model-based dosing algorithms can minimise the need for treatment switch and combination therapy.***

1.3 Evidence generation and evidence synthesis in epilepsy trials

In subsequent chapters VI, VII and VIII, we aimed to determine, amongst other things an answer to the two remaining questions included in the scope of this thesis, namely ***which data are required and which criteria should guide the selection and personalisation of paediatric doses.*** Using a paradigm compound we explored experimental requirements assuming comparable and different exposure-response between adults and children. A special case of prior information is allometry, a theory that states that certain PK parameters correlate to body weight according to pre-defined mathematical rules. Using allometry, we investigated our ability to predict paediatric PK of lamotrigine (LMT) using a model built on adult data. As previously suggested, below the age of 2 years, allometry does not adequately adjust for the observed changes in clearance and thus a maturation function was developed to adjust for these findings. The result was a model that is able to predict for patients ages 1 month to 91 years of age. The model was built on data from several major ethnicities (Black, Asian, Caucasian), for which no significant differences were found in PK. As a result, the developed model may be one of the most versatile models for LMT available. Due to its ability to predict for this wide range of populations, simulations were performed to optimise the typical dose for all ages, under the assumption of similar exposure-response. This is the first attempt to derive, through modelling & simulations, a dose of LMT in patients aged 1-24 months of age. While this dose will achieve average steady-state concentrations within the therapeutic range for most of these patients, large variability remains. Further personalisation and individualisation is still indicated to adjust for the unpredictable variance in the PK parameters, such as the 56.1% of variance in clearance after correcting for covariates. Furthermore, differences in exposure-response between adults and children may require setting a different target

exposure. Using the covariates presented with the PK model of chapter VI in combination with therapeutic drug monitoring and individual parameter estimation approach showcased in chapter V will allow further accuracy and precision in the personalisation of LMT dosing.

As discussed in chapter I, the definition of a clinical endpoint, and thus efficacy, determines the data required to accurately and precisely estimate parameters such as potency and maximum efficacy. Previous work described the estimation of pharmacodynamic models on clinical endpoints such as the ability to achieve at least a 50% reduction in seizure frequency, or the occurrence of a first seizure after start of treatment. These endpoints are binary and thereby the information from seizure diaries is reduced to simple yes and no outcomes. This simplification leads to a large loss in information, which is often compounded in the analysis of clinical trials by thereafter taking means and standard deviations of the study populations. These endpoints are in fact derived from the underlying endpoint which is seizure counts over time. With the description of seizure counts, one may determine the other, more often used, endpoints as they are the automatic result of it. Thus, it is recommended to model seizure counts, as it is closer to the pathophysiology and thus should be more sensitive to disease progression and treatment effect. Chapter VI outlined the use of a population Poisson model for the description of seizure counts in adult patients with partial onset (PO) and primary-generalised tonic-clonic (PGTC) seizures. Our investigation revealed that these patients differ in sensitivity to treatment, and we quantified the correlation between exposure and response. Apart from the typical inter-individual variability, as is normally taken into account by mixed-effects modelling, we also used Markov properties and stochastic differential equations (SDEs) to adjust for changes in the disease activity over time within the individual (intra-individual variability). Now that a PKPD model is available for LMT, individual sensitivity to treatment may be estimated in the clinical population, based on seizure diaries and TDM. More rudimentary dosing applications may be developed using nomograms or stratification of patient groups.

The Poisson model was further evaluated on a paediatric cohort of patients with PO seizures aged 1-24 months. These patients showed a higher

baseline disease activity, but also showed a higher sensitivity (as EC_{50}) to LMT compared to that previously found in adults with PO seizures. On the other hand, a small difference was found with regard to placebo and maximum treatment effect. We used clinical trial simulations to investigate the required number of patient to show efficacy in this population (power calculations), assuming similar PKPD as estimated from the data. It was found that a minimum of 200 patients were needed to achieve sufficient power, a number much higher than what was considered in the original trial. In other words, the original trial of LMT used in this analysis was found to be underpowered, even if LMT in this population can be quite effective. Future clinical trials of AEDs, especially in a patient group where patient inclusion is difficult such as in these young children, may want to use modelling & simulation approaches such as those showcased in chapter VIII to *a-priori* optimise the trial design for sufficient power.

In summary, we have created a model library and overview of PK and PKPD models for AEDs, allowing easy implementation and adaptation of the available literature information. Furthermore, we have shown that personalised and individualised medicine based on modelling approaches is not only feasible, but has a significant impact on achieving pre-set exposure targets, thereby reducing variability in treatment outcome. Finally, new models for the PKPD of lamotrigine were provided, which, assuming their validity in clinical populations, may allow pharmacodynamic personalisation and individualisation, as well as clinical trial simulations for the optimisation of future trial designs.

2. Limitations

In addition to the discussed thesis results and conclusions, a discussion of its limitations is warranted. Our work on the impact of drug-drug interactions and dosing algorithms through PK simulations in chapters IV and V required us to make certain choices in the use of PK models for anti-epileptic drugs in literature from chapter III. Due to the nature of the investigation with regard to drug-drug interactions, models were selected in which many of these interactions were taken into account. Such selection

criteria limited us in the possibility of selecting models that were able to predict for different races and sometimes age groups (notably lamotrigine and valproic acid). Also, by selecting models for this purpose, their appropriateness for parameter estimation in chapter V may have been affected. A more thorough, but much more time-consuming approach would have been to perform a full meta-analysis of the available models listed in chapter III, or to first create an integrated PK model for each AED based on the available literature models and validate it against simulated data from the original models, or ideally, against actual data. This was, in part, performed in chapter VI for the PK of lamotrigine, where we used literature information regarding the relevance of allometric scaling, drug-drug interactions, and changes in PK according to age to construct a model that was validated on actual PK data from several clinical trials. Such an exercise was not feasible for all AEDs discussed in chapter III due to a lack of time and data, but may be performed in the future using the materials provided in the supplements of chapter III.

A further limitation of chapters IV and V is the use of plasma AED concentrations as a substitute marker for cerebral exposure. As mentioned in chapter I, cerebral PK is largely determined by the blood-brain-barrier, which limits the amount of drug that enters the brain. Moreover, evidence exists for steep concentration gradients between different brain compartments, which may lead to differences in the effect of an AED depending on where in the brain it distributes to, further complicating our ability to link AED exposure to effect [7,8]. These issues are a source of variability in correlations between systemic exposure (observed as plasma concentrations) and clinical effect, compounding the disbelief amongst many clinicians regarding the clinical relevance of TDM in anti-epileptic drug therapy. More physiology-based PK models may improve the correlation between the PK of AEDs in plasma and at the target site, resulting in the ability to better correlate exposure to effect. Steps are already being undertaken to the establishment of generic brain PK models to allow the characterisation of system-specific and drug-specific parameters [9,10].

