Taylor & Francis
Taylor & Francis Group

Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: http://www.tandfonline.com/loi/iemt20

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

To cite this article: Sven C. van Dijkman, Ricardo Alvarez-Jimenez, Meindert Danhof & Oscar Della Pasqua (2016) Pharmacotherapy in pediatric epilepsy: from trial and error to rational drug and dose selection – a long way to go, Expert Opinion on Drug Metabolism & Toxicology, 12:10, 1143-1156, DOI: 10.1080/17425255.2016.1203900

To link to this article: https://doi.org/10.1080/17425255.2016.1203900

EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY, 2016
VOL. 12, NO. 10, 1143–1156
http://dx.doi.org/10.1080/17425255.2016.1203900

Taylor & Francis
Taylor & Francis Group

REVIEW

OPEN ACCESS

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

Sven C. van Dijkman[a], Ricardo Alvarez-Jimenez[a], Meindert Danhof[a] and Oscar Della Pasqua[b,c]

[a]Division of Pharmacology, Leiden Academic Centre for Drug Research, Leiden, The Netherlands; [b]Clinical Pharmacology and Discovery Medicine, GlaxoSmithKline, Stockley Park, UK; [c]Clinical Pharmacology and Therapeutics, University College London, London, UK

ABSTRACT

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 pediatric 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 modeling and simulation concepts to prevent further delays in the development of personalised treatments for pediatric patients.

ARTICLE HISTORY
Received 3 April 2016
Accepted 14 June 2016
Published online 21 July 2016

KEYWORDS
Antiepileptic drugs; dose rationale; epilepsy; epileptic seizures; modelling and simulation; paediatrics; personalised medicine; pharmacokinetics; pharmacokinetic-pharmacodynamic relationships; translational pharmacology

1. Introduction

Epilepsy is a debilitating syndrome with an estimated 68 million people worldwide affected by it, which places the disease in the seventh 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 nineteenth 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 younger than 15 years of age [4].

Effective treatment and management of epileptic seizures have an important and direct impact on the quality of life of patients, especially those in the pediatric 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 antiepileptic drugs (AEDs) in children [5,6].

1.1. Current drug and dose selection rationale in pediatric epilepsy

Various guidelines exist on the diagnosis, management, and treatment of epilepsies. However, only a few of them have focused on the use of 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 randomized 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 pediatric trials rely on an 'add-on approach', with the enrollment of patients who may have more severe or refractory forms of epilepsy and consequently 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) versus nonresponder. Dichotomization of the response into two categories can be detrimental for the characterization of dose–exposure–response relationships, especially if one considers that pharmacokinetic (PK) data are not collected systematically in efficacy trials.

CONTACT Oscar Della Pasqua o.dellapasqua@ucl.ac.uk Clinical Pharmacology and Therapeutics, BMA House, Tavistock Square, WC1 H9HX London, UK

Supplemental data for this article can be accessed here.

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 intraindividual differences in pharmacokinetics and pharmacodynamics of AEDs need to be taken into account for the personalization of treatment in pediatric epilepsy.
- Whilst the identification of predictive biomarkers remains a challenging endeavor, 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.

This box summarizes key points contained in the article.

Whereas limited understanding of the exposure–response relationships might be mitigated by the clinical requirement for uptitration and downtitration, tapering procedures offer an opportunity to factor in the effect of interindividual PK and pharmacodynamic (PD) variability. Yet, this information is not fully integrated to support treatment personalization. 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 PK and PD [10,11]. Clearly, there is a substantial amount of PK 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 pediatric epilepsy, 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 pediatric patients to AEDs for years after the seizures have remitted [15]. Thus, the combination of unexplained variability in PK, PD, 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. Personalized treatment of epileptic seizures: advancing clinical practice

The ultimate goal of a (personalized) 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 favorable and unfavorable 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 AEDs. In fact, one needs to recognize 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 include all known covariate factors associated with interindividual and intraindividual variability in PK and PD.

