Antiepileptic Drug Interactions

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A Clinical Guide

Second Edition

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Preface

Since the publication of the first edition of this book in July 2005, much has changed in the field of antiepileptic drug (AED) interactions. Firstly, five new AEDs have been licensed for clinical use (eslicarbazepine acetate, lacosamide, retigabine, rufinamide, and stiripentol); and secondly there has been a surge of publications reporting on interactions involving AEDs, which is reflective of the realization of the importance of drug interaction in clinical therapeutics. In this second edition, a total 27 AEDs are reviewed, in alphabetical order, including AEDs that are not necessarily licensed worldwide but that are prescribed to patients in different countries (e.g., acetazolamide, methsuximide, piracetam, and sulthiame). A noteworthy enhancement in this second edition is the extensive referencing of the various interactions.

AED interactions present a major challenge in the management of epilepsy, and even though our understanding of these interactions has increased substantially, the sheer size of available data has discouraged many physicians from taking an effective approach to minimize the adverse consequences, which may result from these interactions. The purpose of this book is to provide in a systematic fashion a description of the drug interactions that occur between AEDs and between AEDs and non-AED drugs, which may present problems for patients and that often require a drug dose adjustment. With this information, it is anticipated that medical practitioners, who treat patients with epilepsy or patients with morbidities that also require AED use, will be better placed to allow a more rational drug choice when polytherapy regimens are indicated (Patsalos & Bourgeois, 2010).

In addition, the content of this book will allow for a more informed rationale as to how drugs will interact and, therefore, the dosage adjustment that would be consequently necessary to maintain an appropriate therapeutic response (maximal efficacy, minimal adverse effects).

The book is divided into four sections:

The Introduction is a general introduction which explains the basic mechanisms of drug interactions, how to anticipate and predict interactions, and how to prevent and manage adverse interactions.

Part I describes the interactions that occur between AEDs.

Part II describes the interactions that occur between AEDs and non-AED drugs whereby the interaction affects AEDs. The non-AED drugs are listed in drug classes in alphabetical order.

Part III describes the interactions that occur between AEDs and non-AED drugs whereby the interaction affects non-AED drugs. The non-AED drugs are listed in drug classes in alphabetical order.

Because pharmacokinetic interactions represent the majority (>98 %) of described interactions involving AEDs, it is inevitable that the focus of this book is on pharmacokinetic interactions. Nevertheless, pharmacodynamic interactions are equally important and are therefore also described. As a drug class, the number of known interactions involving AEDs is substantial, and while it has been the author's aim to be as complete as possible, the listings may not be exhaustive and the possibility exists that clinically significant interaction will occur with other drugs.

The data used in compiling this book were identified by searches of Medline and PubMed with the terms "antiepileptic drug interactions" combined with individual drug names and drug groups, references from relevant articles, and searches of the author's files. No gender or age limits were imposed but searches, last conducted September 2012, were limited to human subjects. Publications preference in descending

order was as follows: formal interaction studies in patients; formal interaction studies in healthy volunteers; case studies/reports; population pharmacokinetic modeling databases; and therapeutic drug monitoring databases. Papers published in English were preferred but non-English articles were used if they were the sole reference source. Abstracts were included only when a complete published article was not available.

All statements in this book as to the nature of an interaction (pharmacokinetic, pharmacodynamic, or no interaction) are referenced so that the reader can readily identify the appropriate publication. For most such statements, one reference is included (representing the key reference) but where the interaction is controversial two or three references are cited.

The pharmacokinetic interactions presented in this book are described in terms of a change in plasma (blood) levels because physicians treating patients with epilepsy are very familiar with drug plasma levels and how changes in these levels are reflective of a drug's pharmacokinetic characteristics and efficacy/adverse effect profile. However, in some studies, blood levels are not reported and instead clearance, half-life, area under the concentration versus time curve (AUC) and/or maximum blood level (C_{max}) values are quoted. Thus, for these studies, the interactions are described in terms of changes in clearance, half-life, AUC, and/or C_{max} values. Whenever available, pharmacokinetic changes in mean values are quoted; otherwise a value representing the most significant change reported, for example in small case series, is quoted. Finally, some studies do not quote any pharmacokinetic variables and instead describe the interaction in terms of a change in the clinical status; for example, patient(s) experienced an enhanced or a reduced therapeutic response or enhanced toxicity. For these interactions, the interactions are described generically, for example "enhances the metabolism" or "inhibits the metabolism" of the affected drug. Wherever the data are available, interactions are also described in relation to their effects on hepatic enzyme

activity; for example, cytochrome P450, uridine glucuronyl transferases, and epoxide hydrolase. This will allow the reader to ascertain the propensity of similar interactions occurring with other drugs that may have similar enzyme activities as substrates, inhibitors and/or inducers. Where pharmacokinetic interactions have been studied but no interaction observed, they are reported as "does not affect the pharmacokinetics of drug…."

When using the information detailed in this book, the reader should remember that although a drug interaction is considered clinically relevant when it results in the need for dosage adjustment or other medical intervention in the majority of patients, a marked deviation in an unusually susceptible individual is also important. Also, one needs to consider the end result because a marked elevation in a low AED/drug level may improve seizure control/therapeutic response while a small elevation of a nearly toxic level may actually precipitate toxicity. Finally, while an interaction involving a 10 % change in a drug blood level may have little, if any, clinical relevance in the majority of patients, it may be of profound clinical relevance in a significant minority of patients.

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Disclaimer

The contents of this book are presented in a style so as to alert practitioners as to the potential of an interaction (both pharmacokinetic and pharmacodynamic). The absence of drug listing indicates that the interaction has not been investigated and does not necessary indicate that a drug interaction will not occur. While every effort has been made to summarize accurately and illustrate the published literature, the author does not guarantee the accuracy of the information contained herein. No liability will be assumed for the use of the information contained within this book. Readers should consult any relevant primary literature and the complete prescribing information for each drug.

Contents

Part III Drug Interactions Between AEDs and Non-AED Drugs: Interactions Affected by AEDs

Introduction

Epilepsy, which affects approximately 1 % of the world's population, is a chronic disorder that usually persists for many years and often for a lifetime [1]. Antiepileptic drugs (AEDs) are the mainstay of epilepsy treatment and complete seizure control can be achieved in the majority (65 %) of newly diagnosed patients by prescribing a single AED, and this is the ideal situation [2]. For the remaining 35 % of patients, the prescribing of polytherapy regimens (the use primarily of two AEDs but often three or four AEDs), so as to achieve optimal seizure control, is a common practice. However, for the majority of these patients little additional benefit is achieved from the use of polytherapy AEDs as intolerable adverse effects commonly occur as a consequence of pharmacokinetic and/or pharmacodynamic interactions. Furthermore, for those patients that respond to monotherapy, they too may experience the consequences of AED interactions as AEDs are added and withdrawn during the optimization of their monotherapy drug regimen [3–5]. A further confounding factor is that since epilepsy is a chronic condition many patients will inevitably develop comorbid diseases or other debilitating conditions and disorders, which will require the co-administration of non-AED drugs. In this setting the potential for drug interactions is considerable [6]. A further source of potential clinically significant interactions that is being increasingly recognized relates to the increasing use of over-the-counter medications and supplements, many of which have unknown constituents and inconsistent quality [7]. Finally, AEDs are increasingly used to treat other non-epilepsy conditions such as mood disorders, migraine,

and pain, thereby further increasing the possibility of combined use with other drugs [8].

