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Dosing strategies for antiepileptic drugs: from a standard dose for all to individualised treatment by implementation of therapeutic drug monitoring

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ABSTRACT – This review focuses on the evolution of approaches to dosing of antiepileptic drugs (AEDs) in clinical practice through history. There has been a shift in the view of treatment of epilepsy, from "one dose fits all patients" in the early days to individualisation of treatment. Over the past 50 years, our knowledge of pharmacological variability of AEDs has markedly increased through implementation of therapeutic drug monitoring (TDM). The use of TDM has demonstrated extensive pharmacokinetic variability for AEDs and a need to individualise the treatment for an optimal outcome. Factors that contribute to pharmacokinetic variability include external factors (including food and comedication), physiological factors (gender, age, and pregnancy), pathological conditions (organ dysfunction), and genetic factors (polymorphisms in metabolising enzymes). Patient groups of children, pregnant women, and the elderly, in whom the most extensive pharmacokinetic changes occur, need special attention and close follow-up of treatment. Patients with complicated and changing combination treatments are also vulnerable. Therapeutic drug monitoring may be particularly helpful in such situations. There are also challenges regarding the use and misuse of therapeutic drug monitoring, such as the use of drug monitoring without a clear indication, misinterpretation of the reference range, and erroneous sampling times.

Key words: lessons from history, antiepileptic drugs, dosing strategies, efficacy, individualisation, pharmacokinetic variability, tolerability, therapeutic drug monitoring

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The present review covers the evolution of how antiepileptic drugs (AEDs) have been used in the treatment of epilepsy from the early 1900s, with emphasis on dose individualisation. There has been a shift in the view of treatment of epilepsy, from "one dose fits all patients" to individualisation of treatment by implementation of therapeutic drug monitoring (TDM) in order to optimise efficacy and tolerability. This review is restricted to individualised dosing of AEDs. Other aspects of individualisation, such as when to treat and with which drug, are not covered. The concepts and definitions related to the use of TDM in clinical practice are discussed with examples. Challenges regarding use and misuse of TDM, as well as a lack of clinical studies, are also discussed.

One of the founders of modern pharmacotherapy, Sir William Osler, stated in 1903 that "Variability is the law of life, and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under abnormal conditions which we know as disease" (Lesko and Schmidt, 2012). The history of AEDs has confirmed this early observation and demonstrated that pharmacological variability is important for understanding how patients react differently. Pharmacological variability implies variability in pharmacodynamic and pharmacokinetic properties, including genetic variability that may affect both.

The purpose of the present review is to give a historical overview of dosing strategies of AEDs from the early beginning, how AEDs are used today to provide the individual patient with an optimal treatment, and future aspects, specifically related to the role of TDM.

Search criteria and literature review

This review is mainly based on published articles identified by searches in PubMed and Google Scholar from November 2015 to August 2016, in addition to the authors' files. Selected peer-reviewed publications with emphasis on dosing strategies and pharmacological variability of AEDs in recognised international journals in English were included. Primary sources were preferred and selected, but review articles giving a broad and updated overview were also included. Non-English articles, case reports, and clinical studies with methodological and clinical limitations were excluded.

The following search terms were used:

– *All antiepileptic drugs:* brivaracetam, carbamazepine, clobazam, clonazepam, eslicarbazepine acetate, ethosuximide, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, retigabine, rufinamide, stiripentol, sultiame, tiagabine, topiramate, valproic acid, vigabatrin, and zonisamide.

– *Other search terms:* absorption, adverse drug effects, analytical procedures, clinical study, distribution, efficacy, elimination, excretion, formulation, generic substitution, metabolism, pharmacokinetics, pharmacology, pharmacogenetics, safety, special populations, surveillance, therapeutic drug monitoring, teratogenicity, tolerability.

The past: the early era of antiepileptic drugs

The first drug treatment for epilepsy was potassium bromide, introduced as early as 1857 and prescribed in standard doses.

In 1912, phenobarbital was approved for use against epilepsy, prompted by Alfred Hauptmann's studies of this hypnotic agent in patients with severe epilepsy, and when bromide was not effective (Yasiry and Shorvon, 2012). Doses of up to 300 mg/day were used. Today, phenobarbital, listed by the WHO as an essential drug, is still used around the world, though in lower doses.

In 1937, phenytoin was the first drug to be approved with known antiseizure activity, based on animal models. During a number of years after phenytoin's introduction, it was prescribed in many countries as duotherapy with phenobarbital. A daily dose of 300 mg phenytoin and 100 mg phenobarbital, often as fixed combination tablets, was "standard" treatment until the introduction of drug level monitoring during the early 1960s and carbamazepine and valproic acid later on, in around 1980 (Løyning, 1983).

Dosing strategies: assessing efficacy and tolerability in relation to serum concentration measurements

Buchthal and co-workers were the first to publish studies on serum concentrations of phenytoin and phenobarbital and their relation to clinical effects (Buchthal and Svensmark, 1960), findings inspiring further pharmacokinetic studies on AEDs (Kutt *et al.*, 1964). This resulted in a series of books about AEDs starting with *Antiepileptic Drugs* by Woodbury *et al.* (1972). A series of workshops, known as WODADIBOFs (Workshop on the Determination of Antiepileptic Drugs in Body Fluids), took place between 1972 and 1979 (Meijer *et al.*, 1973) that established a multidisciplinary collaboration between pharmacologists, pharmacists, toxicologists, neurologists, and paediatricians. It was anticipated that new information concerning the relationship of serum concentrations to seizure control and toxicity would improve utilisation of AEDs.