Unfortunately, formal assessment of the advantages of dosing algorithms for personalized 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 favorable and unfavorable effects on the symptoms and signs of the disease. Given that the BRB of AEDs is not characterized 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 the 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 for 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 pediatric patients are as effective as possible. We show that some improvement may be achieved in spite of the limitations of the 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 pediatric 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 pediatric epilepsy, personalization of treatment, PK, PD, pharmacogenetics, and biomarkers. Reviews as well as perspective papers were

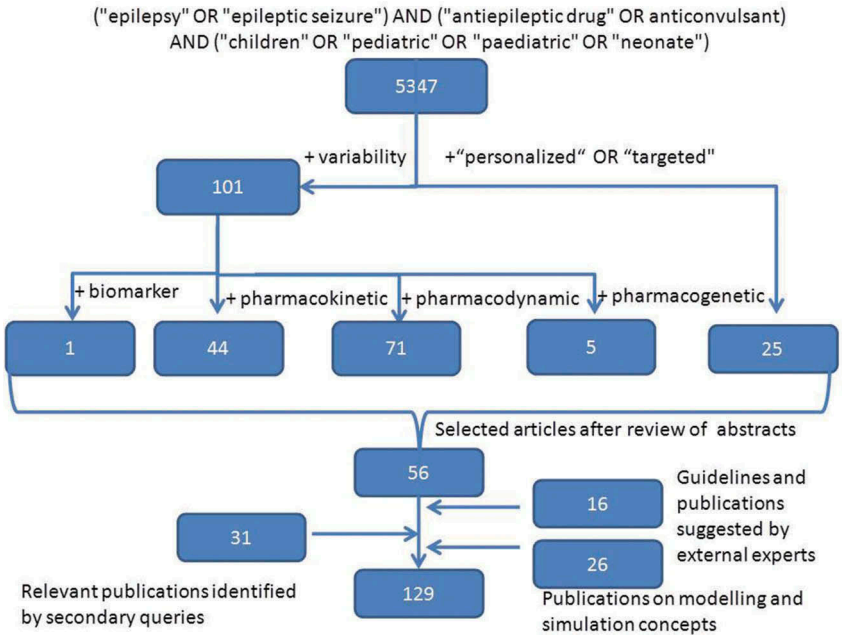

Figure 1. The diagram depicts the search strategy, including MESH terms and keywords used to select the publications included in this review.

included in the analysis if relevant pediatric 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 BRB 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 pediatric clinical pharmacology.

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 individualizing the dose and dosing regimen. Sadly, the notion that plasma levels, even at steady state, may not reflect differences in target exposure or PD is unfamiliar to most prescribing physicians. 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 PK, PD, and in relevant physiological factors for the personalization of treatment.

2.1. Pharmacokinetics

The PK of a drug is determined by up to four physiological processes, namely absorption, distribution, metabolism, and excretion (ADME). Metabolism and excretion are usually summarized by systemic clearance (plasma volume being cleared of the drug per time unit; CL). Summary measures of drug disposition are often limited to the so-called secondary PK parameters such as peak concentration (Cmax), trough concentration (Cmin), and mean steady state (Css or Cavg) concentrations, as well as the area under the concentration versus 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 the absorption rate and volume of distribution, while 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 preterm 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 PK 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.

2.1.1. Drug distribution: differences between plasma and target site concentrations

Plasma protein binding can be an important factor determining differences in PK, with respect to both 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 (e.g. carbamazepine [26], phenytoin [27], and valproate [28]). In these publications, the free plasma concentration of the drug was found to better reflect the

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

Drug	Time to steady state (d)	Half-life (h)	Tentative therapeutic range[a] (μmol/L)	(μg/mL)	Major route of elimination
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 to 8	35–120	8–16	Renal excretion and hydrolysis
Oxcarbazepine	2 to 3	8–15	50–140[b]	12–35	Keto-reduction, then glucuronide conjugation of MHD
Pregabalin	2	6 to 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 to 2	5–8	NA	NA	Renal excretion
Zonisamide	5–12	50–70	45–180	10–38	Glucuronide conjugation, acetylation, oxidation, and renal excretion

[a]The lower limit of the therapeutic range is of limited value, because many patients respond 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.

concentrations of the extracellular space (ECS) 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 comorbidities. 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 as a determinant of the target exposure. Indeed, upregulation 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] analyzed plasma, cerebrospinal fluid (CSF), and 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 extracellular concentrations were lower compared to plasma and CSF, which demonstrates that the assumption of equal concentrations in CSF and ECS in a single, 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 PK problem.

2.1.2. Clearance: influence of genotype, size, and maturation

Interindividual and intraindividual 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 is 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 metabolizing enzymes. Such a variation may lead to significant differences in the 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]. While the impact of 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 makeup of the clearing organ, age-dependent changes also affect the amount of drug that can be cleared. As a child grows, organs develop in terms of both 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 nonlinear. This implies that dosing in milligram per kilogram does not accurately correct for the underlying differences [41]. In fact, unless explicit differences have been identified in the underlying PKPD relationship, dose adjustment in children should aim at achieving comparable exposure or similar PK profile 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 (DDIs) may have a higher impact on clearance than the effect of body size (Figure 2) [42–45].

