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

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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

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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.

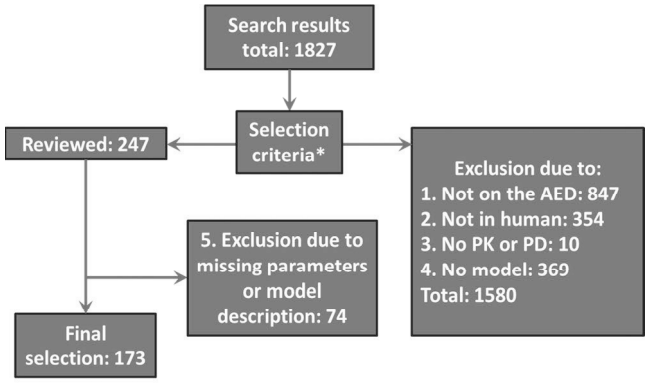

Fig. 1 Diagram of the search strategy including MESH terms used to systematically derive the literature included in this review. *Selection criteria were the description of a human PK, PD or PKPD model in the article.

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.

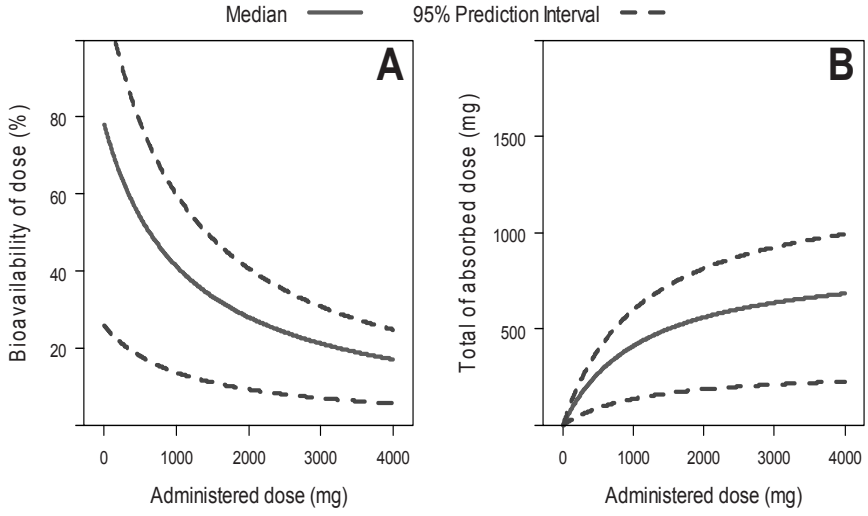

Fig. 2 Relationship between administered gabapentin dose (x-axis both panels) and the absorbed fraction (y-axis panel A) or total absorbed amount (y-axis panel B). Profiles are simulations based on the meta-analysis of Chen [70].

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].

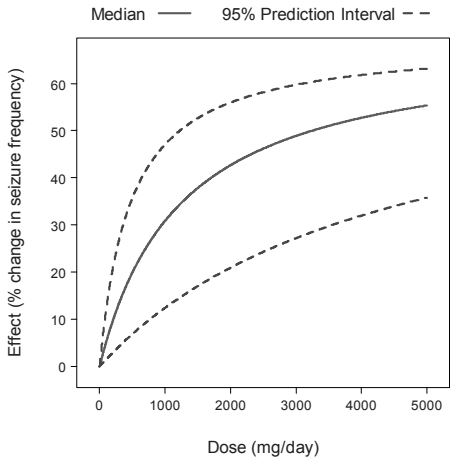

Fig. 3 Relationship between administered LVT dose (x-axis) and effect as percentage of change in seizure frequency compared to baseline (y-axis). Red line: median effect; blue dashed lines: 95% prediction interval of effect. Simulations based on Snoeck et al. [101]

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.