The pharmacokinetic properties of AEDs make them particularly susceptible to pharmacokinetic interactions. Furthermore, many AEDs have a narrow therapeutic index in that the plasma (serum) level (concentration) associated with a desirable antiepileptic effect is close to the plasma level that is associated with undesirable adverse effects. Thus, even a relatively small change in their plasma level, consequent to inhibition or induction, may readily result in signs of intoxication or loss of seizure control respectively. In addition, some AEDs exert a major influence on the activity of hepatic drug metabolizing enzymes, stimulating (e.g., carbamazepine, phenytoin, phenobarbital and primidone) or inhibiting (e.g., valproic acid, stiripentol, sulthiame) their activity thereby leading to a wide variety of pharmacokinetic interactions with other drugs that are also metabolized and eliminated by the same enzymes. Conversely, because most AEDs undergo extensive hepatic metabolism (e.g., carbamazepine, eslicarbazepine acetate, lamotrigine, phenytoin, phenobarbital, tiagabine, topiramate, oxcarbazepine, valproic acid, and zonisamide), they too are vulnerable to the effect of other drugs with inhibiting or inducing properties [9].

Mechanisms of Drug Interaction

Drug interactions can be divided into two groups, pharmacodynamic and pharmacokinetic:

1. Pharmacodynamic interactions
   Pharmacodynamic interactions occur at the cellular level where drugs act and can occur between drugs that have either similar or opposing pharmacological mechanisms of action. Because these interactions are not associated with any change in plasma drug level, they are less well recognized and documented. Nevertheless, they are of major clinical significance and are invariably concluded by default whereby a change in the clinical status of a patient

consequent to a drug combination cannot be ascribed to a pharmacokinetic interaction.

2. Pharmacokinetic interactions
   Pharmacokinetic interactions are characterized by a change in plasma level of either the drug or its metabolite(s) or both. They are particularly prevalent and their magnitude and time course can be readily determined and involve a change in their: absorption, usually gastrointestinal; distribution, usually binding to serum albumin; metabolism, usually by isoenzymes of cytochrome P450 [CYP] and uridine glucuronyl transferases [UGTs]); or elimination, usually renal excretion. Consequently, there is an alteration in the level of the affected drug at the site of drug action.

Pharmacodynamic Interactions

Although pharmacodynamic interactions have been traditionally neglected in epilepsy therapy, increasing evidence indicates that their recognition is essential so as to maximize AED efficacy and minimize AED toxicity. Most pharmacodynamic interactions simply involve additive neurotoxicity, and may be explained by superimposition of adverse events caused by AEDs sharing the same modes of action. For example, combinations of two sodium-channel blockers, such as carbamazepine and oxcarbazepine, or carbamazepine and lamotrigine, are less well tolerated than combinations of drugs acting through different mechanisms. Combinations of drugs that enhance GABAergic inhibition, such as valproic acid and phenobarbital, may result in profound sedation that cannot be explained solely by a pharmacokinetic interaction. Lamotrigine and valproic acid in combination may produce disabling tremor [10]. Examples of potential favorable drug combinations include: valproic acid and ethosuximide in the management of refractory absence seizures [11]; valproic acid and lamotrigine in the management of partial and generalized seizures [12]; and carbamazepine and valproic acid in the management of partial seizures [13].

Pharmacodynamic interactions between AEDs and non-AED drugs can also result in increased toxicity. For example, the concurrent use of lithium and carbamazepine has been associated with a syndrome characterized by somnolence, confusion, disorientation, and ataxia and other cerebella symptoms consequent to a pharmacodynamic interaction [14, 15]. Also, the delirium observed in some patients when quetiapine is co-administered with valproic acid is considered to be the consequence of a pharmacodynamic interaction [16]. Finally, combining carbamazepine with clozapine is generally contraindicated due to concerns about potential additive hematological adverse effects [17].

Pharmacokinetic Interactions

Interactions Affecting Drug Absorption

Interactions affecting the absorption of AEDs are uncommon, although occasionally they do occur and can be important. For example, antacids reduce the absorption of phenytoin, gabapentin, valproic acid, and sulthiame. Furthermore, phenytoin absorption is impaired when the drug is given together with certain nasogastric feeds (e.g., Isocal) so that plasma phenytoin levels are reduced by 72 % [18]. In both examples it is thought that the formation of insoluble complexes may be responsible for the reduced absorption. Other such interactions include a reduction of absorption of primidone by acetazolamide [19] and a reduction in absorption of carbamazepine by colestipol and cisplatin [20, 21].

Plasma Protein Binding Displacement Interactions

Plasma protein-binding displacement interactions are important only with the highly protein-bound (>90 %) AEDs (e.g., phenytoin, tiagabine, valproic acid, and stiripentol). Because these drugs have a low intrinsic hepatic clearance, their

displacement causes an initial transient increase in total drug plasma level prior to re-equilibration and a subsequent decrease. However, the pharmacologically relevant free non-protein bound plasma level is unaffected and thus the clinical effects of the affected AED are unchanged. Consequently, a dosage adjustment is usually unnecessary following displacement of highly protein-bound AEDs from their plasma protein binding sites. A well characterized plasma protein binding displacement interaction is that of phenytoin by valproic acid [22]. However, it is important to recognize that the clinical effects of phenytoin will now correspond to lower total plasma levels and patient management may benefit from monitoring free non-protein bound phenytoin levels [23].

Interactions at the Renal Level

Interactions at the level of renal elimination can be expected to occur with drugs that are predominantly renally eliminated, and indeed such clinically relevant interactions have been described including a decrease in renal clearance and an increase in plasma carbamazepine-10,11-epoxide levels by zonisamide [24] and the decrease in felbamate elimination by gabapentin [25].