2.2. Pathophysiology and pharmacodynamics

Every brain is unique in its structure, connectivity, plasticity, and neurotransmitter homeostasis. As a result, wide intraindividual and interindividual variation is observed in the response to CNS-

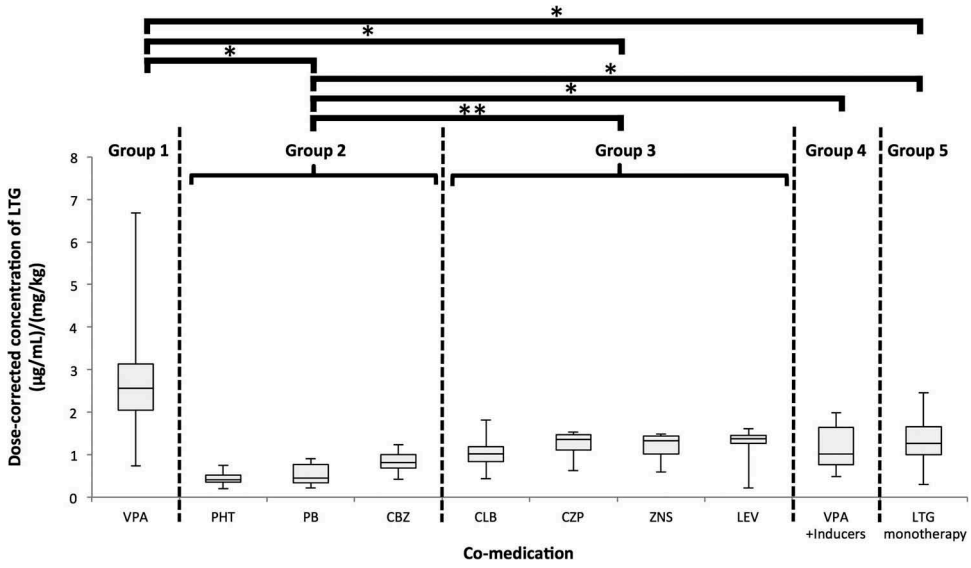

Figure 2. An example of the complex interaction between multiple covariates on the clearance of lamotrigine. In this diagram lamotrigin dose-corrected concentrations (DCC) are stratified by groups: Group 1, samples with VPA co-medication; Group 2, samples with LTG metabolic inducers (inducers) (CBZ, 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 with permission from [42].

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 characterizing such interactions on an individual patient level may be unrealistic in the foreseeable future, personalization 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 et al. 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 characterization of inter-individual differences is the nature of the interaction between drug and receptor or target. From a pharmacological point of view, 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 characterize 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 the 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 AED 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 pediatric 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 newborn has remained unchanged in spite of evidence that 'classic' medications (phenobarbital and phenytoin) are largely ineffective (with more than half of the population being nonresponders 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 newborn 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 pediatric epilepsy, 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 typically occurs between the age of 3 and 14 years and resolves by the age 17 years despite the incidence of cognitive and behavioral disorders [56]. By contrast, Lennox–Gastaut syndrome begins between the age of 1 and 6 years, 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 1 to 2 years [58]. Of the remaining patients, around 60% will respond favorably 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 etiology [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 *ceteris 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 etiology 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 downregulation/upregulation of the target receptors [64–66]. In these circumstances, whereas increases in the dose may offset the effects of downregulation, higher drug exposure may lead to side effects, preventing the achievement of satisfactory response levels. Pharmacoresistance has been reported to affect about 23% of pediatric patients [67], who 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 pediatric population. Here, we focus on the implications of drug-food and DDIs, 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 minimize 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