When it comes to the pharmacodynamic analysis in chapters VII and VIII, some major hurdles may also be identified. It has been reported that self-reporting of seizures, as was performed in the clinical trials from which data was used in chapters VII and VIII, may be subject to large under-reporting of seizure counts of up to 50% [11]. If this under-reporting has occurred fully at random time-points and in random patients, i.e. no underlying mechanism drove the under-reporting, then the impact on our conclusions in these chapters may be small to negligible. Although parameter values may in that case be affected, the models as reported would still predict adequately for numbers of seizures observed and treatment effect, albeit that they do not predict for seizures unobserved or unreported. However, if there is some mechanism of seizure under-reporting, unbeknownst to us, that skews the under-reporting in certain moments or types of patients, we may not be able to accurately determine treatment effect in a subpopulation of our data. For example, if seizure reporting is affected more in patients with PO seizures compared to those with PGTC seizures, or vice-versa, our estimated treatment effect may not compare between the two groups as was our conclusion in chapter VII, even though the models may still predict reported seizure counts in both populations to an acceptable degree. Several devices exist for the direct registration of seizures based on EEG patterns, but the use of these is invasive. It is at this point unrealistic to make predictions on the impact of modelling seizure counts as registered by these devices compared to the patient-reported seizure count.

Unfortunately, apart from seizure types PO and PGTC, no other covariates were found to influence baseline seizure counts, placebo effect, or LMT potency and maximum efficacy (although LMT exposure was found to predict for clinical efficacy). As a result, personalisation of treatment may only be done by a relatively small degree, and the current status-quo with regard to individualisation, i.e. adjustments of AED choice and dose after the start of treatment, will remain necessary until biomarkers may be identified that are sensitive to drug effect. Furthermore, our models were built on data of adults and children that were not treatment-naïve and were already under treatment when enrolled in their respective clinical trials. As mentioned in chapter I, this practice, which is the standard in

paediatric trials, does not allow us to estimate the parameters that determine treatment effect. The thereby increasingly therapy-resistant population that is subjected to these trials may bias drug development in the direction of drugs that work in a small resistant section of patients while the development of drugs that are safer in the general treatment-naïve population may be discarded. In essence, the treatment effect observed in clinical trials may not be directly translatable to the general clinical population, thereby possibly leading to an unfair advantage for the older AEDs that were tested in populations more representative of the typical clinical populations.

Apart from the issue of extrapolation of drug efficacy from add-on trials to the general patient population, there is the matter of drug-drug interactions (DDIs), both in terms of PK and PD. It has been shown in animal models that AEDs show significant PD DDIs [12–14]. While PK DDIs of AEDs are extensively described in literature (chapter III), these are only adjusted for to a limited degree in clinical trials. For example, in the evaluation of LMT in adult patients in our data, patients receiving valproic acid during the trial were given a lower dose, as it was already known that VPA decreases LMT clearance. There is however also variability in the DDIs themselves, i.e. not every patient shows DDIs to the same degree. When this is not taken into account during dose optimisation, observed drug interactions with regard to treatment outcome cannot accurately be attributed to PD. Further, the investigation of PD DDIs requires specific trial designs optimised for the ability to detect DDIs. This may include the start of the second AED after sufficient data has been collected to estimate the PD parameters of the primary AED, and the optimisation of dose levels to make sure sufficient DDIs will be found. Current trial designs do not consider such trial modalities and thus often do not allow the estimation of PD DDIs (if any) and the assumption in practice seems that, if it hasn't been found, it is simply not there. Future trials may be optimised by performing CTS and the application of optimal design criteria using specific software [15,16].

Finally, a major limitation exists with the use of seizures as a clinical endpoint, and by proxy its modelling. Disease activity often exists even when a patient has not had a seizure on a given day. In fact, some patients

only exhibit few seizures per month or even per year. Defining successful treatment in these cases becomes problematic due to a lack of data; how long do we need to wait in these types of patients before we can speak of treatment success? Similar to this issue, the Poisson model may only estimate lambda, i.e. the seizure frequency, if sufficiently long follow-up data is available.

Break-through seizures due to patient non-adherence may then easily be wrongly attributed to resistance to medication, resulting in unnecessary treatment changes. It also limits our ability to accurately estimate drug effect from clinical trials. Biomarkers that are able to accurately detect epileptic activity in patients with a low frequency of seizures may solve this issue in the future.

3. Future Perspectives

Given the conclusions and limitations, some possible future investigations may be discussed. An important question in epilepsy research is whether it is possible to predict disease progression. One notable example of disease progression modelling was undertaken by Berg *et al.* [17] In their work, three Markov states were defined, in remission, no longer in remission, and never in remission. Based on this model, they were able to describe the chance of achieving remission over time. They showed that, over the timespan of up to eight years, disease progression may be observed. In our investigations in chapter VII and VIII, we did not detect any noticeable direction of time-dependent changes in disease activity, nor did we find predictors for disease progression, even if many patients in our data showed large changes in seizure activity over time. This may be due to the limited time-scale in the data with regard to baseline, leading to the inability to differentiate disease progression from a small or negligible treatment effect. Contributing to our inability of measuring any significant disease progression may have been the relatively short follow-up of maximally two years, comparing to up to eight years in the Berg et al. data. Alternatively, predictors may exist, but these were not included in the data. Most probably however, predictors of disease progression will not be found

in demographic properties or easily observed variables. The question is then, how long does one need to have a base-line and follow-up data on a patient to adequately determine whether a started treatment is efficacious. In the following example, we investigate this using the Poisson models with and without SDE for PO type seizures from chapter VII.

AED therapy often results in the occurrence of side-effects. In this thesis, we focused on the modelling of PD in terms of efficacy alone, but similar approaches may be applied w.r.t. PD modelling of the number of side-effects, and their severity. Some novel methodologies are available, based on item response theory, that allow the simultaneous modelling of several clinical outcome markers including their severity scores, including the interaction between the scores [18,19]. Such methods may be further applied to the combined modelling of efficacy and side-effects, as it stands to reason that some correlations may exist between these outcomes.

As described in chapter VII, a Poisson model was built that took into account time-dependent intra-individual changes in seizure activity using SDE. The SDE described random changes in seizure activity with no specific direction (i.e. the average change in seizure activity over the whole population remains 0), but 95% of individual changes in seizure activity (seizures/day, or frequency) were between -0.3 to +0.3 seizures/day (median: 0). In other words, starting at a seizure frequency of one per day, this could change to 1.3^7=6.3 seizures per day in one week. This is, however an extreme scenario, with most patients showing less dramatic changes over time. Efficacy of LMT was described using the typical sigmoidal curve dependent on maximum drug effect (Emax), potency (EC_{50}) and LMT average daily concentrations. Using this model, simulations were performed based on the characteristics of the patients from the original study with regard to demographics, seizure baseline frequencies, placebo effect, and lamotrigine potency and maximum efficacy. Seizure counts were simulated for two baseline weeks and six treatment weeks. Lamotrigine was titrated to a dose of 300 mg/day in steps of two weeks (up-titration to 50 and 100 mg/day) and one week (up-titration to 200 and 300 mg/day). During this treatment phase, one, two, or three pharmacokinetic therapeutic drug monitoring samples were simulated for subsequent PK

parameter estimation, using the methodologies from chapter V. Using the estimated PK parameters, or population-predicted parameters (no TDM samples), individual-predicted average LMT concentrations were derived for all days in all patients. Subsequently, PD parameters were estimated using the original model with and without SDE, and follow-up data of one, two, three, four, five or six treatment weeks. Relative error (RE) of PD parameters were then calculated using equation 1 and plotted between the different follow-up scenarios (between one to six weeks) and between number of TDM samples used (none to three). Plots were split between using the SDE model and non-SDE model.