Metabolic Interactions

Interactions involving changes in hepatic metabolism represent, by far, most of the pharmacokinetic interactions described with AEDs and involve both induction and inhibition of drug metabolism. Because most AEDs undergo hepatic metabolism they are susceptible to inhibitory and/or induction interactions. These processes are catalyzed by various enzyme systems, which can occur in series, and are referred to as Phase I (functionalization) and Phase II (conjugation) enzyme systems. Phase I reactions include hydroxylation (the addition of a polar functional group) or

N-demethylation (deletion of a non-polar alkyl group) by oxidation, reduction, or hydrolysis. Phase II reactions serve to further increase the water solubility of the drug/metabolite and involve conjugation with glucuronic acid, sulphate, acetate, glutathione, or glycine. Although metabolic drug interactions may involve changes in any one of the numerous enzymes involved in drug metabolism, by far the most important are those associated with the CYP and UGT systems. The CYP system is particularly important because it is not only responsible for the oxidative metabolism of many drugs and exogenous compounds but also of many endogenous compounds such as prostaglandins, fatty acids, and steroids. Metabolic processes serve to convert a drug into one or more metabolites, which are more water-soluble than the parent drug and thus facilitate urinary excretion.

CYP Enzymes

The CYP enzyme system consists of a superfamily of isoenzymes that are located in the smooth endoplastic reticulum, primarily in the liver but also in many other tissues (e.g., intestine, kidney, brain, and placenta). They are classified into families (the first Arabic number; there is a >40 % amino acid sequence identity within family members), subfamilies (the capital letter that follows; there is a >59 % amino acid sequence identity within subfamily members), and individual isoenzymes (the second Arabic number). Although in man approximately 60 different CYP isoenzymes have been identified, five isoenzymes (CYP3A4, CYP2D6, CYP2C9, CYP1A2, and CYP2C19) are known to be responsible for the metabolism of 95 % of all drugs, and three (CYP2C9, CYP2C19, and CYP3A4) are of particular importance in relation to AED interactions [26]. Because the activity of these isoenzymes is genetically determined, genetic polymorphism resulting in enzyme variants with higher, lower, or no activity, or even resulting in the absence of an isoenzyme can have a profound effect on the pharmacological expression of an interaction (vide infra). In relation to AEDs, those

polymorphisms that have clinical consequences relate primarily to CYP2C9 and CYP2C19.

Epoxide Hydrolases

Epoxide hydrolases are a family of enzymes whose function is to convert arene oxides to trans-dihydrodiols and simple epoxides to vicinal diols by hydration and consequently are involved in detoxification processes, although sometimes they are involved in bioactivation reactions [27]. Only the microsomal form of epoxide hydrolase is involved in xenobiotic metabolism and plays an important role in the metabolism of carbamazepine, phenobarbital, and phenytoin. Epoxide intermediates have been implicated in teratogenic events and hypersensitivity reactions and in relation to carbamazepine, carbamazepine-10,11-epoxide is considered to be equipotent to carbamazepine and contributes both to its antiepileptic and adverse effects. Furthermore, epoxide hydrolase inhibition has been implicated in various important interactions involving carbamazepine metabolism (e.g., valproic acid and quetiapine inhibit its activity and increase plasma carbamazepine-10,11-epoxide levels while phenobarbital enhances its activity and decreases plasma carbamazepine-10,11-epoxide levels [28–30].

Uridine Glucuronyl Transferases

In man, three families of UGTs have been identified, of which UGT1 and UGT2 appear to be the most important in drug metabolism [31]. The UGT1A3 and UGT2B7 isoforms are involved in the O-glucuronidation of valproic acid, while a variety of isoforms (UGT1A6, UGT2B7, UGT2B17, UGT2B4) are involved in the metabolism of eslicarbazepine. UGT1A4 has been found to be the major isoform responsible for the metabolism (N-glucuronidation) of lamotrigine. Although any substrate of UGT has the potential to competitively inhibit the glucuronidation of other substrates by the same

isoform, there are few data in this regard. Furthermore, unlike the CYP system, no specific UGT inhibitors have been identified. Nevertheless, valproic acid inhibits several UGTs while carbamazepine, phenobarbital, and phenytoin are inducers (e.g., interactions with lamotrigine).

Enzyme Inhibition

Enzyme inhibition is the consequence of a competition by drugs to bind to the same enzymic site resulting in a reduction of enzyme activity and a decrease in the rate of metabolism of the affected drug. Inevitably, plasma levels are elevated and this is commonly associated with clinical toxicity. Inhibition is usually competitive in nature and therefore dose-dependent and tends to begin as soon as sufficient levels of the drug inhibitor are achieved, and this usually occurs within 24 h of inhibitor addition. The time to maximal inhibition will depend on the elimination half-life of the affected drug and the inhibiting agent. When the inhibitor is withdrawn, the time course of de-inhibition is dependent on the elimination half-life of the inhibitor. Among the AEDs valproic acid, stiripentol, sulthiame, topiramate, and felbamate have been associated with inhibitory interactions. Furthermore, while topiramate and felbamate are primarily selective inhibitors of CYP2C19, valproic acid is considered to be a broad-spectrum inhibitor of hepatic metabolizing enzymes as it inhibits CYP2C9, UGTs, and microsomal epoxide hydrolase. Stiripentol inhibits CYP2C19 and CYP3A4 while the isoenzymes inhibited by sulthiame are probably CYP2C9 and CYP2C19.

In some circumstances, inhibitory interactions are complicated and problematic. For example, interactions involving the active metabolite(s) of the co-administered drugs may not always be obvious if concurrent plasma level changes of the parent drug do not occur. Because it is not common practice to monitor plasma metabolite levels, if one is unaware of the interaction, blood level monitoring of the parent drug could be misleading. Such problematic interactions are associated with carbamazepine-10,11-epoxide, the pharmacologically

active metabolite of carbamazepine. For example, during carbamazepine combination therapy with either valproate or quetiapine, patients can experience adverse effects as a result of an elevation of carbamazepine-10,11-epoxide levels resulting from an inhibition of epoxide hydrolase, without concurrent changes in plasma carbamazepine levels [28, 30].

An AED may be the affected drug or the cause of an interaction. In fact, with some drug combinations, both the hepatic metabolism of the AED and that of the other drug are altered. For example, during co-medication with ketoconazole and carbamazepine, carbamazepine plasma levels are increased due to inhibition of carbamazepine metabolism [32]. Conversely, the effectiveness of standard dosages of ketoconazole is reduced because carbamazepine enhances the metabolism of ketoconazole [33]. Other bi-directional interactions include those between topiramate and phenytoin, and between valproic acid and lamotrigine.

Several drugs including macrolide antibiotics (e.g., erythromycin and troleandomycin) and hydrazines (e.g., isoniazid) undergo metabolic activation by CYP enzymes so that the formed metabolites bind to the prosthetic hem of CYPs to form stable metabolic intermediates rendering the CYP inactive. As CYP activity can only be restored by synthesis of new enzyme, the effect of such inhibitors may persist well after the elimination of the precursor (parent) drug. This mechanism is involved in the interaction between erythromycin and troleandomycin with carbamazepine (via inhibition of CYP3A4), and between isoniazid and phenytoin (via inhibition of CYP2C9) [34].