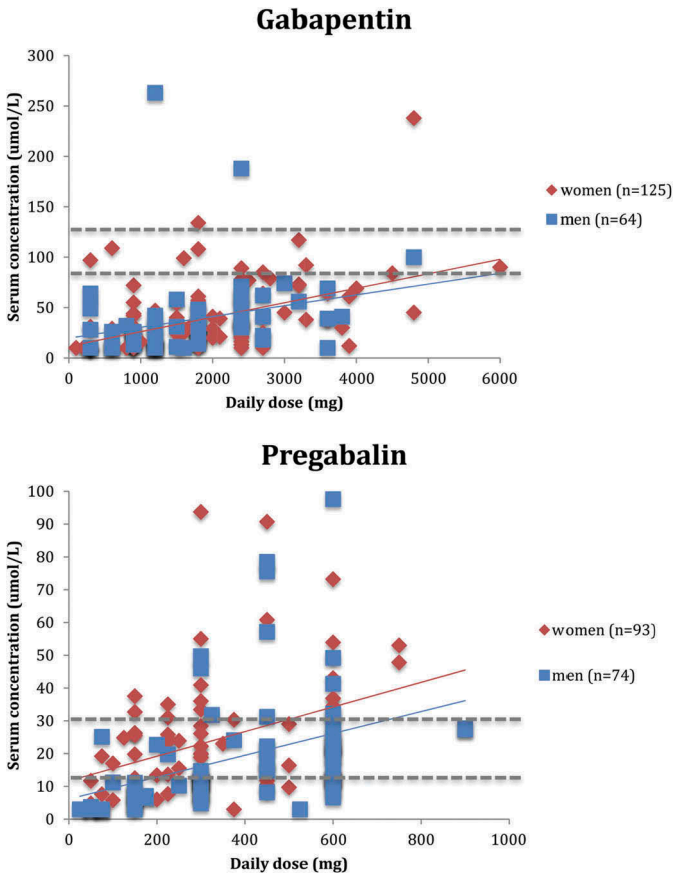

Figure 3. (a) Dose and concentration relationship of (a) gabapentin (n = 189), ref. range (70–120 mmol/L) and (b) pregabalin (n = 167), ref. range (10–30 mmol/L). Factors contributing to variability drug exposure at each dose level includes age, gender and comedication. Reproduced with permission from [71].

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].

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 PD 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, PK DDIs have been identified for many AEDs. Consequently, it may be challenging to disentangle changes in drug effects due to a PD interaction from the effects associated with changes in the exposure to the primary AED. Given safety and ethical constraints, the characterization of possible PD interactions remains difficult in a clinical setting.

3.3. Adherence to treatment

Treatment with AEDs often leads to cognitive, behavioral, 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 on the safety profile of AEDs. This issue is further compounded in pediatric epilepsy, as adherence does not only involve 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 pediatric 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 PD 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 minimize the risk of inaccurate treatment decisions [84].

4. Conclusion

Children are not small adults. In fact, it is known that syndromes in pediatric epilepsy undergo variable progression and variation occurs in the natural course of the disease due to neurodevelopment. Changes in PK, PD, 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 of the large amount of data collected on existing and new AEDs, knowledge is not sufficiently integrated to support the implementation of treatment personalization. Such a lack of integration prevails, despite efforts by health technology assessment organizations 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, these guidelines are not fit-for-purpose, i.e. do not specifically focus on

subgroups in such a way that fully supports the use of personalized treatments in children.

To allow pediatricians 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 modeling [86]. However, to be an effective resource for treatment personalization, biomarkers must be identified that are sensitive to the disease state and progression, so that efficacy and toxicity of drugs can be better characterized in clinical practice. Undoubtedly, the availability of biomarkers would also represent an advancement for the diagnosis of disease, minimizing 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 can 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 dichotomization of the response results in a loss of information, as it does not allow the assessment of the drug effect at the individual patient level. As a result, personalization 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 the 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 of an endpoint which offers more granularity to the evaluation of efficacy, experimental protocol design needs 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 available treatments 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 nonrefractory 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 the 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 modeling and simulation techniques (evidence synthesis), where possible taking into account multiple sources of information (integration). An experiment can then be optimized 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. More specifically with regard to the use of AEDs in pediatric epilepsy, accurate predictions of treatment response may be achieved as a result of systematic integration of data on PK, PD, and disease [93]. Such an approach may have direct implications for the implementation of personalized treatments, including dosing algorithms for pediatric patients.

The use of PKPD and disease models relies on current understanding of the disease and pharmacology. Usually, one endeavors 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 and definitions, which is often referred to as parameterization 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 summarizing drug concentrations only, it is possible to predict the concentration versus time profile following 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 parameterization 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 personalization of the dosing regimen for children [98].