$$Relative\ error\ (\%)\ = \frac{x-tv}{tv} * 100\% \qquad (1)$$

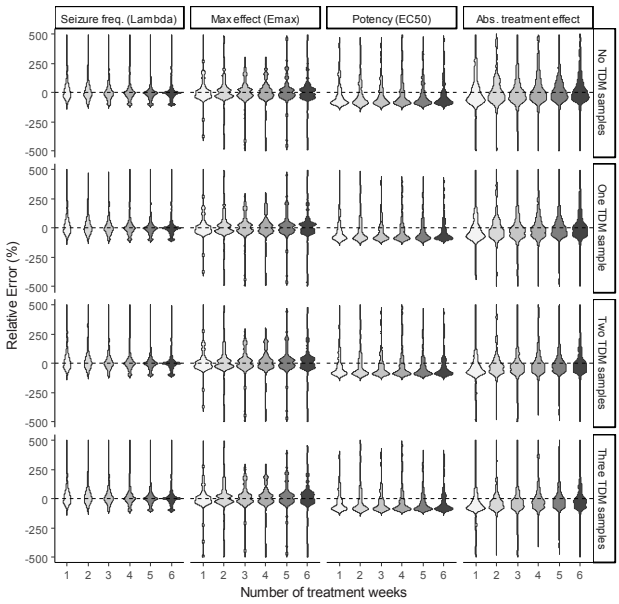


Figure 1. Results from application of the Poisson model with stochastic differential equations. Parameter estimation accuracy (RE%) of seizure frequency, maximum treatment effect, potency and absolute treatment effect between scenarios of different number of follow-up weeks, and differing number of TDM samples used for estimation. Positive values signify overestimation and negative values underestimation.

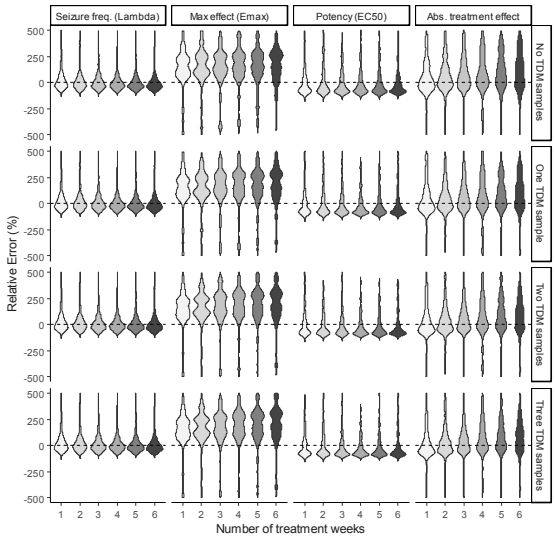


Figure 2. Results from application of the Poisson model without stochastic differential equations. Parameter estimation accuracy (RE%) of seizure frequency, maximum treatment effect, potency and absolute treatment effect between scenarios of different number of follow-up weeks, and differing number of TDM samples used for estimation. Positive values signify overestimation and negative values underestimation.

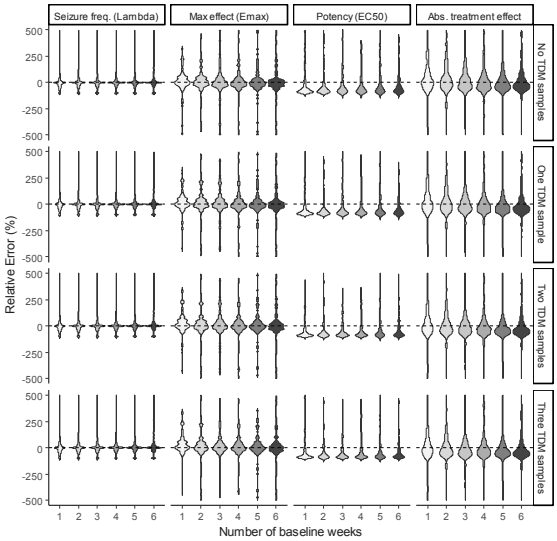


Figure 3. Results from application of the Poisson model without stochastic differential equations. Parameter estimation accuracy (RE%) of seizure frequency, maximum treatment effect, potency and absolute treatment effect between scenarios of different number of baseline weeks, using 6 treatment follow-up weeks, and differing number of TDM samples used for estimation. Positive values signify overestimation and negative values underestimation.

Results of these simulations are not very encouraging. Neither the model with SDE nor that without SDE is able to accurately estimate the potency. Furthermore, using the model without SDEs resulted in large errors in estimation of absolute treatment effect, showing that the issue of individual parameter estimation is one based on parameter identifiability and not on model complexity. This finding may have grave implications in the analysis of clinical trial data, where trial design choices should take into account the long follow-up times required to accurately estimate these parameters. The simplification of analysis by disregarding the changes in seizure frequency over time may result in improper assessment of drug effect in some trials, although if a trial were to be repeated infinite times, the mean estimation of drug effect should still approach the true value (Figure 1). Conversely, depending on duration of treatment follow-up, the absolute treatment effect, i.e. the treatment effect observed in the patient may be estimated to an adequate degree using the model that includes SDEs, with a follow-up of six weeks showing good agreement with the absolute treatment effect that was simulated (Figure 2). Parameter estimation was not significantly improved by increasing the baseline period from 2 to 6 weeks (Figure 3). However, maximum treatment effect and potency are required to make for prediction of treatment outcome, as it is these two parameters in combination with actual exposure (as average daily concentration) which determine the absolute treatment effect. It seems that therapeutic drug monitoring did not improve our ability to estimate pharmacodynamic parameters, but it should not be dismissed, as accurate pharmacokinetic parameters will still be needed to derive the optimal target maintenance dose once the optimal target exposure has been determined. Possibly, it may be required to perform so-called probing tests, in which the potency and maximum effect of the individual patient are explored by testing multiple dose levels or lower doses of multiple drugs. By perturbing the system and collecting data through sensitive biomarkers, we may derive system-specific parameters that inform on the sensitivity of the system to changes induced by AEDs. When this is applied in a systematic manner that evaluates the relevant physiology, a rational decision of pharmacotherapy may be made on the basis of sensitivity of the individual patient.

This example highlights the need for biomarkers to provide a window into the pathophysiology. Such biomarkers may then provide early predictors of the maximum efficacy of the available AEDs, thereby allowing selection of the most probable efficacious treatment *a-priori*, and selecting the appropriate exposure level for the patient, after which techniques as shown in chapters IV and V may be used to optimise for dose. With relation to the Poisson model, these biomarkers (or perhaps other predictors) would adjust the value of lambda, where possible over time. With enough accurate biomarkers, the value of lambda will simply approach the number of seizures for that day. Such biomarkers would also solve the issue discussed in the limitations, regarding difficulties in the estimation of treatment effect in patients with low seizure frequencies. In this sense, the use of a Poisson model, or any of the related models (negative binomial, zero-inflated binomial, etc [20,21]), to model seizure counts is a middle-outward approach to the problem. Using biomarkers, we may explain inter- and intra-individual variation in the lambda due to differences and changes in pathophysiology. Lambda may then be used to predict seizures in the future, from which the two major clinical endpoints seizure freedom and a reduction of at least 50% in seizure frequency may be derived. It is expected that pathophysiological biomarkers will be mostly relevant for 1) predicting sensitivity to treatment, and 2) the probability and amount of seizure frequency changes. On the other hand, biomarkers are required that inform on all links between basic pharmacology and clinical outcome.