From the 1970s, it was possible to measure serum concentrations of AEDs in routine practice in many laboratories. The fact that phenytoin, with the knowledge of its saturation kinetics (Johannessen and Strandjord, 1972; Richens, 1975a), was one of the most commonly used AEDs at that time contributed to rapid establishment of TDM in routine practice. Pronounced pharmacokinetic variability was demonstrated (Johannessen and Strandjord, 1972; Richens, 1975a), but this is not only seen with AEDs.

Further reasons for the rapid establishment of TDM in the treatment of epilepsy are related to the nature of the condition and its treatment. Treatment is prophylactic and symptoms of the disease (*i.e.* seizures) occur with irregular and unpredictable intervals. There are no reliable surrogate markers of effect. At the same time, a therapeutic failure can have drastic consequences for the patient. For these reasons, it is particularly difficult to individualise the AED dose based on clinical response alone.

The significant challenges in epilepsy treatment were clearly highlighted in a comparison between dosing regimens before the introduction of TDM for phenytoin versus warfarin, a drug used for other prophylactic purposes, but for which intermediate measures of efficacy are available (Koch-Weser, 1981). Out of 200 patients on phenytoin, 180 were given 300 mg daily as a standard dose, but when serum concentrations of phenytoin were measured they ranged from 0 to 50 mg/l. Less than 30% of the patients had concentrations within the recommended range, suboptimal concentrations were present in 60%, and potential toxic concentrations in 11% of the patients. In contrast, with warfarin, for which the International Normalised Ratio (INR) could be used as a pharmacodynamic biomarker to guide dosing, the doses varied from less than 2 mg to more than 11 mg daily. Similarly, with the antihypertensive drug guanethidine, for which dose requirements were guided by the patients' blood pressure, the doses varied from <10 mg to >100 mg daily (Koch-Weser, 1981).

The early studies of routine TDM data showed pharmacokinetic variability of phenytoin and phenobarbital, as well as carbamazepine and valproic acid, and the impact of comedication, along with the relationship between serum drug concentrations and clinical effect and tolerability (Johannessen and Strandjord, 1972; Strandjord and Johannessen, 1972, 1980; Lund, 1974; Eichelbaum *et al*., 1976; Henriksen and Johannessen, 1982; Tomson *et al*., 1984; Schmidt and Haenel, 1984; Schmidt *et al*., 1986). This further supported a more general use of TDM for the treatment of epilepsy.

The development of methods to measure serum drug concentrations thus made it possible to study relationships between drug dosage, serum concentrations, and clinical effect. It was soon realised that an optimal clinical effect was often seen within a certain range of serum concentration below which a suboptimal effect was more common, while concentrations above the range were more often associated with side effects (Shorvon *et al*., 1978; Strandjord and Johannessen, 1980; Schmidt and Haenel, 1984; Schmidt *et al*., 1986). Thus, it became apparent that variability in treatment response observed between patients could, to a large extent, be explained by the extensive pharmacokinetic variability that was revealed, highlighting the need to individualise dosing (*e.g.* Koch-Weser, 1981).

Quality assurance of serum concentration measurements

Successful use of serum concentration measurements in patient management relies on simple, accurate, reproducible, and preferably inexpensive, analytical assays. Soon after the introduction of TDM, it was recognised that quality control programmes of drug measurements were needed due to a great variation in analytical results in the early years (Pippenger *et al*., 1978). The first quality control schemes for AED measurements were established in 1972 with later follow-ups (Richens, 1975b; Wilson *et al*., 1989; Williams *et al*., 2003).

The present: 50 years of evolution of knowledge of pharmacological variability

A number of new AEDs have become available during the past 50 years, and the knowledge of variability between patients or within the same patients treated with one AED, or combinations of several AEDs, has evolved. New challenges in dosing of AEDs include the wide range of combinations of AEDs available, a large number of possible pharmacokinetic drug interactions, and changes in pharmacokinetics due to physiological changes in various patient groups.

Implementation of therapeutic drug monitoring

The TDM concept rests on the assumption that clinical effects correlate better with drug concentrations than with dose. TDM has become of particular value in the treatment of epilepsy since it is difficult to determine the optimal dose on clinical grounds alone (Koch-Weser, 1981; Patsalos *et al*., 2008), as discussed above. The aim of TDM is to adjust for pharmacokinetic variability in order to optimise drug therapy in the individual patient (*figure 1*). Proposed indications for TDM of AEDs are summarised in *table 1* and pharmacokinetic characteristics of AEDs in *table 2*.