5.2.1. Personalized 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 generalized, absence, etc.) and age (adults, children, etc.), with etiology playing only a minor role. For each syndrome group, multiple lines of treatment are considered. Given the heterogeneity in the etiology 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 modeling can also contribute to another pressing issue, i.e. the nature and

magnitude of the effect of DDIs. It has been proposed that combining AEDs with different mechanisms of action might have a synergistic effect compared to combining those with 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 preemptive 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 of polytherapy, the concept is appealing especially in children if evidence can be gathered of the implications of early interventions with multiple AEDs. However, advancements will only become tangible after sensitive biomarkers have been identified. In conjunction with disease modeling, biomarkers may allow one to discriminate the contribution of each single compound in polytherapy 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 characterize the pros and cons of a given intervention. It is regrettable that no attempts have been made to apply disease modeling concepts to (pharmaco)epidemiological studies. Despite the retrospective nature of such an approach, important insight may be gained about potential predictors and determinants of response in children.

5.2.2. Personalized 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 nonrefractory 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 TDM have not addressed this issue and caused PK considerations to be misinterpreted during clinical decisions regarding 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 the published literature, such data can be used with PK models, including the contribution of covariates to identify suitable titration and maintenance dosing algorithms. Unfortunately, these ranges are generally determined in the adult population, making their relevance for the different epilepsy subtypes in the pediatric population questionable. Nevertheless, the development of dosing algorithms is particularly important for the pediatric 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 DDIs 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 in refractory patients. While one needs to acknowledge the role of disease progression over time in pediatric epilepsy, efforts to ensure comparable exposure to drugs, irrespective of their age or body weight, represent a more robust approach than trial and error.

We also note that despite the considerable number of publications focused on PK modeling of AEDs, most authors deal with this topic in a somewhat technical manner. 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 the implementation of personalized treatment options, with a stronger rationale for drug and dose selection. Dosing regimens could be enhanced by algorithms, which are more efficient than typical titration procedures and TDM. Combined with dried blood spot or saliva analysis techniques, the burden of TDM on the pediatric patient could be minimized [103,104]. The benefits of a model-based approach are illustrated in a simulation study [online supplement 1], using published data as an example of what dosing algorithms can represent to clinical practice in pediatric epilepsy [105]. Clearly, effective development 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

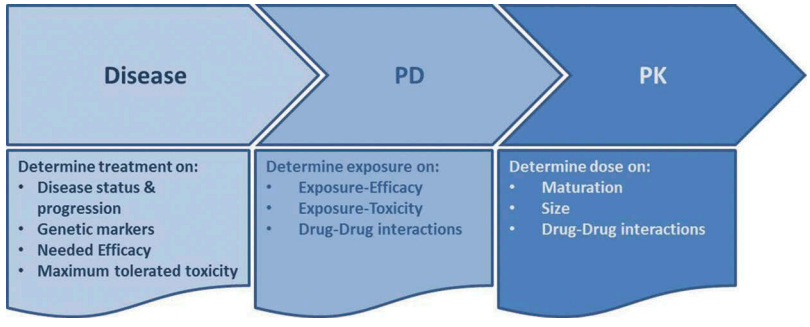

Figure 4. Information on disease processes, PK and PD must be integrated to ensure accurate personalization of AED treatment and rational dose selection in children. Whereas interindividual differences in disease and PD of AEDs can play an important role in treatment selection, understanding of the effect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

protocols. The potential impact to such efforts is highlighted 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 PK 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]. While its implementation is often limited to stand-alone experimental protocols, translational steps can be demonstrated by 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 preclinical *in vitro* (cell lines, tissue, and organs), *in vivo* (mice, rats, dogs, etc.), and clinical data [109,110]. Of interest is the role that extrapolations can have to characterize differences and similarities between pediatric and adult patients [111–113]. As recently defined by the European Medicines Agency, 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].

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 [120]. Clearly, early, sensitive biomarkers and endpoints are essential to accurately characterize interactions between 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 to establish the potential prognostic rather than predictive value of the variables of interest (Figure 5) [114]. 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 and positron emission tomography represent promising opportunities, but their evaluation as biomarkers in epilepsy has not yet been fully explored [115–117] and may be too burdensome to use in pediatric 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 modeling and simulation has led to better trial design, in particular with regard to the dose selection and identification of influential factors on PK, PD, and response [121,122]. Although successful studies have been conducted to derive pediatric dosing based on empirical designs, others failed and possibly could have been successful based on modeling 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 personalized treatment for the pediatric 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.

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

Extrapolation of	From	To	Acceptability	References
Disease mechanisms and PD	Animals	Humans	Unclear	[59,60,109,113,114]
Disease progression and PD with similar etiology	Adults	Children	Possibly acceptable	[5,115]
Disease progression and PD with different etiologies	Adults	Children	Not acceptable	[116]
Pharmacokinetics (allometrically)	Animals	Humans	Possibly acceptable	[117]
Pharmacokinetics (allometrically)	Adults	Children >3 yo	Probably acceptable	[13,118,119]

>3 yo: older than 3 years.

