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

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CHAPTER 1

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

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

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SUMMARY

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

Article highlights

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

1. Introduction

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

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

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

1.1 Current drug and dose selection rationale in paediatric epilepsy

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

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

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

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

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

1.2 Personalised treatment of epileptic seizures: advancing clinical practice

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

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

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

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

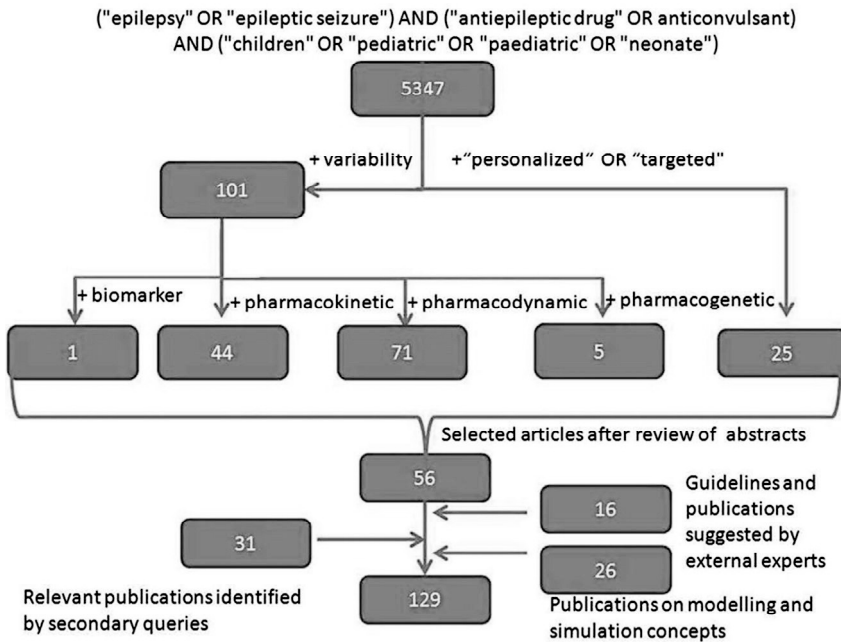


Figure 1. The diagram depicts the search strategy, including MESH terms and keywords used to select the publications included in this review.

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

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

2.1 Pharmacokinetics

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

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

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

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

a The lower limit of the therapeutic range is of limited value, because many patients do well at serum concentrations below this limit.

b Monohydroxy derivative.

c nmol/L.

d ng/mL.

MHD = monohydroxy metabolite; NA = not applicable; NE = not established

2.1.1 Drug distribution: differences between plasma and target site concentrations

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

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

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

2.1.2 Clearance: influence of genotype, size, and maturation

Inter-individual, and intra-individual variability in drug elimination processes mostly results from differences in the availability of the drug at the clearing organ, changes in the clearing capacity due to varying intrinsic clearance, and the size of the organ.

Although it is known that organ perfusion varies with age [34], specific quantitative information regarding hepatic and renal changes are still sparse in some groups of the pediatric population. Consequently, it is unclear to what degree variability in organ perfusion determines the changes in clearance between adults and children. Similarly, very limited information is available regarding AED protein binding in young children and its implications for differences in systemic clearance between adults and children [35,36].

Intrinsic clearance can also be influenced by polymorphisms in genes coding for metabolising enzymes which may lead to significant differences in hepatic clearance of many AEDs [37], with increase or reduction in metabolic capacity resulting in different phenotypes [38]. Similarly, renal clearance can be affected by differences in the expression level of renal transporters [39,40]. Whilst the impact of such genetic differences can be accounted for when defining the dose and dosing regimen, genotyping or phenotyping are not used in standard practice when initiating or changing therapy, and is most probably not encouraged in children. Apart from the differences in the genetic make-up of the clearing organ, age-dependent changes also affect the amount of drug that can be cleared. As a child grows organs develop both in terms of size and metabolic capacity (i.e., enzyme activity). It has been postulated that the influence of increasing size on clearance can, at least in part, be accounted for by adjusting for body weight. However, the relation between size (e.g. body weight) and elimination rate has been demonstrated to be non-linear. This implies that dosing in mg/kg does not accurately correct for the underlying differences [41]. In fact, unless explicit differences have been identified in the underlying pharmacokinetic-pharmacodynamic relationship, dose adjustment in children should aim at achieving comparable exposure or similar PK 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 may have a higher impact on clearance than the effect of body size (Figure 2) [42–45].