Finally, inhibitory interactions can be irreversible in nature in that drugs containing certain functional groups can be oxidized by CYPs to reactive intermediates that subsequently cause irreversible inactivation of the CYP by alteration of hem or protein or a combination of both. An example of these "suicide inhibitors" is the furanocoumarins that are contained in grapefruit juice and irreversibly inhibit CYP3A4. Thus, grapefruit juice inhibits the metabolism of carbamazepine so that mean plasma carbamazepine C_{max} and AUC values are increased by 40 % [35] (Table 1).

Table 1 Antiepileptic drug effects on hepatic enzymes

Drug	Effect	Enzymes affected
Acetazolamide	None	–
Carbamazepine	Inducer	CYP2C, CYP3A, CYP1A2, EH and UGT
Clobazam	None	–
Clonazepam	None	–
Eslicarbazepine acetate	Inducer (weak)	CYP3A4
	Inducer (moderate)	UGT1A1
	Inhibitor (moderate)	CYP2C9, CYP2C19
Ethosuximide	None	–
Felbamate	Inducer	CYP3A4
	Inhibitor	CYP2C19, β-oxidation
Gabapentin	None	–
Lacosamide	None	–
Lamotrigine	None/weak inducer	UGT
Levetiracetam	None	–
Methsuximide	None	–
Oxcarbazepine	Inducer (weak)	CYP3A4, UGT
Phenobarbital	Inducer	CYP2C, CYP3A, EH, UGT
Phenytoin	Inducer	CYP2C, CYP3A, EH, UGT
Piracetam	None	–
Pregabalin	None	–
Primidone	Inducer	CYP2C, CYP3A, EH, UGT
Retigabine	None	–
Rufinamide	None	–
Stiripentol	Inhibitor	CYP2D6, CYP2C19, CYP3A2

Table 1 (continued)

Drug	Effect	Enzymes affected
Sulthiame	Inhibitor	CYP2C9, CYP2C19
Tiagabine	None	–
Topiramate	Inducer (weak)	CYP3A4, β-oxidation
	Inhibitor (weak)	CYP2C19
Valproic acid	Inhibitor	CYP2C9, EH, UGT
Vigabatrin	None	–
Zonisamide	Inhibitor	CYP2C9, CYP2C19, CYP2A6, CYP2E1

The above data are based on both in vitro and in vivo data
CYP cytochrome P450, *EH* epoxide hydrolase (microsomal), *UGT* uridine glucuronyl transferases

Enzyme Induction

Enzyme induction is the consequence of an increase in enzyme protein resulting from an increase in gene transcription that is mediated by intracellular receptors. However, enzyme induction may also occur by an inducer-mediated decrease in the rate of enzyme degradation, through stabilization of proteins, as occurs with ethanol induction. Thus, although there are several different mechanisms of enzyme induction, the phenobarbital "type" has been best characterized. Indeed, even though phenobarbital is the prototype enzyme-inducing drug, many other drugs (e.g., carbamazepine, phenytoin, primidone, and rifampicin) also enhance drug metabolizing enzymes with induction patterns that overlap that of phenobarbital. The enzymes associated with phenobarbital "type" induction include CYP1A2, CYP2B6, CYP2C8, CYP3C9, and CYP3A4, epoxide hydrolase, and some UGTs.

Enzyme induction results in an increase in enzyme activity, which in turn results in an increase in the rate of metabolism of the affected drug and therefore leads to a decrease in plasma level and possibly a reduction in the therapeutic response. If the affected drug has a pharmacologically active metabolite, induction can result in increased metabolite

levels and possibly an increase in drug toxicity. The amount of enzyme induction is generally proportional to the dose of the inducing drug. As enzyme induction requires synthesis of new enzymes, the time course of induction (and indeed the reversal of induction upon removal of the inducer) is dependent on the rate of enzyme synthesis and/or degradation and the time to reach plasma steady-state levels of the inducing drug. The latter is usually the rate-limiting step and only occurs at a time which is approximately five elimination half-lives of the inducing drug. Thus, the time course of induction is usually gradual and dose-dependent.

Enzyme induction represents a common problem in the management of epilepsy. Carbamazepine, phenobarbital, phenytoin, and primidone are potent inducers of CYPs, although phenytoin and carbamazepine appear to be less potent inducers at doses used clinically. The elderly appear to be less sensitive than younger adults to inducers and thus there is reduced induction of drug metabolism in the elderly, although the evidence for this is contradictory. The reason for the age-dependent response to inducers is not fully understood. Although enzyme induction generally reduces the pharmacological effect of a drug because of increased drug metabolism, sometimes the formed metabolite has the same pharmacological activity as the parent drug. Thus, the clinical consequence of enzyme induction will be determined by the relative reactivity of the parent drug and the formed pharmacologically active metabolite.

Of the AEDs presently used in clinical practice, carbamazepine, felbamate, oxcarbazepine, phenobarbital, phenytoin, primidone, and topiramate at doses of ≥200 mg/day are the only drugs that are associated with clinically important hepatic enzyme inducing properties.

Anticipating and Predicting Metabolic Interactions

In the clinical setting, an important objective of the AED treatment is to anticipate and minimize the risks of interactions with other agents. An unexpected loss of seizure control

or development of toxicity during AED therapy often accompanies the addition or removal of a concurrently administered drug.

In the past, drug interactions were identified essentially by serendipity. Typically, patients would complain of adverse effects or an increase in seizure frequency subsequent to the introduction of an additional drug to their drug regimen and upon investigation a drug interaction would be confirmed or refuted. In the late 1980s, formal drug interaction studies became an integral component of AED clinical trial development programs but most drug interaction studies were conducted relatively late in Phase II and Phase III clinical development programs and were based on a strategy that was in turn based on the therapeutic indices of drugs and the likelihood of their concurrent use. More recently, with the availability of human hepatic tissue and recombinant CYP enzymes, in vitro systems have been used as screening tools to predict the potential for in vivo drug interaction at a much earlier stage of drug development. The use of in vitro systems for investigating the ability of a drug to inhibit the metabolism of other drugs provides some of the most useful information in predicting potential drug-drug interactions. Nevertheless, the in vitro and clinical evaluation of all drugs with the potential to interact with an AED is not possible prior to licensing and thus interactions continue to come to light subsequent to licensing and during the drugs' availability for general clinical use. Particular sources of such interaction data include case reports, therapeutic drug monitoring databases, and population pharmacokinetic modeling databases [36].