Biomarkers can be divided into several categories, based on their place in the cascade from low-level determinants of drug effect up to clinical outcome [22]. The currently available biomarkers were recently categorised according to this system [23]. Based on this categorisation, several important gaps in epilepsy biomarkers were identified. Many of the biomarkers found in literature are qualitative, i.e. based on the need to categorise patients into one of several convenient and easy-to-grasp groups such as responders and non-responders. However, for rational polytherapy, biomarkers are required that inform *quantitatively* on aspects such as target occupancy and activation. These types of biomarkers are essential to the estimation of AED sensitivity of the individual patient, corresponding to the EC_{50} in our Poisson models. When biomarkers enable the accurate

estimation of the individual patient's EC_{50} before treatment, or early after initiation, a target maintenance dose can be set early and titrated towards. Conversely, if the EC_{50} is simply too high, a switch may be indicated to an AED that the patient will be more sensitive to. Similarly, such methodologies may be used to prevent the occurrence of side-effects. For the prevention of epileptogenesis, one needs quantitative information on pathophysiological processes occurring in the patient at risk of developing seizures. Assuming anti-epileptogenic efficacy exists for some AEDs, such information, combined with biomarkers on target sensitivity may be used to derive a low but sufficiently bioactive dose to prevent epileptogenesis while minimising the risk of side-effects. At the moment, determining whether a patient's seizures are simply suppressed or their epilepsy has remitted is based on clinical presentation. Some patients will show renewed seizure activity after treatment cessation, resulting in severe risk of harm. Biomarkers on disease status may prove a rational decision tool for the cessation of treatment. The occurrence of seizures and exposure to AEDs can have significant impact on mental ability in children, which may result in worse school performance and stinted development. When biomarkers are available allowing us to predict epileptogenesis, disease progression and sensitivity to AEDs, seizures may be optimally prevented and AED exposure minimised by providing the minimum-required dose and stopping treatment as early as possible.

Based on the methodologies described in this thesis, we may develop clinical trials more robustly; we may perform clinical trial simulations for power calculations, trial population selection (in terms of disease severity), duration of the trial and duration of baseline and treatment periods. Furthermore, we may be able to better investigate whether a drug is an actual anti-epileptic drug (i.e. does it treat the disease?) or an anti-convulsant (i.e. does it suppress seizures?). Although we have used the term anti-epileptic drug throughout this thesis, no results from chapters VII and VIII suggested that lamotrigine has any disease-modifying effects. To accurately answer whether a compound has disease-modifying properties, study designs need to be very carefully considered. Another important question in epilepsy research is whether pharmacodynamic drug-drug interactions exist, and whether these are beneficial (i.e. synergy) or

detrimental (i.e. antagonism) to treatment outcome. Through CTS, we may develop special trials that are sufficiently powered and designed to answer these, and other questions. To be able to do so, it is required to first estimate the parameters of the Poisson model with regard to mono-therapy in treatment-naïve patients. For now, the models provided in chapters VII and VIII showed no interactions between lamotrigine and the other existing AEDs involved in the studies. Whether these findings may be extrapolated to treatment-naïve patients remains to be shown in external validation studies.

Our introduction was named “Pharmacotherapy in paediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go”. This thesis provides signposts that highlight the path towards rational anti-epileptic pharmacotherapy with the help of modelling and simulations. It is our hope that future investigations in paediatric epilepsy will recognise the importance of exposure-response relationships and take into account the methods, and approaches proposed and implemented throughout this thesis. The use of PKPD principles and drug-disease models will lead to rational pharmacotherapy of AEDs in paediatric epilepsy. Our current prescription paradigm needs to evolve. Exposure considerations are important for assessing efficacy and safety. This point was raised by Paracelsus in 1538, and is stated in the adage, the dose makes the poison. Model-based dosing algorithms may make the medicine.

References

1. Egnew TR. Suffering, Meaning, and Healing: Challenges of Contemporary Medicine. 2009;7:170–5.

2. Sillanpää M, Schmidt D. Natural history of treated childhood-onset epilepsy: Prospective, long-term population-based study. Brain. 2006 Mar;129(3):617–24.

3. Schmidt D, Sillanpää M. Evidence-based review on the natural history of the epilepsies. Curr Opin Neurol. 2012 Apr;25(2):159–63.

4. National Institute for Health and Care Excellence. Epilepsies: diagnosis and management (CG137) [Internet]. Available from: http://www.nice.org.uk/guidance/cg137

5. Holford N, Heo Y, Anderson B. A Pharmacokinetic Standard for Babies and Adults. J Pharm Sci. 2013;102(9):2941–52.

6. Ogungbenro K, Aarons L, Groups the Cres& EP. A physiologically based pharmacokinetic model for Valproic acid in adults and children. Eur J Pharm Sci. 2014;63(Oct 15):45–52.

7. Friis ML, Christiansen J, Hvidberg EF. Brain concentrations of carbamazepine and carbamazepine-10,11-epoxide in epileptic patients. Eur J Clin Pharmacol. 1978 Nov 9;14(1):47–51.

8. Rambeck B, Jürgens UH, May TW, Wolfgang Pannek H, Behne F, Ebner A, et al. Comparison of brain extracellular fluid, brain tissue, cerebrospinal fluid, and serum concentrations of antiepileptic drugs measured intraoperatively in patients with intractable epilepsy. Epilepsia. 2006;47(4):681–94.

9. de Lange ECM. The mastermind approach to CNS drug therapy: translational prediction of human brain distribution, target site kinetics, and therapeutic effects. Fluids Barriers CNS. 2013;10(1).

10. Yamamoto Y, Välitalo PA, van den Berg D-J, Hartman R, van den Brink W, Wong YC, et al. A Generic Multi-Compartmental CNS Distribution Model Structure for 9 Drugs Allows Prediction of Human Brain Target Site Concentrations. Pharm Res. 2016;34(2):333–51.

11. Kalamangalam GP, Slater JD, Ferrendelli JA. What You See Is Not What You Get. Believing Patient-Reported Seizure Counts. Arch Neurol. 2007;64(11):1565–6.

12. Jonker DM, Voskuyl RA, Danhof M. Pharmacodynamic Analysis of the Anticonvulsant Effects of Tiagabine and Lamotrigine in Combination in the Rat. Epilepsia. 2004;45(5):424–35.

13. Jonker DM, Visser S a G, van der Graaf PH, Voskuyl R a, Danhof M. Towards a mechanism-based analysis of pharmacodynamic drug-drug interactions in vivo. Pharmacol Ther. 2005 Apr;106(1):1–18.