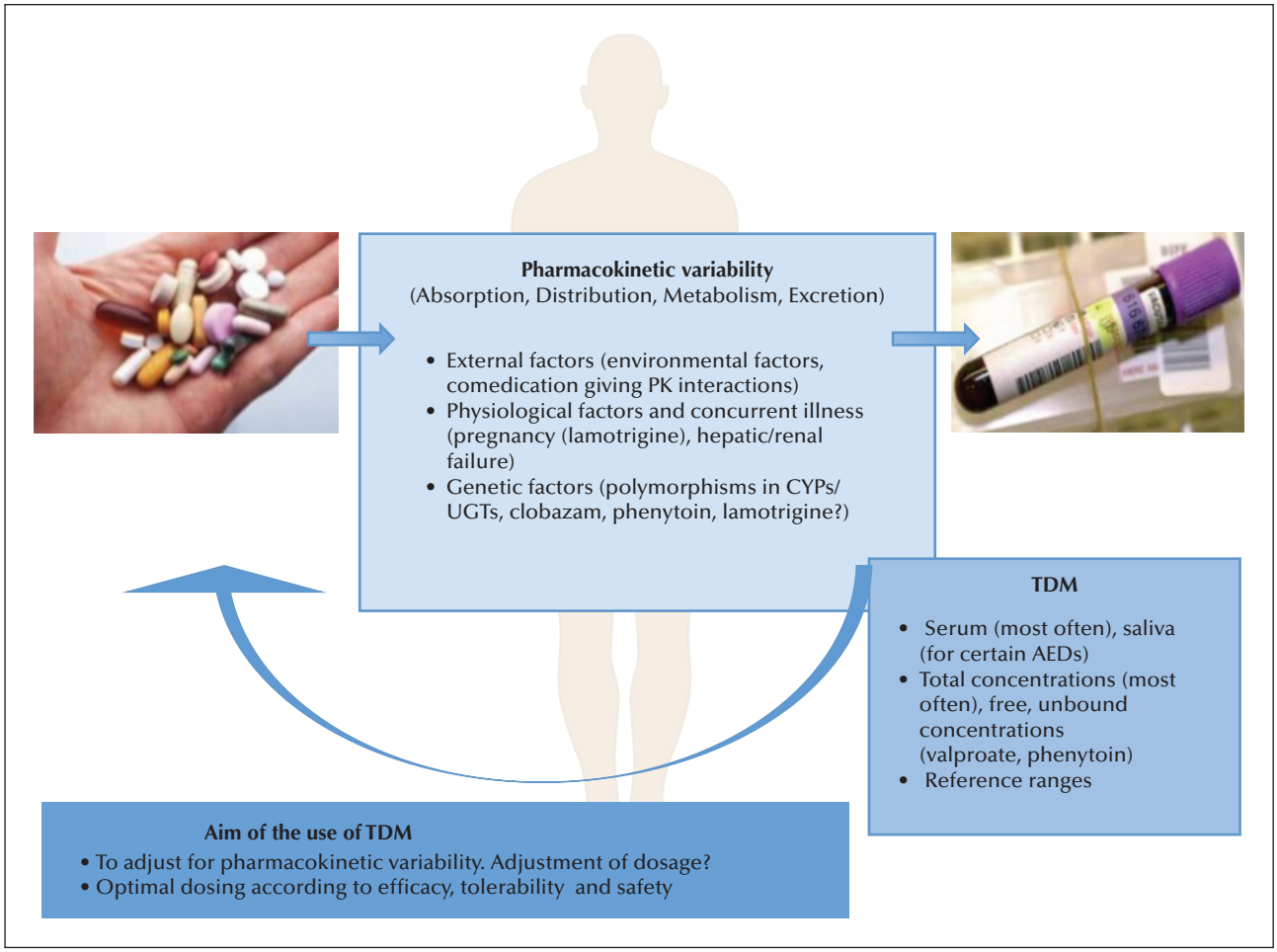

Figure 1. Dosing of antiepileptic drugs, reasons for pharmacokinetic variability, and implementation of therapeutic drug monitoring (TDM) in the optimisation of treatment outcome. PK: pharmacokinetic; CYP: cytochrome P450; UGT: uridine glucuronosyl transferase.

From the concept of therapeutic ranges to individual reference concentrations

In 1993, the International League Against Epilepsy (ILAE) issued its first guidelines for TDM of AEDs (Commission on Antiepileptic Drugs, 1993). This was extensively revised and updated recommendations were published in 2008 as a position paper from the ILAE: *Antiepileptic drugs-best practice guidelines for therapeutic drug monitoring* (Patsalos *et al.*, 2008).

Terminology and definitions

The ILAE position paper recommends the use of two different terms to define drug concentration ranges in relation to their clinical effects (Patsalos *et al.*, 2008).

A *reference range* is defined as a range of drug concentrations quoted by a laboratory with a lower limit for therapeutic response and an upper limit above which toxicity is more likely to occur.

A *therapeutic range* is defined as the range of drug concentrations associated with the optimal response in a certain patient and may vary between patients. This individual therapeutic concentration is considered a better guide to individualisation than reference ranges (Patsalos *et al.*, 2008).

Reference ranges

Most of the older AEDs have a more or less well-defined reference range of steady-state serum concentrations (Tomson and Johannessen, 2000; Johannessen *et al.*, 2003) with a high probability of seizure control and low risk of toxicity, but this must not be strictly interpreted. In less severe epilepsy, seizure control may frequently be attained at concentrations below the reference range (Lund, 1974; Shorvon *et al.*, 1980; Strandjord and Johannessen, 1980; Beardsley *et al.*, 1983; Perucca, 2000). The dose should then not be increased in order to reach suggested "therapeutic" serum concentrations. On the other hand, some patients with severe epilepsy require concentrations above the reference range in order to have optimal

Table 1. Therapeutic drug monitoring (TDM): practical recommendations.

Indications for TDM
After initiation of drug therapy and when preliminary assessment of effect is possible, to establish an individual therapeutic concentration After a dose change. Especially important for AEDs with non-linear pharmacokinetics In special patient populations (children, pregnant women, elderly, comorbidity) Adverse effects, intoxications Therapeutic failure Suspected/expected pharmacokinetic interactions Special pathological situations (renal failure, hepatic failure, *etc.*) Suspicion of poor adherence Change of drug formulation In emergency situations or status epilepticus
What to measure?
Serum or plasma concentrations at steady-state at a standard blood sampling time, or during the day if concentration-related side effects are suspected Free/unbound concentrations in certain cases only (for highly bound AEDs, >90% protein bound) Saliva sampling. Only when unbound concentrations are needed and when blood sampling is not possible Measure with standardisation of blood/saliva sampling time and drug fasting in the morning, to have comparable measurements and a reference value
How to measure?
Chromatographic methods (HPLC, UPLC, UV/MS-detection)* Immunological methods (various immunoassays) A quality assurance programme is essential

*HPLC: high performance liquid chromatography; UPLC: ultra performance liquid chromatography; UV: ultraviolet; MS: mass spectrum.

response. Patients may also experience adverse effects with serum concentrations within the reference range. The optimal serum concentrations may also differ with regards to seizure type. The dose should therefore be adjusted to an optimal serum concentration for the individual patient.