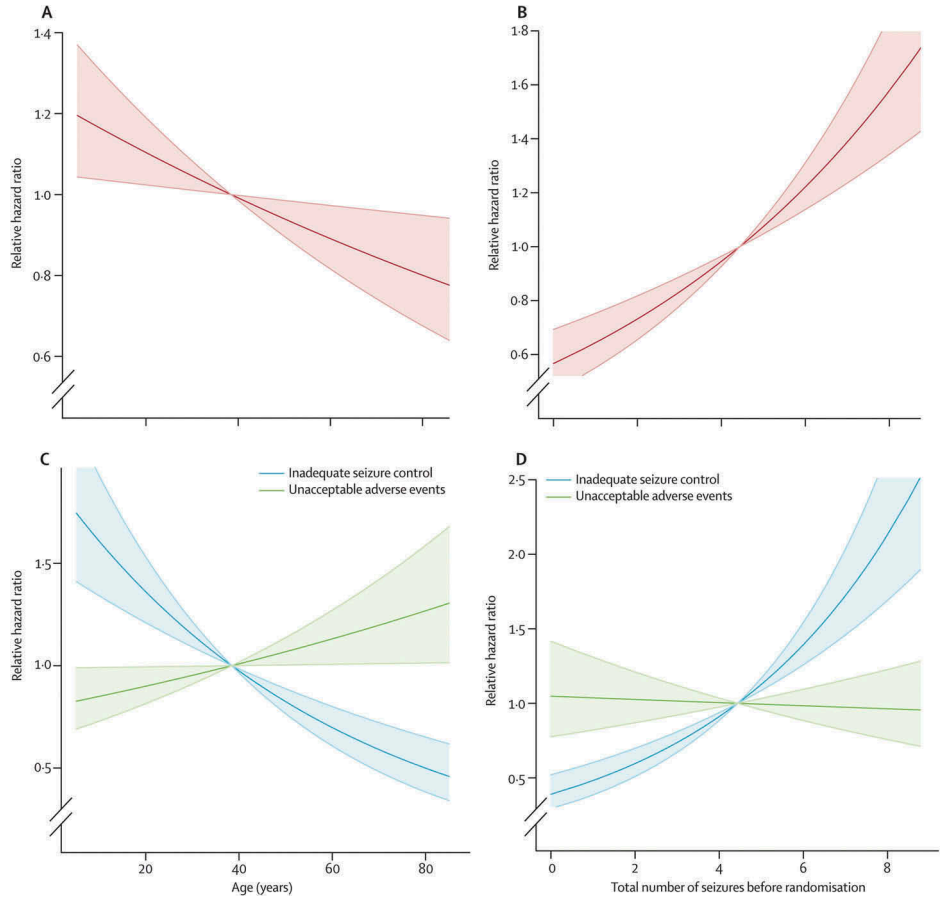

Figure 5. In this example, plots show the relative hazard ratio for age and total number of seizures before randomisation for the time to treatment failure. Hazard ratio estimates with 95% CIs are shown for overall time to treatment failure, for age (a) and total number of seizures (b), and for time 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. Reproduced with permission from [114].

Funding

The research leading to these results 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).

Declaration of interest

SC van Dijkman has been funded by FP7 project (Global Research in Paediatrics (GRIP). O Della Pasqua is a member of GRiP and is also Senior Director Clinical Pharmacology at GlaxoSmithkline. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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;51:883–890.
2. England MJ, Liverman CT, Schultz AM, et al. Epilepsy across the spectrum: promoting health and understanding. In: Institute of Medicine, editor. Committee on the public health dimensions of the epilepsies. 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;19:155–162.
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;79:1482–1489.
• **This review shows the issues and possibilities in extrapolating efficacy of AEDs.**
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: 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 [cited 2016 May 15]. Available from: https://www.kinderformularium.nl/