14. Jonker DM, Voskuyl RA, Danhof M. Synergistic combinations of anticonvulsant agents: what is the evidence from animal experiments? Epilepsia. 2007 Mar;48(3):412–34.

15. Foracchia M, Hooker A, Vicini P, Ruggeri A. POPED, a software for optimal experiment design in population kinetics. Comput Methods Programs Biomed. 2004 Apr;74(1):29–46.

16. Bazzoli C, Retout S, Mentré F. Design evaluation and optimisation in multiple response nonlinear mixed effect models: PFIM 3.0. Comput Methods Programs Biomed. 2010;98(1):55–65.

17. Berg AT, Lin J, Ebrahimi N, Testa FM, Levy SR, Shinnar S. Modeling remission and relapse in pediatric epilepsy: application of a Markov process. Epilepsy Res. 2004 Jun;60(1):31–40.

18. Reckase MD. Multidimensional Item Response Theory. 2009.

19. Ueckert S, Lockwood P, Schwartz P, Riley S. Modeling the Neuropsychiatric Inventory (NPI) - Strengths and Weaknesses of a Multidimensional Item Response Theory Approach. J Pharmacokinet Pharmacodyn. 2015;42(1):S92.

20. Trocóniz IF, Plan EL, Miller R, Karlsson MO. Modelling overdispersion and Markovian features in count data. J Pharmacokinet Pharmacodyn. 2009 Oct;36(5):461–77.

21. Tharayil JJ, Chiang S, Moss R, Stern JM, Theodore WH, Goldenholz DM. A big data approach to the development of mixed-effects models for seizure count data. 2017;835–44.

22. Danhof M, Alvan G, Dahl SG, Kuhlmann J, Paintaud G. Mechanism-based pharmacokinetic-pharmacodynamic modeling-a new classification of biomarkers. Pharm Res. 2005 Sep;22(9):1432–7.

23. van Dijkman SC, Voskuyl RA, de Lange EC. Biomarkers in epilepsy–A modelling perspective. Eur J Pharm Sci. 2017;In press.

CHAPTER 10

Appendices

Nederlandse samenvatting

1. Introductie

Epilepsie is een episodische aandoening met een significante invloed op de kwaliteit van leven [1]. De prevalentie van epilepsie wereldwijd wordt geschat op circa 70 miljoen [2], waarvan circa 25% kind is [3]. Ondanks de beschikbaarheid van ongeveer 20 anti-epileptica (anti-epileptic drugs; AED's) leidt behandeling, met soms wel tot vier verschillende AED's, in slechts twee-derde (60-70%) van de patiënten tot complete aanvalsvrijheid, ook in kinderen [4,5]. Toch, bij patiënten die onvoldoende respons op het geneesmiddel behaalden, bleek in 10-20% van die gevallen nog verbetering van de behandeling door het optimaliseren van de dosering mogelijk [6]. In de gevallen waarbij aanvalsvrijheid wel bereikt wordt is het vaak onduidelijk hoe lang de behandeling met het geneesmiddel voortgezet moet worden omdat de aanvallen vaak terug komen bij het staken van behandeling.

Epilepsie werd reeds in de oudheid beschreven en Hippocratische schrijvers probeerden destijds al mythe van rationele factoren te scheiden [7,8]. Ondanks voortschrijdend inzicht in de farmacologie van de afgelopen decennia blijft de behandeling van epilepsie gebaseerd op empirische methoden die ontstaan zijn uit een gebrek aan farmacologische kennis en simplificatie van het onderliggende probleem [9]. In essentie is de praktijk van farmacotherapie van epilepsie gebaseerd op het behandelen van de symptomen in plaats van het aanpakken van een onderliggende ziekte. Het bepalen van de optimale behandelingskeuze en doseringsregime is nog altijd een proces van *trial-and-error* waarin gestart wordt met een AED zonder

daarbij rekening te houden met het specifieke ziekteproces van de patiënt. Dit AED wordt vervolgens gegeven in lage dosering en deze wordt geleidelijk verhoogd totdat voldoende effect is verkregen of teveel bijwerkingen optreden. Daarbij wordt veelal geen gebruik gemaakt van plasmaconcentratie metingen; er wordt meestal geen initiële doelstelling gesteld in termen van blootstelling (bijvoorbeeld gemiddelde concentraties), ondanks dat dit door sommigen wel aangeraden wordt [10]. Alleen in geval van uitzondering, onder andere wanneer er wordt getwijfeld aan de therapietrouw, wordt de concentratie van het geneesmiddel in het bloed van de individuele patiënt bepaald om te controleren dat de blootstelling in die patiënt binnen een eerder bepaalde therapeutische gebied ligt [11,12]. Dat wil zeggen dat de concentratie hoger is dan de minimaal effectieve concentratie voor een gemiddelde patiënt, maar lager is dan de concentratie waarboven in het algemeen bijwerkingen optreden. Daarbij moet worden opgemerkt dat er voor de meeste AED's weinig bekend is over de variatie in de correlatie tussen effectiviteit, bijwerkingen en concentratie [13]. Door dit empirische proces kan het lang duren voor het juiste AED en de juiste dosering gevonden wordt in de individuele patiënt.

De behandeling van epilepsie in kinderen is des te meer gebaseerd op *trial-and-error*, doordat de meeste farmacologische kennis en ervaring opgedaan wordt in volwassenen en de benodigde kennis in kinderen veelal ontbreekt. Ondanks dat er beweerd wordt dat de effectiviteit van AED's direct vertaalbaar is tussen volwassenen en kinderen [14], moet hierbij gewezen worden naar de vaak grote verschillen in farmacokinetiek [15], waardoor de juiste dosering nog altijd niet zeker is. Daarnaast is het absoluut nog niet bewezen dat bij een vergelijkbare effectiviteit op populatieniveau ook de farmacodynamiek direct vertaalbaar is tussen volwassenen en kinderen, vooral ook met betrekking tot kinderen in de jongere

leeftijdsgroepen waarbij zeer verschillende ziekteprocessen tot hetzelfde fenotype aanval kunnen leiden.

In de afgelopen jaren is een groot aantal farmacokinetische en farmacodynamische modellen voor een verscheidenheid van AED's beschreven in de literatuur. Daarbij is vastgesteld dat een groot aantal factoren zoals gewicht, leeftijd en type aanvallen bepalend kan zijn voor variatie in de blootstelling en effect. Als alternatief voor de empirische benadering wordt in dit proefschrift voorgesteld de behandeling met AED's te optimaliseren op basis van farmacokinetische en farmacodynamische modellen in combinatie met data van de individuele patiënt. Daarbij wordt speciale aandacht besteed aan het optimaliseren van de dosering in kinderen. Het belang van een modelmatige aanpak bij de behandeling met AED's werd vastgesteld in **hoofdstuk 1**. Het onderzoek in sectie 2 van dit proefschrift heeft betrekking op het integreren van kennis over de farmacokinetiek en farmacodynamiek van AED's. Sectie 3 heeft vervolgens betrekking op de vraag hoe deze kennis kan worden benut bij het optimaliseren van de dosering. In sectie 4 wordt ingegaan op de vraag hoe het klinisch onderzoek naar variatie in de farmacokinetiek en farmacodynamiek van AED's kan worden geoptimaliseerd. In sectie 5 worden tenslotte de belangrijkste conclusies geformuleerd en worden aanbevelingen gedaan voor toekomstig onderzoek.