Individual therapeutic concentrations

This is defined as the serum concentration in which the individual patient shows the optimal response. It can be achieved by adjusting the dosage on clinical grounds, whereafter serum concentrations are measured over time (Perucca, 2000). A period without seizures is not necessarily the same as a period of seizure control, as the occurrence of seizures may be unpredictable. The individual therapeutic concentration is useful for subsequent management. It can be used to identify causes of intercurrent events leading to seizure recurrence or toxicity (*e.g.* due to poor adherence or a drug interaction). The concept of individual therapeutic concentrations may be applied to AEDs regardless of the existence of a well-defined reference range (Perucca, 2000).

Reasons for pharmacokinetic variability

Most AEDs are metabolised in the liver and this process is susceptible to influence from various individual host factors, including genetics, age, physiological state, and hepatic failure. Also, concomitant use of drugs with enzyme inducing or inhibiting properties contributes to their pharmacokinetic variability. This variability may be detected and controlled for by measurement of serum concentrations (*figure 1*).

External factors

External factors affecting the pharmacokinetics include environmental factors, such as cigarette smoking, food, and drink. Hepatic enzymes, such as phase I cytochrome P-450 (CYP), more specifically CYP3A4, may be inhibited by intake of grapefruit juice. Smoking may induce certain CYPs (CYP1A2) and phase II uridine glucuronosyltransferases (UGTs) (UGT1A4). Comedication with AEDs or other drugs is the most important external factor since many AEDs have a pronounced potential to cause pharmacokinetic interactions, as there are both strong enzyme inhibitors (valproic acid, stiripentol, and felbamate) and inducers (carbamazepine, phenytoin, and phenobarbital), as well

Table 2. Antiepileptic drugs (AEDs): pharmacokinetic properties and variability.

AED	Bioavailability (%)	T-max (hours)	Protein binding (%)	Volume of distribution (l/kg)	Enzymes involved in metabolism	Half life (hours)	Drugs inducing metabolism	Drugs inhibiting metabolism	Factors contributing to pharmacokinetic variability (PK) among patients
Brivaracetam	100	0.25-3	17.5	0.5	CYP 2C19	9	AED inducers	Rifampicin	CYP 2C19 poor metabolisers One of the newest AEDs, incomplete knowledge of PK variability
Carbamazepine	75-85	2-9	70-80	0.9-1.4	CYP 1A2, 2C8, 3A4	12-20	AED inducers, rifampicin, St. John's wort	AED inhibitors, a number on non-AEDs, antibiotics, cimetidine, antidepressants, haloperidol	Food slows absorption Autoinduction occurs Strong enzyme inducing properties
Clobazam	100	1-3	85	1	CYP 3A4, 2C19	10-30	AED inducers	Oxcarbazepine, eslicarbazepine, stiripentol, felbamate, sultiame	Food slows absorption Active metabolite (desmethyl-clobazam) CYP 2C19 poor metabolisers Affected by enzyme inducers and inhibitors
Clonazepam	100	1-4	85	1.5-4.4	CYP 3A4	17-56	AED inducers	Not identified	
Diazepam	100	0.5-1.5	98	1-2	CYP 2B, 2E1, 3A4	24-48	AED inducers	Valproic acid, cimetidine, disulfiram, omeprazol	Age-dependent decrease in CYP-activity

Table 2. (*Continued*)

AED	Bioavailability (%)	T-max (hours)	Protein binding (%)	Volume of distribution (l/kg)	Enzymes involved in metabolism	Half life (hours)	Drugs inducing metabolism	Drugs inhibiting metabolism	Factors contributing to pharmacokinetic variability (PK) among patients
Eslicarbazepine acetate*	Prodrug, active metabolite ≈100	2-3	40	2.7	Esterases, UGTs?	20-24	AED inducers	Not identified	One of the newest AEDs, incomplete knowledge of PK variability
Ethosuximide	90-95	1-4	0	0.62-0.65	CYP 2B, 2E1, 3A4	40-60	AED inducers, rifampicin	Valproic acid, isoniazid, ritonavir	
Felbamate	>90	2-6	25	0.76	CYP 3A4, 2E1	16-22	AED inducers	Valproic acid	strong enzyme inhibitor
Gabapentin	Dose-limited, 40-100	2-3	0	0.9	No	5-9	Not identified	Not identified	Dose-dependent absorption, variability in capacity of L-transport system and variable bioavailability. Food slows absorption Renal excretion only route of elimination, and thus ↓ dose in patients with renal impairment
Lacosamide	100	0.5-4	15	0.6	CYP2C19, 2C9, 3A4?	≈13	AED inducers	Not identified	One of the newest AEDs, incomplete knowledge of PK variability CYP 2C19 poor metabolisers
Lamotrigine	100	1-3	55	1.2	UGT 1A4, 2B7	15-35	AED inducers, eslicarbazepine acetate, acetaminophen, olanzapine, rifampicin, ritonavir, OCs	Valproic acid, sertraline	Food slows absorption ↑CL during pregnancy, extensive variability between patients Affected by enzyme inducers and inhibitors and OCs

Table 2. (*Continued*)