In recent years our understanding of how individual drugs are metabolized has greatly facilitated the prediction of metabolic interactions. While AEDs are metabolized in the liver via numerous pathways such as β-oxidation (e.g., valproic acid) and conjugation involving UGTs (e.g., eslicarbazepine, lamotrigine, oxcarbazepine, retigabine, and valproic acid), by far the most important system for AED metabolism is the CYP system (e.g., clobazam, clonazepam, carbamazepine, ethosuximide, felbamate, phenytoin, phenobarbital,

stiripentol, topiramate, tiagabine, and zonisamide). For an accurate prediction of a drug's potential to interact, it is essential to identify the enzyme(s) responsible for the metabolism of the drug. Furthermore, in order to be able to anticipate the possible clinical relevance of an interaction, it is important to determine the relative contribution of the metabolic pathway(s) being inhibited or induced to the overall elimination of the drug. In some cases, a single metabolic reaction may involve multiple isoforms or different enzyme systems, while in other cases all the metabolic reactions of a drug are catalyzed by a single enzyme. The metabolism (S-oxidation) of 10-(*N*,*N*-dimethylaminoalkyl) phenothiazines is an example of the first scenario in which numerous CYP isoforms, including CYP2A6, CYP2C8, and CYP2D6, are involved in its metabolism. On the other hand the metabolism of indinavir, an HIV protease inhibitor, via four oxidative metabolic reactions (N-oxidation, N-dealkylation, indan hydroxylation, and phenyl hydroxylation), is catalyzed by a single isoform of CYP, namely CYP3A4.

While in vitro data can be used to anticipate in vivo inhibitory interactions, such data are of very limited value in assessing the enzyme inducing properties of a drug. For AEDs that do not undergo hepatic metabolism (e.g., gabapentin, levetiracetam, pregabalin, and vigabatrin), or those that are metabolized by non-CYP isoenzymes (e.g., lacosamide, rufinamide) and neither inhibit nor induce CYP isoenzymes, these characteristics provide a powerful predictor that these AEDs are unlikely to be associated with pharmacokinetic interactions. Indeed, clinically these AEDs are observed to be non-interacting.

The clinical consequences of enzyme inhibition depend on the plasma level of the inhibitor, its inhibition constant for the enzyme, and the relative contribution of the pathway to the elimination of the affected drug. If the inhibited pathway accounts for only a small fraction (e.g., <30–40 %) of the drug's total clearance, the impact of the interaction on the drug's plasma level and clinical effect will be minimal. Age, genetics, and environmental factors may also influence the

extent of inhibition. The effects of inhibition interactions are usually apparent within 24 h of addition of the inhibitor, with time to the maximal increase in plasma levels determined by the time required for both the inhibitor and affected drug, which will now have a more prolonged half-life, to achieve steady-state. After discontinuation of the inhibitor, the time course for the decrease in plasma levels depends on the same factors.

In contrast to inhibitory interactions, interactions involving induction can be substantial even if induction involves a minor pathway of drug elimination. In this setting, the minor pathway may become the major pathway responsible for drug clearance causing a clinically relevant decrease in plasma levels.

Interactions with phenytoin, whereby the hepatic enzyme primarily responsible for the metabolism of phenytoin is the isoenzyme CYP2C9 (>80 %) while CYP2C19 contributes <20 % to the metabolism of phenytoin, need more thoughtful consideration. Thus, if amiodarone, fluconazole, miconazole, ketoconazole, propoxyphene, or valproic acid (which inhibit CYP2C9) are co-administered with phenytoin, they will have a substantial potential to inhibit phenytoin metabolism and elevate plasma phenytoin levels. In contrast, if topiramate, cimetidine, felbamate, omeprazole, fluoxetine, or ticlopidine (which inhibit CYP2C19) are co-administered with phenytoin they will only have a small potential to inhibit phenytoin metabolism and elevate plasma phenytoin levels. However, while CYP2C19 is a minor pathway for phenytoin metabolism, its relative contribution increases at higher plasma phenytoin levels due to saturation of the primary phenytoin pathway, CYP2C9. Thus, interactions with CYP2C19 inhibitors, while of minor importance at low phenytoin plasma levels, assume greater significance as plasma phenytoin levels increase. Consequently, patients with phenytoin plasma levels above the saturable level for CYP2C9, which occur at or below the therapeutic range, are more prone to significant elevations in phenytoin plasma levels with the addition of CYP2C19 inhibitors.

Many interactions are associated with large inter-subject variability. In the case of interactions involving phenytoin, this can be explained by various factors. Firstly, there is significant inter-subject variability in the contribution of CYP2C9 and CYP2C19 to its metabolism. Secondly, it is known that drugs that inhibit CYP2C19 (without inhibiting CYP2C9), including carbamazepine, omeprazole, ticlopidine, felbamate, and topiramate, produce inconsistent elevations in phenytoin plasma levels. Thirdly, there is pharmacogenetic variability in CYP expression and a significant proportion of Caucasians and Asians exhibit the "poor metaboliser phenotype" of CYP2C19. In such subjects, inhibition of CYP2C19 is not manifested. Lastly, in the case of the interaction with carbamazepine, carbamazepine may increase the clearance of phenytoin through induction of CYP2C9 and/or CYP2C19.

A further confounding factor relates to the fact that drug interactions may relate to specific competitive inhibition of polymorphic enzymes. For example, omeprazole and diazepam are predominantly metabolized by CYP2C19. The CYP2C19 isoform is known to be polymorphic and approximately 2–6 % of Caucasians and 18–22 % of Asians have been found to be poor metabolizers. Thus, patients that are extensive metabolizers of omeprazole, and consequently have a higher baseline metabolism of omeprazole, are more susceptible to enzyme inhibition interactions than are patients that are poor metabolizers of omeprazole. Similarly, extensive metabolizers are more susceptible to enzyme induction than poor metabolizers.

Databases listing substrates, inhibitors, and inducers of different CYP isoenzymes provide an invaluable resource in helping the physician to predict and eventually to avoid potential interactions (Table 2). For example, knowledge that carbamazepine is an inducer of CYP3A4 allows one to predict that it will reduce the plasma level of CYP3A4 substrates such as ethosuximide, tiagabine, steroid oral contraceptives, and cyclosporine. Likewise, the ability of ketoconazole to inhibit CYP3A4 explains the clinically important rise in plasma carbamazepine levels after ingestion of this antifungal agent.