2. Resultaten

Sectie 2 – Integratie van kennis

Farmacologische modellen maken het mogelijk bestaande en nieuwe kennis te integreren. Daardoor is het mogelijk om nieuwe inzichten te verwerven en nieuwe data binnen de reeds bekende context te plaatsen middels een coherente methodologie. Het onderzoek dat is

beschreven in **hoofdstuk 3** heeft betrekking op de beschikbaarheid van (populatie) farmacokinetische en farmacodynamische modellen die variatie in de concentraties en de effecten van AED's beschrijven. Daartoe hebben we systematisch alle publicaties over farmacokinetische en farmacodynamische modellen voor 11 van de belangrijkste AED's verzameld. Op basis van de gevonden artikelen hebben we per AED een paragraaf geschreven waarin de bekende factoren die leiden tot verschillen in farmacokinetiek en farmacodynamiek worden samengevat. Voor de meeste AED's en patiëntengroepen (volwassenen, kinderen) waren er farmacokinetische modellen beschikbaar. Er bleek echter voornamelijk een groot tekort te zijn aan farmacokinetische modellen voor zeer jonge kinderen. Verder was er een algemeen gebrek aan farmacodynamische modellen. Deze lacunes zijn mede een gevolg van het feit dat studies naar AED's vaak alleen in volwassenen uitgevoerd worden en dat, in de weinige studies in kinderen, de verzameling van data beperkt is. Verder is het gebrek aan farmacodynamische modellen voor AED's ook een gevolg van de complexiteit van de meting van de werking van AED's en de modellering van de effecten in de mens, gebaseerd op de analyse van aantallen aanvallen over tijd.

Sectie 3 – Dosering op basis van modellen

Zoals in hoofdstuk 3 van sectie 2 beschreven wordt zijn er vele populatie farmacokinetische modellen beschikbaar voor volwassenen en kinderen (ouder dan vier jaar). In theorie vormen deze modellen, in het bijzonder de informatie over de interindividuele variabiliteit, een basis voor het aanpassen van de dosering, Ondanks de beschikbaarheid worden deze modellen in de praktijk niet gebruikt voor het optimaliseren van de dosering van AED's.

In **hoofdstuk 4** gebruiken we een selectie van farmacokinetische modellen voor het optimaliseren van de dosering door het beloop van de concentraties van AED's voor verscheidene scenario's te simuleren. Gemiddelde concentraties werden daarbij vergeleken met de in de literatuur vastgestelde therapeutische concentratiegebieden [12]. De simulaties laten zien dat van de verscheidenheid van factoren, vooral geneesmiddel interacties, gewicht en leeftijd, bepalend zijn voor variatie in het beloop van de concentraties en derhalve voor het doseren van AED's. Vele mensen met epilepsie gebruiken meer dan één AED [16]. Wanneer een extra AED toegevoegd wordt aan de behandeling blijkt dat de blootstelling aan het initiële middel in veel gevallen zeer sterk verandert. Vaak resulteert dat, als gevolg van enzym inductie, tot veel lagere concentraties waardoor het effect vermindert. Omgekeerd kan enzym inhibitie leiden tot zeer hoge concentraties met daaraan gekoppeld bijwerkingen. Door middel van doseringsalgoritmen op basis van populatie farmacokinetische modellen zou men hiermee rekening kunnen houden en dus stabielere blootstelling kunnen behouden [17].

In **hoofdstuk 5** gebruiken we dezelfde selectie aan farmacokinetische modellen om op basis van covariaat modellen te bepalen in welke mate oorzaken van variabiliteit zoals gewicht en leeftijd van invloed zijn op de blootstelling. Ondanks het corrigeren voor deze factoren zal in de praktijk altijd nog een flink percentage aan variabiliteit overblijven. De mogelijkheid een nauwkeuriger schatting van de klaring van AED's te bereiken op basis van gemeten AED concentraties in het bloed werd onderzocht aan de hand van gesimuleerde scenario's. Hieruit bleek dat *a-priori* bepaalbare factoren slechts in beperkte mate ervoor kunnen zorgen dat een doel concentratie bereikt wordt. Zelfs bij gebruik van 1, 2 of zelfs 3 concentratie bepalingen zal nog enige spreiding in de behaalde concentraties binnen de populatie blijven [18].

Sectie 4 – Optimalisatie van synthese en analyse van wetenschappelijk onderzoek

Farmacokinetische en farmacodynamische modellen stellen onderzoekers in staat tot analyse van complexe data, mede door integratie van eerdere bronnen van informatie. In sectie 4 gebruikten we data van klinische studies naar de farmacokinetiek en effectiviteit van het AED lamotrigine om het belang van een modelmatige analyse als essentieel paradigma binnen de pediatrische klinische farmacologie aan te tonen. In **hoofdstuk 6** gebruikten we bestaande kennis ten aanzien van allometrie, de correlatie tussen gewicht en farmacokinetische parameters, om een farmacokinetisch model voor lamotrigine op te stellen. Lamotrigine concentraties bij patiënten in de leeftijd van 1 maand tot en met 91 jaar werden beschreven. Hierbij bleek dat de verandering in de klaring samenhangt met zowel de leeftijd als het lichaamsgewicht volgens niet-lineaire relaties. Daarnaast werden interacties met carbamazepine, fenytoïne en valproïnezuur gekwantificeerd. Het model vormt een basis voor personalisering van de dosis leidend tot een concentratie in een vooraf gedefinieerd concentratie gebied. Hiermee is dit het eerste model dat een rationele farmacokinetische benadering toelaat voor de dosering van jonge kinderen onder de 4 jaar.

Onderzoek naar de effectiviteit van AED's in kinderen is een complex multifactorieel probleem. Ten eerste is inclusie van voldoende patiënten in een studie beperkt door eisen aan studieopzet onder andere met betrekking tot tijdsduur en mate van blootstelling aan het te onderzoeken middel. Door deze beperkingen is effectiviteit vaak moeilijk aan te tonen door een gebrek aan data. Ten tweede wordt de mogelijkheid tot aantonen van een relatie tussen blootstelling en effectiviteit beperkt door de meest prevalente methodologie van analyse, waarbij data van aanvallen over tijd vaak

gereduceerd wordt tot een simpele binaire variabele, te weten wel of geen respons op het geneesmiddel. Vervolgens wordt de informatie in deze variabele verder gereduceerd door het gemiddelde binnen de studie-arm te nemen. Het gevolg van deze simplificaties is dat veel informatie in de data verloren gaat en dat de relatie tussen AED concentratie en effect vaak niet gekwantificeerd kan worden. In tegenstelling tot deze aanpak is het mogelijk de ruwe aanvalsdata direct te analyseren op basis van maximale waarschijnlijkheidsschatting (maximum likelihood estimation; MLE) en de Poisson distributie, daarbij maximaal gebruik makende van de beschikbare informatie in de data [19–21].