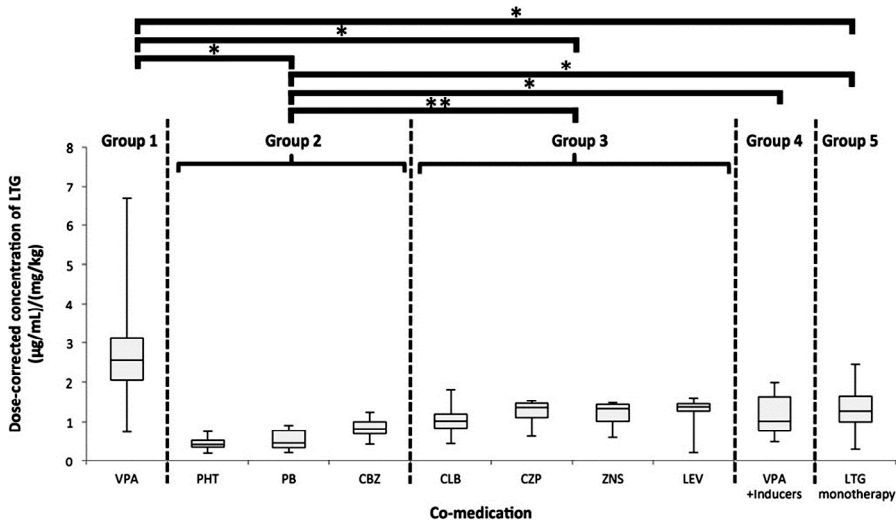


Figure 2. An example of the complex interaction between multiple covariates on the clearance of lamotrigine. In this diagram lamotrigine dose-corrected concentrations (DCC) are stratified by groups: Group 1, samples with VPA co-medication; Group 2, samples with LTG metabolic inducers (inducers) (CBZ,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

2.2 Pathophysiology and pharmacodynamics

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

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

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

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

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

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

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

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

2.2.2 Disease progression and maturation

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

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

2.2.3 Target receptor polymorphisms, density, and adaptation

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

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

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

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

3.1 Drug-food interaction and formulation variability

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

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

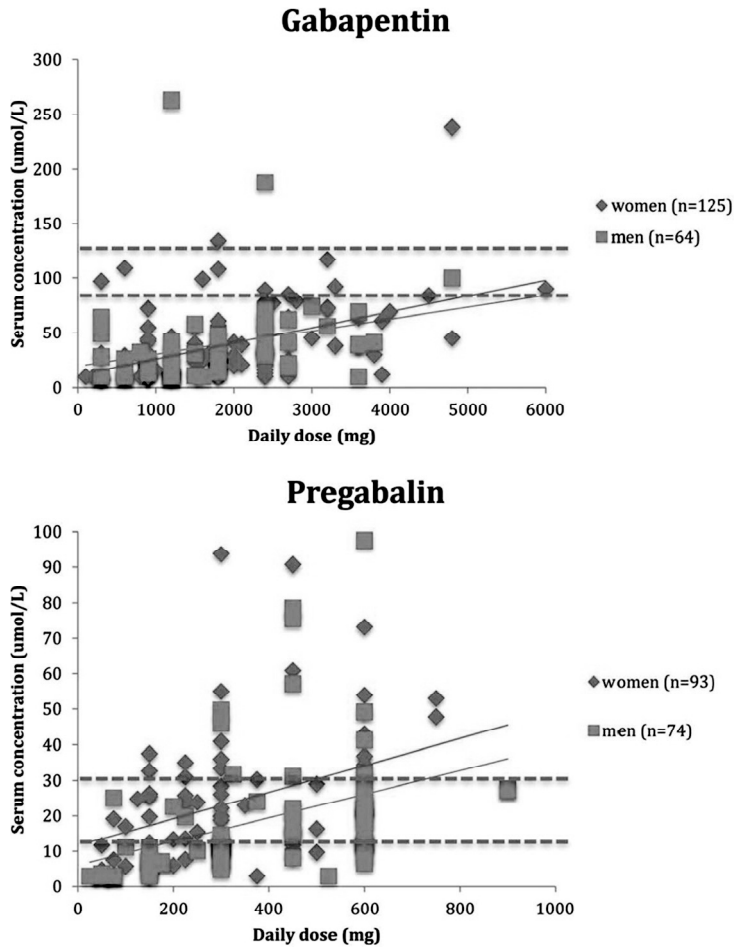


Figure 3. (a) Dose and concentration relationship of (a) gabapentin (n = 189), ref. range (70–120 mmol/L) and (b) pregabalin (n = 167), ref. range (10–30 mmol/L) (with permission from [71]).