Table 2 Metabolic characteristics of antiepileptic drugs and their propensity to affect hepatic metabolism and cause a pharmacokinetic interaction with other AEDs

AED	Hepatic metabolism (%)	Enzymes involved in metabolism	Elimination by renal excretion (%)	Propensity to interact
Carbamazepine	Substantial (98)	CYP1A2, CYP2C8, CYP3A4	Minimal (2)	Substantial
Phenytoin	Substantial (95)	CYP2C9, CYP2C19	Minimal (2)	Substantial
Phenobarbital	Substantial (80)	CYP2E1, CYP2C19	Minimal (20)	Substantial
Primidone	Minimal (35)	CYP2E1, CYP2C9, CYP2C19	Moderate (65)	Substantial
Stiripentol	Substantial (73)	CYP1A2, CYP2C19, CYP3A4	Minimal (27)	Substantial
Sulthiame	Moderate (68)	Not identified but involve CYP isoenzymes	Minimal (32)	Substantial
Valproic acid	Substantial (97)	CYP2A6, CYP2C9, CYP2C19, CYP2B6, UGT1A3, UGT2B7	Minimal (3)	Substantial
Lamotrigine	Substantial (90)	UGT1A4, UGT1A1, UGT2B7	Minimal (10)	Moderate
Clobazam	Substantial (100)	CYP3A4	None (0)	Minimal
Clonazepam	Substantial (99)	CYP3A4	Minimal (1)	Minimal

(continued)

Table 2 (continued)

AED	Hepatic metabolism (%)	Enzymes involved in metabolism	Elimination by renal excretion (%)	Propensity to interact
Eslicarbazepine acetate	Substantial (>99)	Not identified but UGTs are involved	Minimal (1)	Minimal
Ethosuximide	Substantial (80)	CYP2B, CYP2E1, CYP3A4	Minimal (20)	Minimal
Felbamate	Moderate (50)	CYP3A4, CYP2E1	Moderate (50)	Minimal
Methsuximide	Substantial (99)	CYP2C19	Minimal (1)	Minimal
Oxcarbazepine	Substantial (>99)	Not identified but UGTs are involved	Minimal (<1)	Minimal
Retigabine	Moderate (50–65)	UGT1A1, UGT1A3, UGT1A4, UGT1A9	Minimal (20–30)	Minimal
Rufinamide	Substantial (96)	Unknown (but not CYP-dependent)	Minimal (4)	Minimal
Tiagabine	Substantial (98)	CYP3A4	Minimal (<2)	Minimal
Topiramate	Moderate (50)	Not identified but involve CYP isoenzymes	Moderate (50)	Minimal

Zonisamide	Moderate (65)	CYP3A4	Minimal (35)	Minimal
Acetazolamide	Not metabolized	None	Substantial (100)	Non-interacting
Gabapentin	Not metabolized	None	Substantial (100)	Non-interacting
Lacosamide	Moderate (60)	Demethylation	Minimal (40)	Non-interacting
Levetiracetam	Minimal (30) – non-hepatic, occurs in whole blood	Type-B esterase	Moderate (66)	Non-interacting
Piracetam	Not metabolized	None	Substantial (100)	Non-interacting
Pregabalin	Not metabolized	None	Substantial (98)	Non-interacting
Vigabatrin	Not metabolized	None	Substantial (100)	Non-interacting

Factors That Impact on the Relevance of a Metabolic Interaction

Although the number of theoretically possible interactions based on knowledge of the CYP and other enzyme systems (Table 3) are increasing, it must be appreciated that not all will be of clinical importance. The factors to be considered when evaluating the practical relevance of a potential interaction are as follows:

1. The nature of the interaction at the enzyme site – is it a substrate, an inhibitor, or an inducer?
2. The spectrum of isoenzymes that are induced or inhibited by the interacting agent.
3. The potency of the inhibition/induction – a potent effect will result in a more ubiquitous interaction affecting many/most patients.
4. The concentration (level) of the inhibitor/inducer at the isoenzyme site – drugs that achieve low levels in blood may never reach the level threshold necessary to elicit an interaction.
5. The extent of metabolism of the substrate through the particular isoenzyme – if the affected enzyme is only responsible for a small fraction of the drug's clearance, its inhibition is not going to result in a substantial interaction. Conversely, enzyme induction may increase the activity of the affected enzyme many-fold, and therefore it may increase substantially the total clearance of the drug.
6. The saturability of the isoenzyme – isoenzymes that are saturable at drug levels encountered clinically are more susceptible to significant inhibitory interactions.
7. The route of administration – for drugs showing extensive first-pass metabolism, any change in plasma drug level caused by enzyme induction or inhibition will be much greater after oral than after parenteral administration.
8. The presence of pharmacologically active metabolites – such metabolites complicate the outcome of a potential interaction, and may themselves act as enzyme inducers or inhibitors.

Table 3. AED and non-AED drug substrates, inhibitors, and inducers of the major CYP and UGT isoenzymes involved in drug metabolism.

Isoenzymes	Substrates	Inhibitors	Inducers
CYP1A2	**AEDs:** Carbamazepine, stiripentol **Non-AEDs:** Aminophylline, amitriptyline, caffeine, clomipramine, chlorpromazine, clozapine, dacarbazine, fluvoxamine, haloperidol, imipramine, lidocaine, melatonin, mirtazapine, olanzapine, paracetamol, phenacetin, propranolol, ropivacaine, sulindac, tacrine, tamoxifen, theophylline, tizanidine, verapamil, *R*-warfarin, zolpidem, zopiclone	***Non-AEDs*:** Ciprofloxacin Clarithromycin Enoxacin Fluvoxamine Furafylline Methoxsalen Rofecoxib Oral contraceptives	***AEDs*:** Carbamazepine Phenobarbital Phenytoin Primidone ***Non-AEDs*:** Rifampicin Ritonavir St. John's wort[b]
CYP2C9	**AEDs:** Phenobarbital, phenytoin, primidone, valproic acid **Non-AEDs**: Amitriptyline, celecoxib, diclofenac, dicoumarol, fluoxetine, fluvastatin, ibuprofen, losartan, miconazole, naproxen, olanzapine, phenylbutazone, piroxicam, quetiapine, theophylline, tolbutamide, torasemide, voriconazole, *S*-warfarin, zidovudine, zolpidem	***AEDs*:** Valproic acid Zonisamide[a] ***Non-AEDs*:** Amiodarone Chloramphenicol Delavirdine Efavirenz Fluconazole Fluoxetine Fluvoxamine Miconazole Sulfaphenazole Voriconazole	***AEDs*:** Carbamazepine Phenobarbital Phenytoin Primidone ***Non-AEDs*:** Hyperforin Rifampicin Ritonavir St. John's wort

(continued)

Table 3 (continued)

Isoenzymes	Substrates	Inhibitors	Inducers
CYP2C19	**AEDs:** Diazepam, phenobarbital, phenytoin, primidone, stiripentol, valproic acid **Non-AEDs:** Amitriptyline, citalopram, clomipramine, imipramine, esomeprazole, lansoprazole, moclobemide, omeprazole, pantoprazole, proguanil, propranolol, voriconazole, *R*-warfarin	***AEDs*:** Eslicarbazepine Felbamate Oxcarbazepine Stiripentol Topiramate[a] Zonisamide[a] ***Non-AEDs*:** Cimetidine Delavirdine Efavirenz Esomeprazole Fluconazole Fluvoxamine Lansoprazole Miconazole Omeprazole Ticlopidine Voriconazole	***AEDs*:** Carbamazepine Phenobarbital Phenytoin Primidone ***Non-AEDs*:** Rifampicin Ritonavir