Klinische studie data was beschikbaar voor patiënten met epileptische aanvallen van het tonisch-clonische type (volwassenen) en patiënten met aanvallen van het focale type (volwassenen en kinderen met leeftijd 1-24 maanden). Het in hoofdstuk 6 beschreven farmacokinetische model werd gebruikt om voor de individuele patiënten in deze klinische studies dagelijkse piek-, gemiddelde en dal-concentraties te bepalen. In **hoofdstuk 7** werd een farmacodynamisch model gebouwd gebaseerd op de Poisson statistische distributie. Dit model werd verder aangevuld met Markov eigenschappen (verschil in aanvalsfrequentie tussen opeenvolgende dagen) en een adaptatie voor overdispersie (verschil tussen gemiddelde en variantie van aanvalsfrequentie) van de Poisson distributie [19–21]. Door de data op deze manier te beschrijven werd het mogelijk om het aantal epileptische aanvallen over tijd te beschrijven en in zekere mate te voorspellen. Geneesmiddeleffect en dagelijkse concentratie van lamotrigine bleken aan elkaar gecorreleerd volgens de typische sigmoïde Emax formule [22]. Significante verschillen in de gevoeligheid van de patiënten werden gevonden tussen patiënten met primair focale aanvallen vergeleken met patiënten met primair gegeneraliseerde tonisch-clonische aanvallen. Het gebruik van stochastische differentiaal vergelijkingen

om veranderingen van aanvalsfrequentie over tijd in kaart te brengen liet zien dat in de tijdsspanne van circa twee jaar van de klinische trials geen sprake is van significante ziekteprogressie [23].

In **hoofdstuk 8** werd hetzelfde model toegepast op data in kinderen variërend in leeftijd tussen 1-24 maanden oud met focale aanvallen. Patiënten in deze populatie bleken vooral een hogere basislijn aanvalsfrequentie te hebben, maar ook gevoeliger te zijn voor lamotrigine vergeleken met volwassenen met focale aanvallen. Op basis van dit model werden simulaties uitgevoerd ter evaluatie van de benodigde data om effectiviteit van lamotrigine binnen deze populatie aan te tonen, gebaseerd op de originele methodologie van analyse. Hieruit bleek dat de originele studie slechts een fractie van de patiënten bevatte welke nodig was om tot een positief resultaat te komen. De bevindingen uit deze analyse laten zien dat een modelmatige methodologie gevoeliger is voor het schatten van geneesmiddeleffect bij dit type data en dat een nieuwe evaluatie van de effectiviteit van lamotrigine in deze populatie op zijn plek is.

3. Conclusie

In hoofdstuk 1 schreven we dat de huidige aanpak van anti-epileptische farmacotherapie gebaseerd is op empirische methoden. In het onderzoek dat beschreven is in dit proefschrift hebben we verscheidene stappen ondernomen om een pad te banen richting meer rationele farmacotherapie van AED's. We hebben een bibliotheek en overzicht gecreëerd van farmacokinetische en farmacodynamische modellen voor AED's, wat snelle en effectieve integratie en synthese van kennis op basis van bestaande modellen mogelijk maakt. Gebruik makende van bestaande modellen lieten we zien dat personalisatie van dosering aan de hand van farmacokinetische modellen en plasma concentraties niet alleen mogelijk, maar ook nodig is om te corrigeren voor zowel voorspelbare evenals onvoorspelbare bronnen van variabiliteit. Verder hebben we farmacodynamische modellen opgesteld waarmee, in tegenstelling tot wat vaak beweerd wordt, het mogelijk is de relatie tussen concentratie en effectiviteit van AED's te beschrijven. Met deze modellen wordt het mogelijk om individuele parameters zoals klaring en gevoeligheid voor de AED in de patiënt te bepalen en meer rationele keuzes te maken wat betreft het geneesmiddel en de dosering. Tevens is het mogelijk om nieuwe klinische studies te optimaliseren aan de hand van *optimal design* principes en klinische studie simulaties [24–28]. Onze bevindingen zullen verbeteringen kunnen geven zowel in het opzetten van nieuwe klinische studies als in de dagelijkse praktijk bij de behandeling van patiënten.

Referenties

1. Sajobi TT, Wang M, Ferro MA, Brobbey A, Goodwin S, Speechley KN, et al. Multivariate trajectories across multiple domains of health-related quality of life in children with new-onset epilepsy. Epilepsy Behav. 2017;75:72–8.

2. Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia. 2010 May;51(5):883–90.

3. Cardarelli WJ, Smith BJ. The Burden of Epilepsy to Patients and Payers. Am J Manag Care. 2010;16(12):331–6.

4. Sillanpää M, Schmidt D. Natural history of treated childhood-onset epilepsy: Prospective, long-term population-based study. Brain. 2006 Mar;129(3):617–24.

5. Schmidt D, Sillanpää M. Evidence-based review on the natural history of the epilepsies. Curr Opin Neurol. 2012 Apr;25(2):159–63.

6. Kwan P, Brodie MJ. Epilepsy after the first drug fails: substitution or add-on? Seizure. 2000 Oct;9(7):464–8.

7. Magiorkinis E, Sidiropoulou K, Diamantis A. Hallmarks in the history of epilepsy : Epilepsy in antiquity. Epilepsy Behav. 2009;17(1):103–8.

8. Todman D. Epilepsy in the Graeco-Roman World: Hippocratic Medicine and Asklepian Temple Medicine Compared. J Hist Neurosci. 2008;17(4):435–41.

9. van Dijkman SC, Alvarez-Jimenez R, Danhof M, Della Pasqua O. Pharmacotherapy in pediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go. Expert Opin Drug Metab Toxicol. 2016;12(10):1143–56.

10. Perucca E, Dulac O, Shorvon S, Tomson T. Harnessing the clinical potential of antiepileptic drug therapy: dosage optimisation. CNS Drugs. 2001;15(8):609–21.

11. Neels HM, Sierens AC, Naelaerts K, Scharpé SL, Hatfield GM, Lambert WE. Therapeutic drug monitoring of old and newer anti-epileptic drugs. Clin Chem Lab Med. 2004 Jan;42(11):1228–55.

12. Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser T a, Johannessen SI, et al. Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008 Jul;49(7):1239–76.

13. Patsalos PN, Berry DJ, Bourgeois BFD, Cloyd JC, Glauser T a., Johannessen SI, et al. Antiepileptic drugs - best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia. 2008 Jul;49(7):1239–76.

14. Pellock JM, Carman WJ, Thyagarajan V, Daniels T, Morris DL, D'Cruz O. Efficacy of antiepileptic drugs in adults predicts efficacy in children: a systematic review. Neurology. 2012 Oct 2;79(14):1482–9.

15. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. Clin Pharmacokinet. 2013 Aug;52(8):627–45.

16. Meyer J, Fardo D, Fleming ST, Hopenhayn C, Gokun Y, Ryan M. Generic antiepileptic drug prescribing: a cross-sectional study. Epilepsy Behav. 2013 Jan;26(1):1–6.

17. van Dijkman SC, Rauwé WM, Danhof M, Della Pasqua O. Pharmacokinetic interactions and dosing rationale for antiepileptic drugs in adults and children. Br J Clin Pharmacol. 2017;In press.

18. Dijkman SC Van, Wicha SG, Danhof M, Pasqua OE Della. Individualized Dosing Algorithms and Therapeutic Monitoring for Antiepileptic Drugs. Clin Pharmacol Ther. 2017;(June).