AED	Bioavailability (%)	T-max (hours)	Protein binding (%)	Volume of distribution (l/kg)	Enzymes involved in metabolism	Half life (hours)	Drugs inducing metabolism	Drugs inhibiting metabolism	Factors contributing to pharmacokinetic variability (PK) among patients
Levetiracetam	≈100	1	0	0.5-0.7	Type B esterase	6-8	Not identified	Not identified	Food slows absorption ↑CL during pregnancy
Oxcarbazepine	100	3-5	40	0.75	Arylketone reductase, UGTs	12	AED inducers, verapamil, OCs	Viloxazine	↑CL during pregnancy
Phenobarbital	100	0.5-4	50-60	0.54-0.73	CYP 2E1, 2C19	73-139	Not identified	AED inhibitors, dicumarol, propxyphene	Food slows absorption
Phenytoin	≈100	1-3	90	0.7	CYP 2C9, 2C19	22-40	AED inducers, a number of non-AEDs, acyclovir, carboplatin, cisplatin, methotrexate, rifampicin, St. John's wort	AED inhibitors, clobazapm, a number of non-AEDs, antibiotics, antidepressants, neuroleptics, isoniazid, dicumarol, propxyphene	Food slows absorption Saturation kinetics, half-life dependent on dose Displacement of protein binding with other highly protein-bound drugs Pharmacogenetic variability in CYP2C)/19
Perampanel	≈100	0.5-1.5	96	77	CYP 3A4	70-110	AED inducers	Not identi-fied	AED inducers increase CL >2-3-fold Long half-life (>100 h). One of the newest AEDs, incomplete knowledge of PK variability

Table 2. (*Continued*)

AED	Bioavailability (%)	T-max (hours)	Protein binding (%)	Volume of distribution (l/kg)	Enzymes involved in metabolism	Half life (hours)	Drugs inducing metabolism	Drugs inhibiting metabolism	Factors contributing to pharmacokinetic variability (PK) among patients
Pregabalin	>90	1.3	0	0.4	No	4.6-6.8	Not identified	Not identified	Food slows absorption Renal excretion ↓ dose in patients with renal impairment
Primidone	≈100	2.7-4.2	15	0.6	CYP 2E1, 2C9?, 2C19?	3-22	See phenobarbital	See phenobarbital	See phenobarbital
Retigabine	60	0.5-2	80	6.2	UGT, N-acetylation	8	Not identified	Not identified	
Rufinamide	Dose limited, not determined	4-6	26-35	0.7-1.1	Hydrolysis, non CYP-dependent	6-10	AED inducers, vigabatrin	Valproic acid	Dose-dependent absorption. Food increases bioavailability by 34%. Enzyme inducer One of the newest AEDs, incomplete knowledge of PK variability
Stiripentol	≈100	1.5	99	Not determined	CYP 1A2, 2C19, 3A4	2-13	AED inducers	Not identified	Saturation kinetics, half-life dependent of dose Displacement of protein binding with other highly protein-bound drugs Strong enzyme inhibitor
Sultiame	100	1-5	29	Not determined	Moderate metabolism by undefined isoenzymes	8-15	AED inducers	Not identified	Inhibits CYPs and UGTs

Table 2. (*Continued*)

AED	Bioavailability (%)	T-max (hours)	Protein binding (%)	Volume of distribution (l/kg)	Enzymes involved in metabolism	Half life (hours)	Drugs inducing metabolism	Drugs inhibiting metabolism	Factors contributing to pharmacokinetic variability (PK) among patients
Tiagabine	90-95	0.5-2	96	1.4	CYP 3A4	5-8	AED inducers	Not identified	Food slows absorption Displacement with other highly protein-bound drugs
Topiramate	81-95	2-4	15	0.6-1	CYP-dependent?	20-30	AED inducers, eslicar-bazepine acetate	Amitryptiline, lithium, metformin, propranolol, sumatriptan	↑CL during pregnancy, moderate enzyme inducer (doses >200 mg/day)
Valproic acid	≈100	1-2	90	0.15-0.2	CYP 2A6, 2C9, 2C19, 2B6, UGT 1A3, 2B7	13-15	AED inducers, stiripentol, meropenem, paripenem, naproxen, rifampicin, ritonavir, OCs	Clobazapm, felbamate, chlorpromazine, fluoxetine, isoniazid, sertraline	Food slows absorption Displacement with other highly protein-bound drugs Enzyme inhibitor (UGTs), other?
Vigabatrin	≈100	1	0	0.8	No	6-8	Not identified	Not identified	Renal excretion ↓ dose in patients with renal impairment
Zonisamide	≈100	2-4	40-60	1.5	CYP 3A4	50-70	AED inducers, risperidone	Not identified	Food slows absorption

*Active metabolites; eslicarbazepine. Enzyme-inducing AEDs (AED inducers) include carbamazepine, phenobarbital, phenytoin, primidone, felbamate and rufinamide. Enzyme-inhibiting AEDs (AED inhibitors) include stiripentol and valproic acid. Felbamate, rufinamide, oxcarbazepine and eslicarbazepine may be inducers and inhibitors of various enzymes.

CYP: cytochrome P450 isoenzymes; UGTs: uridine glucuronosyl transferases; OCs: oral contraceptives; CL: clearance.

In general, all AEDs require dosage adjustments in case of impaired hepatic or renal function, and due to physiological changes that affect the pharmacokinetics in children and the elderly. The absorption is not delayed by food where this is not noted. The table is based on the summary of product characteristics (SPC) and reports from Burns *et al.* (2016), Johannessen and Johannessen Landmark (2010), Johannessen Landmark and Patsalos (2010), and Johannessen Landmark *et al.* (2012b). See the text for more references.

as AEDs which are substrates for interactions. Drugs like lamotrigine and clobazam are affected by both inducers and inhibitors and thus pronounced changes in serum concentrations are observed (Bartoli *et al*., 1997; Johannessen Landmark *et al*., 2012a; Burns *et al*., 2016). One example is the interaction between lamotrigine and oral contraceptives, in which the serum concentrations of lamotrigine are reduced by 50% on average, as compared to women not using oestradiol-containing oral contraceptives (Sabers *et al*., 2003). About 20% of the population of patients with epilepsy use AEDs as polytherapy, and 30% of patients with epilepsy are prescribed drugs for psychiatric comorbid disorders (Karouni *et al*., 2010; Johannessen Landmark *et al*., 2011). Numerous pharmacokinetic interactions exist for AEDs used in combination and when AEDs are used concomitantly with other CNS-active drugs (Johannessen Landmark and Patsalos, 2010).