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;74:525–535.
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;48:303–332.
15. Stagi S, Lasorella S, Piccorossi A, et al. Cessation of epilepsy therapy in children. Expert Rev Neurother. 2016;16:549–559.
16. Park K, Hur Y, Kim 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;9:464–468.
18. Sillanpää M, Schmidt D. Predicting antiepileptic drug response in children with epilepsy. Expert Rev Neurother. 2011;11:877–885; quiz 886.
19. Bellanti F, van Wijk RC, Danhof M, et al. Integration of PKPD relationships into benefit-risk analysis. Br J Clin Pharmacol. 2015;80:979–991.
20. EMA Benefit-Risk Methodology Project Team. Benefit-risk methodology project. Work package 4 report: benefit-risk tools and processes. European Medicines Agency [Internet]. 2012;1–20. [cited 2016 Jun 30]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2012/03/WC500123819.pdf
21. Holmes E, Plumpton C, Duerden M, et al. New advice on switching antiepileptic drugs might be a false economy. BMJ. 2013;347:f7471.
22. Plumpton CO, Yip VLM, Alfirevic A, et al. Cost-effectiveness of screening for HLA-A*31:01 prior to initiation of carbamazepine in epilepsy. Epilepsia. 2015;56:556–563.
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;45:1061–1075.
25. Italiano D, Perucca E. Clinical pharmacokinetics of new-generation antiepileptic drugs at the extremes of age: an update. Clin Pharmacokinet. 2013;52:627–645.

•• **A unique overview of differences in the pharmacokinetics of mostly used antiepileptic drugs across different age groups.**

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. Aarons L, Ahmed IA, Deleu D. 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;33:31–38.
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;47:1253–1284.
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.

•• **A unique study showing the large variation in AED exposure between brain areas, which may explain why plasma concentrations often do not correlate with AED efficacy.**

33. Christensen J, Højskov CS, Dam M, et al. Plasma concentration of topiramate correlates with cerebrospinal fluid concentration. Ther Drug Monit. 2001;23:529–535.
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. ter Heine R, 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. 2014;E6:377–386.
38. Chang Y, Yang L, Zhang M, et al. 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;70:941–946.
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, Della Pasqua O. 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.

• **A thorough explanation of the use of allometric scaling for pharmacokinetic predictions.**

42. Takeuchi T, Natsume J, Kidokoro H, et al. The effects of co-medications on lamotrigine clearance in Japanese children with epilepsy. Brain Dev. 2016; S0387–7604(16):30021–30023.
43. Mikaeloff Y, Rey E, Soufflet C, et al. Topiramate pharmacokinetics in children with epilepsy aged from 6 months to 4 years. Epilepsia. 2004;45:1448–1452.
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;33:1176–1182.
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;99:15089–15094.
50. Meador KJ, Baker GA, 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, et al. 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;33:73–79.
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. Epilepsia. 2014;55(Suppl 4):10–20.
58. Schmidt D, Sillanpää M. Evidence-based review on the natural history of the epilepsies. Curr Opin Neurol. 2012;25:159–163.
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, et al. Functional evaluation of polymorphisms in the human ABCB1 gene and the impact on clinical responses of antiepileptic drugs. Pharmacogenet Genomics. 2008;18:390–402.
- **The idea of using genotyping to proactively find responders to a drug before starting treatment is one that possibly in the future will become common practice.**
64. Weaver DF, Pohlmann-Eden B. Pharmacoresistant epilepsy: unmet needs in solving the puzzle(s). Epilepsia. 2013;54(Suppl 2):80–85.
65. Vega-Hernández A, Felix R. Down-regulation of N-type voltage-activated Ca 2 + channels by gabapentin. Cell Mol Neurobiol. 2002;22:185–190.
66. Byrnes JJ, Miller LG, Greenblatt DJ, et al. Chronic benzodiazepine administration. Chronic benzodiazepine administration. XII. Anticonvulsant cross-tolerance but distinct neurochemical effects of alprazolam and lorazepam. Psychopharmacology (Berl). 1993;111(1):91–95.
67. Berg AT, Rychlik K. The course of childhood-onset epilepsy over the first two decades: a prospective, longitudinal study. Epilepsia. 2015;56(1):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. Epileptic Disord. 2015;17(1):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.
70. Crawford P, Feely M, Guberman A, et al. 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;91:483–488.
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 Y-T, 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;19:126–137.
76. Jonker DM, Voskuyl RA, Danhof M. Synergistic combinations of anticonvulsant agents: what is the evidence from animal experiments? Epilepsia. 2007;48:412–434.
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;23:157–163.
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;24:1055–1068.
80. Stephen LJ, Brodie MJ. Antiepileptic drug monotherapy versus polytherapy: pursuing seizure freedom and tolerability in adults. Curr Opin Neurol. 2012;25:164–172.
81. Zaccara G, Giovannelli F, Giorgi FS, et al. Analysis of nocebo effects of antiepileptic drugs across different conditions. J Neurol. 2016;263(7):1274–1279.
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. J Pediatr Psychol. 2015;40(1):66–74.
84. Smithson WH, Hukins D, Colwell B, et al. Developing a method to identify medicines non-adherence in a community sample of adults with epilepsy. Epilepsy Behav. 2012;24:49–53.
85. De Castro FA, 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;98:104–115.
87. Danhof M, Alvan G, Dahl SG, et al. Mechanism-based pharmacokinetic-pharmacodynamic modeling-a new classification of biomarkers. Pharm Res. 2005;22:1432–1437.
- **A clear explanation of different levels of biomarkers, how they tie in with clinical end points, and what their significance is in drug research.**
88. Engel J, Pitkänen A, Loeb JA, et al. Epilepsy biomarkers. Epilepsia. 2013;54(Suppl 4):61–69.
89. Chen X, de Haas S, de Kam M, et al. 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;89:602–607.
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.
•• **This article highlights clearly the issues in the regulations around clinical trials in epilepsy and how the definition of efficacy and safety limits our understanding of AEDs.**
92. Sheiner LB. Learning versus confirming in clinical drug development. Clin Pharmacol Ther. 1997;61:275–291.
•• **A must read for the modeling novice, the learn-confirm paradigm, and its merits are explained very clearly.**
93. Pennell PB, Peng L, Newport DJ, et al. Lamotrigine in pregnancy: clearance, therapeutic drug monitoring, and seizure frequency. Neurology. 2008 May 27;70(22 Pt 2):2130–2136.
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;50:627–635.
98. Knibbe CAJ, 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. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care [CG137] [Internet]. 2016.