19. Plan E, Maloney A, Trocóniz IF, Karlsson MO. Maximum likelihood estimation methods: performance in count response model's population parameters. Page 2009. 2009;(1).

20. Trocóniz IF, Plan EL, Miller R, Karlsson MO. Modelling overdispersion and Markovian features in count data. J Pharmacokinet Pharmacodyn. 2009 Oct;36(5):461–77.

21. Plan EL. Modeling and simulation of count data. CPT pharmacometrics Syst Pharmacol. 2014;3(August 13):e129.

22. Danhof M, de Lange ECM, Della Pasqua OE, Ploeger B a, Voskuyl R a. Mechanism-based pharmacokinetic-pharmacodynamic (PK-PD) modeling in translational drug research. Trends Pharmacol Sci. 2008 Apr;29(4):186–91.

23. Deng C, Plan EL, Karlsson MO. Approaches for modeling within subject variability in pharmacometric count data analysis: dynamic inter-occasion variability and stochastic differential equations. J Pharmacokinet Pharmacodyn. 2016;43(3):305–14.

24. Roberts JK, Stockmann C, Balch A, Yu T, Ward RM, Spigarelli MG, et al. Optimal design in pediatric pharmacokinetic and pharmacodynamic clinical studies. Pediatr Anesth. 2015;25(3):222–30.

25. Jadhav PR, Kern SE. The Need for Modeling and Simulation to Design Clinical Investigations in Children. J Clin Pharmacol. 2010;50(9):121S–129S.

26. Holford N, Ma SC, Ploeger BA. Clinical trial simulation: a review. Clin Pharmacol Ther. 2010 Aug;88(2):166–82.

27. De Cock RFW, Piana C, Krekels EHJ, Danhof M, Allegaert K, Knibbe CAJ. The role of population PK-PD modelling in paediatric clinical research. Eur J Clin Pharmacol. 2011;67(SUPPL. 1).

28. Chain ASY, Dieleman JP, van Noord C, Hofman A, Stricker BHC, Danhof M, et al. Not-in-trial simulation I: Bridging cardiovascular risk from clinical trials to real-life conditions. Br J Clin Pharmacol. 2013 Dec;76(6):964–72.

Curriculum vitae

Sven van Dijkman was born in Amsterdam, the Netherlands on the 3rd of April 1984. He graduated Bonaventura College in Leiden in 2002 before studying computer science for one year and obtaining a biology certificate. He started his medical studies at Leiden University in 2004, during which he spent 2008-2009 at the Università degli Studi di Roma 'La Sapienza' to study, and research the use of EEG as a biomarker for Alzheimer's disease, as well as the influence of mobile phone emittance on the brain at the department of human physiology, led by Professor Babiloni. In 2010- 2011 he completed his Master's thesis in Medicine on the dose rationale and design of a clinical pilot trial of dexmedetomidine in neonates. Subsequently, in 2011, he began his PhD at the Leiden Academic Centre for Drug Research (LACDR), under the supervision of Professor Meindert Danhof and Professor Oscar Della Pasqua, which resulted in this thesis.

Since 2015, he has contributed to pharmacometric research in collaboration with Professor Mats Karlsson at Uppsala University in Sweden and is currently in clinical rotations to obtain his medical license at the Leiden University Medical Centre.

List of publications

1. van Dijkman SC, de Jager NCB, Rauwé WM, Danhof M, Della-Pasqua O. Impact of age-related factors on the pharmacokinetics of lamotrigine and implications for the dose rationale in epilepsy patients. Accepted for publication in Clin Pharmacokinet, 2017;

2. van Dijkman SC, Rauwé WM, Danhof M, Della Pasqua O. Pharmacokinetic interactions and dosing rationale for antiepileptic drugs in adults and children. Br J Clin Pharmacol. 2017;In press:Aug 16.

3. van Dijkman SC, Wicha SG, Danhof M, Della Pasqua OE. Individualised dosing algorithms and therapeutic monitoring for antiepileptic drugs. Clin Pharmacol Ther. 2017;In press:June 27.

4. Antunes NDJ, van Dijkman SC, Lanchote VL, Wichert-Ana L, Coelho EB, Alexandre Junior V, Takayanagui OM, Tozatto E, van Hasselt JC, Della Pasqua O. Population pharmacokinetics of oxcarbazepine and its metabolite 10-hydroxycarbazepine in healthy subjects. Eur J Pharm Sci. 2017;In press:May 17.

5. van Dijkman SC, Voskuyl RA, de Lange EC. Biomarkers in epilepsy – A modelling perspective. Eur J Pharm Sci. 2017;In press:May 17.

6. De Cock PAJG, van Dijkman SC, DeJaeger A, Willems J, Carlier M, Verstraete AG, Delanghe JR, Robays H, Vande Walle J, Della-Pasqua OE, De Paepe P. Dose optimization of piperacillin/tazobactam in critically ill children. J Antimicrob Chemother. 2017;72(7):2002–11.

7. van Dijkman SC, Alvarez-Jimenez R, Danhof M, Della Pasqua O. Pharmacotherapy in pediatric epilepsy from trial and error to rational drug and dose selection a long way to go. Expert Opin Drug Metab Toxicol. 2016;12(10):1143–56.

8. Babiloni C, Frisoni G, Vecchio F, Lizio R, Pievani M, Geroldi C, Fracassi C, Vernieri F, Ursini F, Rodriguez G, Nobili F, Salinari S, van Dijkman S, Ferri R, Rossini PM. Global Functional Coupling of Resting EEG Rhythms is Abnormal in Mild Cognitive Impairment and Alzheimer's Disease. J Psychophysiol. 2010. p. 224–34.

9. Vecchio F, Babiloni C, Ferreri F, Buffo P, Cibelli G, Curcio G, van Dijkman S, Melgari JM, Giambattistelli F, Rossini PM. Mobile phone emission modulates inter-hemispheric functional coupling of EEG alpha rhythms in elderly compared to young subjects. Clin Neurophysiol. 2010;121(2):163–71.

SVEN VAN DIJKMAN

Sven van Dijkman was born in Amsterdam, the Netherlands on the 3rd of April 1984. He graduated Bonaventura College in Leiden in 2002 before studying computer science for one year and obtaining a biology certificate. He started his medical studies at Leiden University in 2004, during which he spent 2008-2009 at the Università degli Studi di Roma 'La Sapienza' to study, and research the use of EEG as a biomarker for Alzheimer's disease, as well as the influence of mobile phone emittance on the brain at the department of human physiology, led by Professor Babiloni. In 2010-2011 he completed his Master's thesis in Medicine on the dose rationale and design of a clinical pilot trial of dexmedetomidine in neonates. Subsequently, in 2011, he began his PhD at the Leiden Academic Centre for Drug Research (LACDR), under the supervision of Professor Meindert Danhof and Professor Oscar Della Pasqua, which resulted in this thesis.

Since 2015, he has contributed to pharmacometric research in collaboration with Professor Mats Karlsson at Uppsala University in Sweden and is currently in clinical rotations to obtain his medical license at the Leiden University Medical Centre.