The most recent example of the importance of measuring AEDs is the concomitant use of cannabinoids and clobazam, which has been shown to increase the concentration of N-desmethylclobazam, the active metabolite of clobazam, by a factor of five, causing adverse effects (Geffrey *et al*., 2015).

Physiological factors and concurrent illness

Physiological changes affect the pharmacokinetic characteristics, *e.g*. age and pregnancy. Concurrent illness, such as hepatic or renal failure, can also have an impact. In children, elimination organs develop fast during the first year of life. Metabolising capacity in the early years of life may vary according to isoenzyme. Both blood flow and metabolising capacity for drugs are at a peak at the age of 5-6 years. After that age, pharmacokinetics are similar to adults until 65 years of age when a gradual decrease in clearance is seen (Johannessen Landmark *et al*., 2012b; Italiano and Perucca, 2013).

Pronounced physiological changes occur during pregnancy. Studies of lamotrigine revealed extensive changes in metabolism during pregnancy, with up to a three-fold increase in clearance with a rapid return to baseline values shortly after delivery (Öhman *et al*., 2000; Pennell *et al*., 2004; Reimers *et al*., 2005). Other newer AEDs, such as oxcarbazepine, levetiracetam, and topiramate, also show pronounced pharmacokinetic changes throughout pregnancy (Christensen *et al*., 2006; Tomson *et al*., 2007a; Westin *et al*., 2009). Even though the experience of handling AED dosage during pregnancy has increased considerably over the years, the importance of taking pharmacokinetic changes into account was already suggested in 1977 (Eadie *et al*., 1977). These authors stated that the altered anticonvulsant requirement is more likely to depend mainly on an increased rate of biotransformation, and anticonvulsant plasma levels should be monitored regularly from the outset of pregnancy and more frequently after birth (Eadie *et al*., 1977).

Genetic factors

Another cause of pharmacokinetic variability is genetic polymorphisms in drug metabolising enzymes, which may be revealed by genotyping (Sirot *et al*., 2006; Löscher *et al*., 2009; Cascorbi, 2010). However, in many cases it is easier to monitor the serum concentration. Complementary pharmacogenetic testing may, however, elucidate the reason for unexpected relationships between dose and serum concentrations of certain AEDs when CYP2C9 and 2C19, and to some extent UGTs, are shown to have polymorphisms that may give rise to a poor metaboliser phenotype. Susceptible AEDs are clobazam, phenytoin, and to a lesser extent, lamotrigine (Lee *et al*., 2007; Gulcebi *et al*., 2011; Burns *et al*., 2016; Reimers *et al*., 2016). Genetic variability in drug transporters, as a mechanism for pharmacoresistance, is still under debate and needs further research (Löscher *et al*., 2009).

Non-adherence

The use of TDM may reveal poor or variable adherence to the prescribed medication. By using TDM data, poor adherence has been shown to be a major reason for hospitalisation due to break-through seizures (when serum concentrations were <50% of baseline values), even in patients denying non-adherence (Samsonsen *et al*., 2014).

Experience with the recent and most recent AEDs

Among the newer, second generation AEDs, the following may be good candidates for TDM: felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, and zonisamide, since these drugs show marked pharmacokinetic variability likely to contribute to differences in dosage requirements (Krasowski and McMillin, 2014; Johannessen Landmark *et al*., 2012b). The most recently available AEDs include eslicarbazepine acetate, lacosamide, perampanel, rufinamide, and stiripentol. Various studies demonstrate extensive pharmacokinetic variability and potential for interactions also for these drugs (Perucca *et al*., 2008; May *et al*., 2012; Markoula *et al*., 2014; Johannessen Landmark *et al*., 2016; Patsalos *et al*., 2016).

For AEDs with short half-lives (levetiracetam, gabapentin, pregabalin, and tiagabine), interpretation of TDM data may be complicated due to fluctuations in serum concentrations within the dosing interval, causing variability if the blood sampling time is not well standardised. Gabapentin and rufinamide have a

capacity-limited absorption, and thus the dose itself is not a good measure of drug exposure. Stiripentol exhibits extensive pharmacokinetic variability, saturation kinetics similar to those of phenytoin, and many interactions with other AEDs (May *et al*., 2012).

What and how to measure?

For most AEDs, the total concentration of bound and unbound drug of the main active compound is measured. The blood sampling time should be standardised in the morning before intake of the dose at assumed steady state (Tomson and Johannessen, 2000).

Serum concentrations of metabolites

Some AEDs have pharmacological active metabolites. For instance, primidone is metabolised to phenylethylmalonamide and phenobarbital. Most often, the concentration of the derived phenobarbital is used. The main metabolite of carbamazepine, carbamazepine 10-11-epoxide, accounts for 10-50% of the serum concentration of the parent drug, but there is no constant relationship between the concentration of the epoxide and carbamazepine. Measuring the metabolite is usually not included in routine monitoring. Oxcarbazepine is rapidly metabolised to its monohydroxyderivative, (R)/(S)-licarbazepine. The prodrug eslicarbazepine acetate is rapidly converted to (S)-licarbazepine or eslicarbazepine. These derivatives can be measured for monitoring purposes by the same analytical method or by a stereoselective method.