CYP2D6	***Non-AEDs:*** Alprenolol, amitriptyline, bufuralol, chlorpromazine, citalopram, clomipramine, clozapine, codeine, debrisoquine, desipramine, dextromethorphan, encainide, flecainide, fluoxetine, fluphenazine, fluvoxamine, haloperidol, imipramine, maprotiline, metoprolol, mianserin, mirtazapine, nefazodone, nortriptyline, olanzapine, paroxetine, perphenazine, phenformin, pindolol, propafenone, propranolol, quetiapine, risperidone, ritonavir, sertindole, tamoxifen, thioridazine, timolol, tramadol, venlafaxine, zuclopenthixol	***AEDs*:** Stiripentol ***Non-AEDs*:** Cimetidine Fluoxetine Haloperidol Lansoprazole Paroxetine Perphenazine Propafenone Quinidine Terbinafine Thioridazine Verapamil	*No inducer known*
CYP2E1	***AEDs:*** Ethosuximide, felbamate, phenobarbital, primidone ***Non-AEDs:*** Chlorzoxazone, dapsone, ethanol, halothane, isoniazid	***AEDs*:** Zonisamide[a] ***Non-AEDs*:** Disulfiram	***Non-AEDs*:** Ethanol Isoniazid

(continued)

Table 3 (continued)

Isoenzymes	Substrates	Inhibitors	Inducers
CYP3A4	***AEDs:*** Carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, felbamate, stiripentol, tiagabine, valproic acid, zonisamide ***Non-AEDs:*** Alfentanil, amiodarone, amitriptyline, astemizole, atorvastatin, cisapride, citalopram, clarithromycin, clomipramine, clozapine, cyclophosphamide, cyclosporine A, dexamethasone, diltiazem, docetaxel, doxorubicin, erythromycin, etoposide, felodipine, fentanyl, fluoxetine, fluvoxamine, glucocorticoids, haloperidol, ifosfamide, imipramine, indinavir, irinotecan, isoniazid, itraconazole, ketoconazole, lacidipine, lercanidipine, lidocaine, lopinavir, lovastatin, methadone, mirtazapine, nefazodone, nevirapine, nifedipine, nimodipine, olanzapine, oral contraceptives, paclitaxel, procarbazine, proguanil, quetiapine, quinidine, rifampicin, risperidone, ritonavir, saquinavir, sertindole, sertraline, sildenafil, simvastatin, steroids, tacrolimus, tamoxifen, teniposide, terfenadine, theophylline, thiotepa, topotecan, trazodone, troleandomycin, venlafaxine, verapamil, vinblastine, vincristine, vindesine, voriconazole, ziprasidone, zolpidem	***AEDs*:** Stiripentol ***Non-AEDs*:** Amprenavir Cimetidine Clarithromycin Cyclophosphamide Cyclosporine A Delavirdine Dexamethasone Dextropropoxyphene Diltiazem Docetaxel Doxorubicin Efavirenz Erythromycin Etoposide Fluconazole Fluoxetine Fluvoxamine Grapefruit juice Ifosfamide	***AEDs*:** Carbamazepine Eslicarbazepine Felbamate[a] Oxcarbazepine[a] Phenobarbital Phenytoin Primidone Topiramate[a] ***Non-AEDs*:** Cyclophosphamide Dexamethasone Docetaxel Efavirenz Glucocorticoids[a] Nefazodone Nevirapine Paclitaxel Rifabutin Rifampicin St. John's wort Tamoxifen Teniposide

Indinavir
Isoniazid
Itraconazole
Ketoconazole
Lidocaine
Lopinavir
Methadone
Miconazole
Nefazodone
Nelfinavir
Nifedipine
Paclitaxel
Posaconazole
Propoxyphene
Ritonavir
Teniposide
Troleandomycin
Venlafaxine
Verapamil
Vinblastine
Vindesine
Zidovudine

(continued)

Table 3 (continued)

Isoenzymes	Substrates	Inhibitors	Inducers
UGT1A4	**AEDs:** Lamotrigine, eslicarbazepine **Non-AEDs:** Amitriptyline, clozapine, imipramine, olanzapine	Sertraline Valproic acid	**AEDs:** Carbamazepine Phenobarbital Phenytoin Primidone **Non-AEDs:** Oral contraceptives
UGT1A6	**AEDs:** Valproic acid **Non-AEDs:** Acetaminophen	Probenecid	**AEDs:** Carbamazepine Phenobarbital Phenytoin Primidone **Non-AEDs:** Oral contraceptives
UGT1A9	**AEDs:** Eslicarbazepine, valproic acid **Non-AEDs:** Acetaminophen, propofol, tolcapone	Probenecid	**AEDs:** Carbamazepine Phenobarbital Phenytoin Primidone **Non-AEDs:** Oral contraceptives

UGT2B7	**AEDs:** Eslicarbazepine, valproic acid **Non-AEDs:** Codeine, ibuprofen, morphine, naloxone, naproxen, zidovudine	Atovaquone Fluconazole Probenecid	**AEDs:** Carbamazepine Phenobarbital Phenytoin Primidone **Non-AEDs:** Oral contraceptives
UGT2B17	**AEDs:** Eslicarbazepine		**AEDs:** Carbamazepine Phenobarbital Phenytoin Primidone
UGT2B4	**AEDs:** Eslicarbazepine		**AEDs:** Carbamazepine Phenobarbital Phenytoin Primidone

The list is not exhaustive and is intended for guidance only. Prediction of drug interactions based on this table (see text) are involved in determining whether a clinically significant drug interaction will or will not occur
CYP Cytochrome P450, UGT uridine glucuronyl transferases
[a]These drugs are weak inducers or inhibitors
[b]Only an inducer in females

9. The therapeutic window of the substrate – interactions affecting drugs with a narrow therapeutic window are more likely to be of clinical significance.
10. The plasma level of the affected drug at baseline – any change in plasma drug level will have greater consequences if the baseline level is near the threshold of toxicity (or near the threshold required to produce a desirable therapeutic effect).
11. The genetic predisposition of the individual patient – for example, subjects who show deficiency of a genetically polymorphic isoenzyme (e.g., CYP2D6 or CYP2C19) will not exhibit interactions mediated by induction or inhibition of that isoenzyme.
12. The susceptibility and the sensitivity of the individual in relation to adverse effects – the elderly are more susceptible to interactions because as a patient group they are more likely to receive multiple medications. Also the elderly are more sensitive to the adverse effects of drugs.
13. The probability of the potential interacting drugs being co-prescribed – if a particular combination is unlikely to be co-prescribed, then any potential interaction will be of no clinical relevance.