[cited 2016 Jun 30]. Available from: 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;38:570–575.
102. French JA, Faught E. Rational polytherapy. Epilepsia. 2009;50(Suppl 8):63–68.
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;299:211–213.
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;29:186–191.
• **A more technical conceptual review discussing the points to keep in mind when performing model-based translational research.**
108. Donovan MD, Boylan GB, Murray DM, et al. 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;106:256–262.
•• **A unique translational piece of research connecting the dots between target site concentration in muro and in human, and the resulting target occupation based on *in vitro* and *in vivo* experiments.**
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;34:1779–1788.
114. 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. 2012;11:331–340.
115. Ronan L, Alhusaini S, Scanlon C, et al. Widespread cortical morphologic changes in juvenile myoclonic epilepsy: evidence from structural MRI. Epilepsia. 2012;53:651–658.
116. Laufs H, Duncan JS. Electroencephalography/functional MRI in human epilepsy: what it currently can and cannot do. Curr Opin Neurol. 2007;20:417–423.
117. Kim S, Salamon N, Jackson HA, et al. PET imaging in pediatric neuroradiology: current and future applications. Pediatr Radiol. 2010;40:82–96.
118. Wang Y, Bhattaram AV, 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;48:146–156.
119. EFPIA MID3 Workgroup, Marshall SE, Burghaus R, et al. Good practices in model-informed drug discovery and development: practice, application, and documentation. CPT Pharmacometrics Syst Pharmacol. 2016;5(3):93–122.
120. Stefan H, Lopes da Silva FH, Löscher W, et al. Epileptogenesis and rational therapeutic strategies. Acta Neurol Scand. 2006;113:139–155.
121. Piana C, Surh L, Furst-Recktenwald S, et al. Integration of pharmacogenetics and pharmacogenomics in drug development: implications for regulatory and medical decision making in pediatric diseases. J Clin Pharmacol. 2012;52(5):704–716.
122. Cohen AF. Developing drug prototypes: pharmacology replaces safety and tolerability? Nat Rev Drug Discov. 2010;9:856–865.
123. Harnisch L, Shepard T, Pons G, et al. 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.
•• **Provides the reader with good examples of the need for model-based clinical trial design in children.**
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. 2005;9(15):1–157.
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;47:1094–1120.
127. Perucca E. Designing clinical trials to assess antiepileptic drugs as monotherapy: difficulties and solutions. CNS Drugs. 2008;22:917–938.
128. Perucca E. When clinical trials make history: demonstrating efficacy of new antiepileptic drugs as monotherapy. Epilepsia. 2010;51:1933–1935.
129. Della Pasqua O. PKPD and disease modeling: concepts and applications to oncology. In: Kimko HH, Peck CC, editors. Clinical trial simulations: applications and trends. New York (NY): Springer; 2011. p. 281–310.