For drugs for which the parent molecule and active metabolite are present at high concentrations (*i.e*. clobazam and N-desmethylclobazam), both can be measured and various metabolite/parent compound ratios used in the interpretation of the results (Burns *et al*., 2016).

Unbound drug concentrations

Measurement of the unbound drug concentration may be of importance in special situations, since this is the fraction of the drug that is pharmacologically active. In certain situations, the level of binding of a drug to plasma proteins may be lower than normal, in which case measuring the total concentration can be misleading and may lead to an underestimation of the amount of pharmacologically active drug. This is, however, only relevant when interpreting the serum concentrations of highly-protein-bound (>90%) drugs, such as phenytoin and valproic acid (Patsalos *et al*., 2008), as well as some of the newer AEDs, *i.e*. tiagabine, stiripentol, and perampanel (Krasowski and McMillin, 2014).

In conditions with hypoalbuminaemia, for example during neonatal age, old age, pregnancy, chronic liver disease and uraemia, protein binding may be decreased. The net effect of such a decrease in protein binding is a decline in the total (bound plus unbound) serum concentration of the drug, while the unbound drug concentration, the pharmacologically active concentration, may be essentially unchanged. Measurement of the free concentration might be preferable in *e.g*. pregnant women using valproic acid if a more precise estimate of the exposure of the drug to the foetus is considered necessary (Tomson *et al*., 2013). This may facilitate the interpretation of therapeutic monitoring data since therapeutic and toxic effects may be observed at lower total concentrations than usual and inappropriate dosage adjustments can be avoided.

Saliva concentrations and blood spots

Most often, serum or plasma samples are used for TDM, but saliva can be an alternative medium for several AEDs (Patsalos and Berry, 2013) since the concentration in saliva reflects the unbound concentration in serum (except for valproic acid and phenobarbital due to their physicochemical properties). Saliva sampling is simple and non-invasive and is useful in children who fear venepuncture. The saliva concentrations may, however, be affected by the sampling conditions and contamination of mucus and the presence of residual drug and food.

Many publications are available regarding the use of dried blood spots, although there are some methodological limitations. A recent study demonstrated its use in children with epilepsy, in the assessment of adherence of their prescribed drugs, but the method is not yet well established in clinical routine practice (Shah *et al*., 2013).

The future: dosing strategies towards improved personalised medicine

More studies are warranted in special patient populations regarding pharmacokinetic variability. This will contribute to better understanding of the need to individualise treatment with AEDs. Currently, 50% of prescriptions of AEDs are for indications other than epilepsy (Baftiu *et al*., 2016), *e.g*. neuropathic pain, psychiatric disorders, and migraine, with new and partly unexplored possibilities of drug interactions. Thus, TDM of AEDs may be important in patient populations beyond epilepsy as part of pharmacovigilance (Haen, 2011).

Recent initiatives from the European Medicines Agency (EMA) now support further the implementation of pharmacogenomics in drug development and surveillance (Ehmann *et al*., 2014). Genetically susceptible subgroups of patients can avoid certain drugs

and hence possible toxic or fatal effects. Consequently, more tailored therapy might be offered to the individual patient in the future using a combination of TDM and pharmacogenomic test panels (Hiemke and Shams, 2013).
For research purposes, TDM databases are suitable for identification and monitoring of safety aspects related to intra- and inter-patient pharmacokinetic variability. The potential for pharmacokinetic interactions of new drugs is usually incompletely described prior to and early after marketing, and therefore deserves more attention (Johannessen Landmark and Johannessen, 2012).

Lessons learned with retrospect

The past experience of the last 50 years with TDM have clearly shown that one AED dose does not fit all patients, and that doses need to be adjusted over time in the individual patient. There are, however, certain requirements for TDM to be useful. The concept rests on the assumption that there is a correlation between the serum concentration and clinical effect, and that this is stronger than between dose and effect. For most AEDs, the serum concentration can be considered a measure of the exposure of the drug at its site of action in the brain. However, the drug effect at the site of action also needs to be reversible in order to obtain a meaningful concentration-effect relationship.

Use and misuse of TDM

Criticism has been directed towards the overuse of TDM and the method should obviously not be used without clear indications (*see table 1 for details and recommendations*). Routine overuse of TDM without a proper clinical evaluation was pointed out as an issue many years ago. It was stated that "*treating patients is much more important than treating blood concentrations*" (Chadwick, 1987).
There are also several pitfalls regarding the interpretation of TDM results. There is no strict correlation between efficacy and toxicity of an AED and the corresponding serum concentration in individual patients (St. Louis, 2009). The establishment of individual therapeutic concentrations that differ from the suggested reference ranges may be challenging to accept for the clinician and the patient. Furthermore, changes in the underlying seizure condition may require reestablishment of these individual therapeutic concentrations (Krasowski, 2010).
Erroneous or random sampling times are also a cause of variability, which may cause difficulties in interpreting the results in a patient over time. Standardisation of blood sampling time and drug-fasting in the morning (before intake of the morning dose) at steady state should be the standard procedure for possible comparisons of the measurements over time in the individual patient and in relation to the reference ranges for each AED (Tomson and Johannessen, 2000; Patsalos *et al*., 2008). In cases where adverse effects are suspected at peak concentrations, as sometimes seen with *e.g*. oxcarbazepine (Nunes *et al*., 2013), a blood sample may be drawn a few hours after drug intake when adverse effects are suspected.