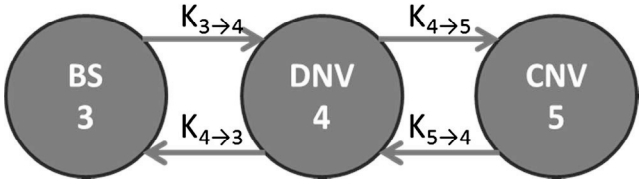

Fig. 4 States and transition rates in the neonatal aEEG Markov model, reproduced with permission from Van Den Broek et al. [125]. BS: burst suppression; DNV: discontinuous normal voltage; CNV: continuous normal voltage. Kx->y: transition rate from state x to state y

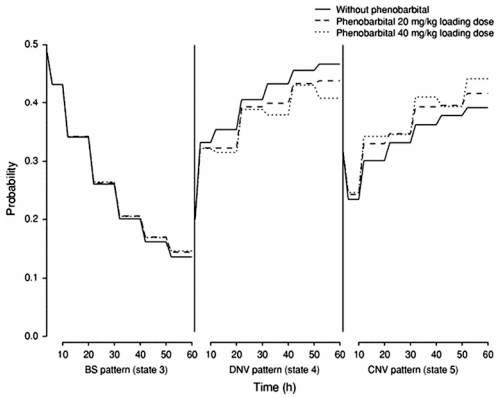

Fig. 5 Probability of a typical neonate showing a burst suppression (state 3, left panel), discontinuous normal voltage (state 4, middle panel) or continuous normal voltage pattern (state 5, right panel) on aEEG evaluation. Probabilities are given for untreated patients (full lines) and patients receiving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

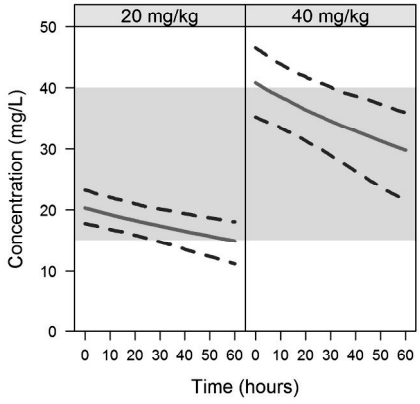

Fig. 6 Pharmacokinetic profiles (median: red solid line; 95% prediction interval: blue dashed lines), based on simulations of 1000 neonates receiving 20 mg/kg PHB (left panel), and 1000 neonates receiving 40 mg/kg PHB (right panel) as a single IV bolus loading dose using the PK model from Van Den Broek 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].

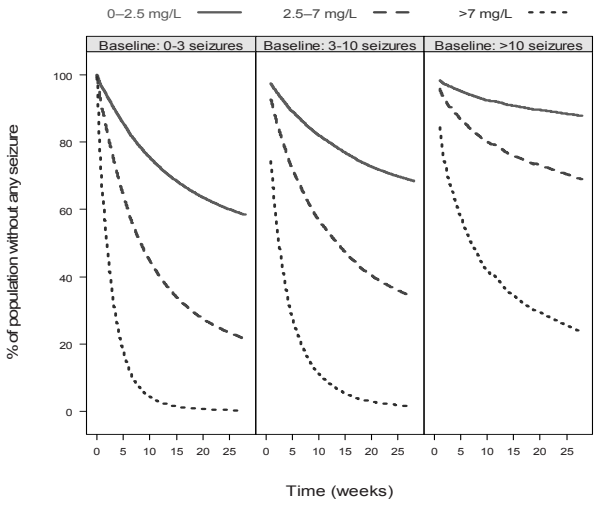

Fig. 7 Median seizure free percentage of the population over time, depending on exposure to TPM at trough (solid line: 0-2.5 mg/L; dashed line: 2.5-7 mg/L; dotted line: above 7 mg/L) and low (left panel), medium (middle panel), or high (right panel) baseline seizure frequency, from a simulation of 1000 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.

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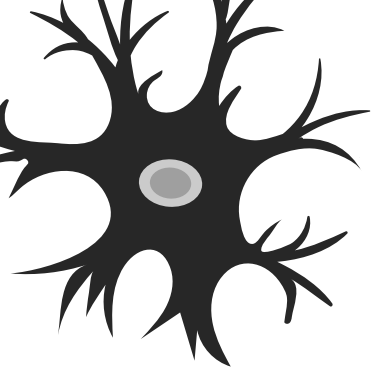

SECTION III

MODEL-BASED DOSING ALGORITHMS