3.2. Drug combinations and drug-drug interactions

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

3.2 Adherence to treatment

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

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

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

4. Conclusion

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

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

5. Expert Opinion

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

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

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

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

5.2 Understanding and predicting variability

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

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

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

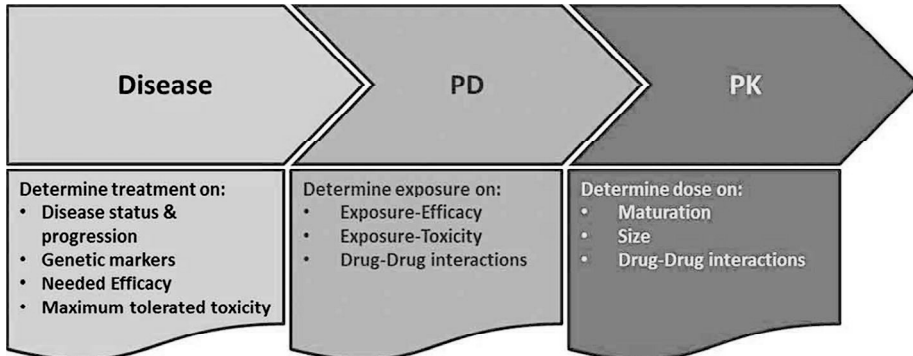


Figure 4. Information on disease processes, pharmacodynamics and pharmacokinetics must be integrated to ensure accurate personalisation of AED treatment and rational dose selection in children. Whereas interindividual differences in disease and pharmacodynamics of AEDs play an important role in treatment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

5.2.1 Personalised treatment

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

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

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

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

5.2.2 Personalised dose and dosing regimen

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

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

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

5.3 Evidence synthesis

5.3.1 Integration of historical and new evidence

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

5.3.2 Extrapolations

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

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

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

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

>3yo: older than 3 years

5.4 Evidence generation

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

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

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

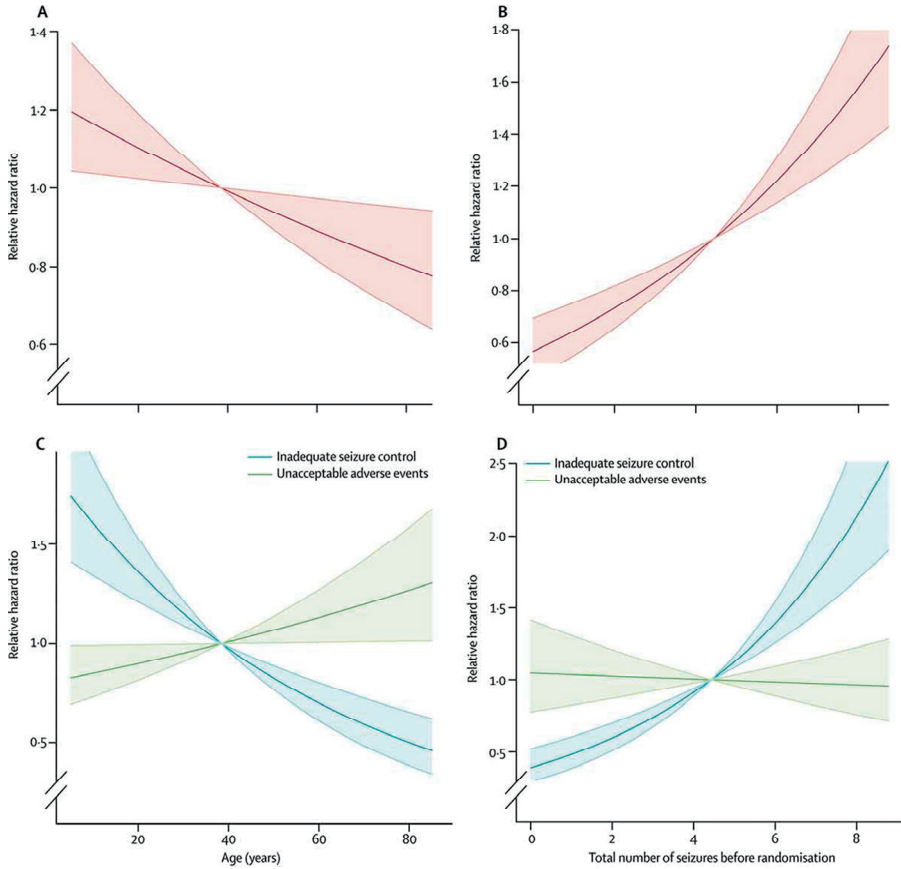


Figure 5. In this example, plots show the relative hazard ratio for age and total number of seizures before randomisation for the time to treatment failure. Hazard ratio estimates with 95% CIs are shown for overall time to treatment failure, for age (A) and total number of seizures (B), and for time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

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