Other challenges

Despite what has been discussed above, there is a lack of class I evidence of the clinical impact of TDM on treatment outcome in epilepsy. In a Cochrane review of TDM of AEDs in epilepsy patients from 2007, only one study met the inclusion criteria by assessing efficacy outcomes of AED monotherapy with or without TDM (Tomson *et al*., 2007b). In this randomised study, 180 patients with newly diagnosed epilepsy, treated with carbamazepine, valproate, phenytoin, phenobarbital or primidone, were followed for one year. Efficacy and tolerability measures were similar between those randomised to dosing guided by TDM or those without TDM. It was concluded that there was no clear evidence to support aiming at predefined target ranges (Januzzi *et al*., 2000), which, however, no longer is recommended practice (Patsalos *et al*., 2008). So far, there are no other studies in which the impact of implementation of TDM on outcome of epilepsy treatment has been investigated as a primary goal.
For several of the new AEDs it has been claimed, sometimes for commercial reasons, that TDM is not useful or needed; the claimed disadvantage of TDM being the inconvenience of undertaking the sampling and analysis, and the consequent costs relating to the analysis (Perucca, 2000). The example of lamotrigine interactions with contraceptives (Sabers *et al*., 2003) and drastic changes in pregnancy (Öhman *et al*., 2000) has demonstrated the importance of a critical attitude towards such claims. The role of TDM of the newer generation and future AEDs needs investigation and is a continuous challenge. Development and testing of newer AEDs should include an evaluation of TDM early in specifically designed clinical studies, preferably using monotherapy. Proper use of TDM should therefore be an integrated part of drug development (Commission on Antiepileptic Drugs, 1989, 1993; Perucca, 2000).
The FDA and the American Association for Clinical Chemistry have suggested early availability of drug assays. This strategy has not, however, so far been implemented as an integrated part of drug development and investigations. Hopefully, more commercial low-cost reagents will be available for TDM of the

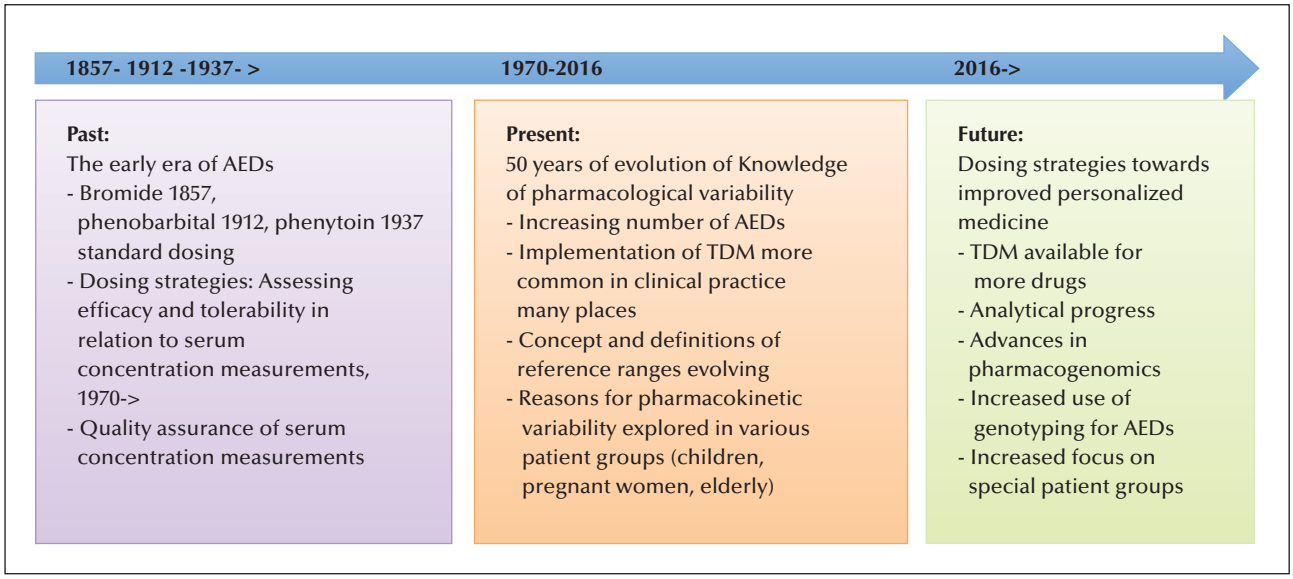

Figure 2. Overview of dosing strategies of antiepileptic drugs through the past, present, and future.

newer AEDs in more countries. Better understanding of individual therapeutic serum concentrations and reference ranges, especially for the newer AEDs, is needed *e.g.* in children and the elderly, as well as during pregnancy and breastfeeding. It was recently highlighted that future research is needed to define better reference ranges also for non-epilepsy applications (Krakowski and McMillin, 2014).

Conclusions

The past, present, and future perspective of dose individualisation is summarised in *figure 2*. In a historical perspective, in which AEDs have been used to treat epilepsy for more than a century, we have learned that a standard dose is not an optimal dosing strategy. We have learned from history, and through application of TDM, that the use of AEDs implies variability regarding dose and serum concentration relationships, due to external, physiological, as well as genetic factors. Patient groups, such as children, pregnant women, and the elderly, in whom the most extensive pharmacokinetic changes occur, need special attention and close follow-up of their treatment, as do patients with complicated and changing combination treatments. The main reasons for misuse of TDM include use of TDM without a clear indication, misinterpretation of the reference range, and erroneous sampling times. AED therapy should be tailored to the individual patient for an optimal treatment outcome and balance between efficacy and tolerability, and TDM can, in many situations, facilitate this strategy. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Disclosures.
None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) Which factors contribute to pharmacokinetic variability of antiepileptic drugs that may be discovered by measuring the serum concentration?

(2) What is meant by a "reference range"?

(3) What is meant by "individual therapeutic concentrations?"

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".