Prevention and Management of Adverse AED Interactions

From a therapeutic viewpoint, drug interactions are best avoided by use of drugs that are not potent CYP inhibitors or inducers and are not readily inhibited by other drugs. In reality, drug interactions caused by mutual inhibition are almost inevitable, because CYP-mediated metabolism represents a major route of elimination of many drugs and because the same CYP enzymes can metabolize numerous drugs. The clinical significance of a metabolic drug interaction will depend on the magnitude of the change in the concentration of the active species (parent drug and/or metabolites) at the site of pharmacological action and the therapeutic index of

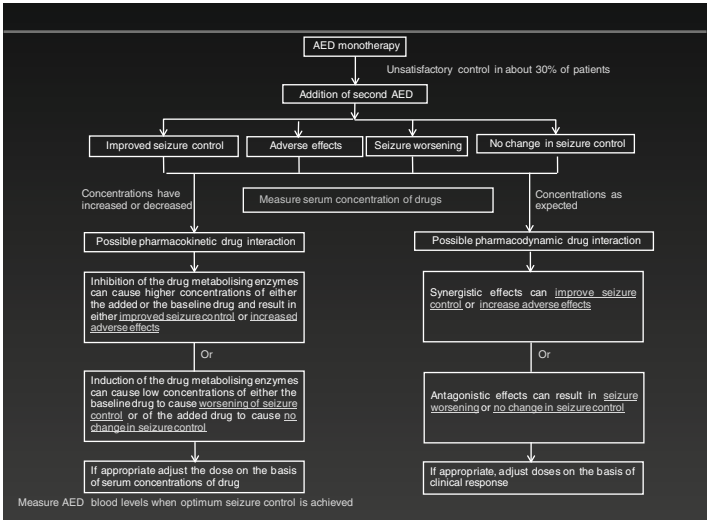

FIGURE 1 Effect of AED interactions on therapeutic outcome (Adapted from Patsalos et al. [3] with permission John Wiley and Sons)

the drug. The smaller the difference between toxicity and efficacy, the greater the likelihood that a drug interaction will have serious clinical consequences.

Prevention of AED interactions is best achieved by avoiding unnecessary polytherapy or by selecting alternative agents that have less potential to interact. The management of interactions begins with anticipating their occurrence and being familiar with the mechanisms involved (Fig. 1). Indeed, awareness of the mechanism of a drug interaction can be used to clinical advantage. For example, when one drug decreases the rate of elimination of another and increases the half-life of the affected drug, this can have an impact on the frequency of dosing, which in turn may improve compliance, or it may mean that a reduction of the dose of the affected drug is necessary. Also, in patients with a sub-therapeutic plasma drug level, elevation of the level may actually result in better seizure control. By following a few simple rules, potential adverse consequences of AED interactions can be minimized or even avoided:

Rule 1
Utilize multiple drug therapy only when it is clearly indicated. Most patients with epilepsy can be best managed with a carefully individualized dosage of a single AED.

Rule 2
If a patient suffers from co-morbidities requiring multiple medications, it is preferable to treat the seizure disorder with an AED having a low interaction potential. Eslicarbazepine acetate, ethosuximide, lamotrigine, topiramate, lacosamide, levetiracetam, retigabine, tiagabine, gabapentin, and pregabalin have little or no ability to cause enzyme induction or inhibition. Among AEDs, the lowest interaction potential is associated with the renally eliminated agents acetazolamide, gabapentin, levetiracetam, piracetam, pregabalin, and vigabatrin.

Rule 3
Be aware of the most important interactions and their underlying mechanisms and any corrective action required (e.g., altered dosing requirements). Most interactions are metabolically based and can be predicted from knowledge of the isoenzymes responsible for the metabolism of the most commonly used drugs and the effects of these drugs on the same isoenzymes.

Rule 4
Avoid combining AEDs with similar adverse effects profiles – for example, benzodiazepines and barbiturates – or drugs associated with additive neurotoxicity, for example, two sodium-channel blockers (carbamazepine and oxcarbazepine, or carbamazepine and lamotrigine). Combining drugs acting through different mechanisms are much better tolerated. Always choose drug combinations for which there is clinical evidence of favorable pharmacodynamic interactions (e.g., ethosuximide and valproate in refractory absence seizures or valproate and lamotrigine in the management of a wide variety of refractory seizures).

Rule 5
Observe clinical response carefully whenever a drug is added or discontinued from the patient's regimen. Consider the

possibility of an interaction if there is an unexpected change in response. Adjust dosage when appropriate.

Rule 6
Be aware that some patient groups (e.g., the elderly, patients with renal or hepatic insufficiency, and during pregnancy) may be more susceptible to interactions and/or more sensitive to the adverse effects of drugs. A contributing confounding factor among these patients is that their pharmacokinetic handling of drugs is altered.

Rule 7
If a pharmacokinetic interaction is anticipated, monitor, if appropriate, the plasma level of the affected drug. Be aware that under certain circumstances (e.g., in the presence of drug displacement from plasma proteins), routine total drug level measurements may be misleading and patient management may benefit from monitoring of free non-protein bound drug levels (e.g., the interaction between valproic acid and phenytoin). In some cases, dosage adjustments may have to be implemented at the time the interacting drug is added or removed. Also, with some drugs, monitoring of surrogate therapeutic markers is preferable over blood level monitoring (e.g., with warfarin and dicoumarol it is advisable to monitor the INR [international normalized ratio] whenever a significant change in therapy of a concomitant enzyme inducing AED is made).

Rule 8
When adding a drug to treat intercurrent or concomitant conditions, choose the one which within a given class is least likely to be involved in worrisome problematic interactions. For example, famotidine would be preferable to cimetidine as an H_2 antagonist, and atenolol would be preferable to metoprolol as a β-adrenoceptor blocker.

Rule 9
Ask patients to report any symptoms or signs suggestive of overdosage or insufficient therapeutic cover.

Rule 10
Inform patients of potential hazards associated with over-the-counter medicines, vitamin supplements, and herbal products.

Many such products are known to interfere with the metabolism of AEDs. Discuss in advance with patients and appropriate alternatives should be suggested, e.g., cold or allergy preparations containing a sympathomimetic amine rather than antihistamines, non-alcoholic formulations of medications, and use of parenteral or oral nonsteroidal anti-inflammatory drugs rather than narcotic analgesics for mild-to-moderate pain control.

The Role of Therapeutic Drug Monitoring in the Management of AED Interactions

Since AED interactions are primarily pharmacokinetic in nature and therefore characterized by a change in drug plasma levels, the role for therapeutic drug monitoring in managing these interactions is very important [23, 37]. For most AEDs there are well-accepted target/therapeutic ranges, however, this is not the case for non-AED drugs. Indeed, for many non-AED drugs there is still debate as to what would be the best parameter for measurement (trough [C_{min}] or peak [C_{max}] blood level or the area under the concentration versus time curve [AUC]). The best approach, in most clinical settings, is to undertake a drug level measurement before adding a second drug and then to undertake further drug level measurements and to use the latter values, as necessary, to adjust dosage to achieve the previously effective plasma level and response. It should be remembered, however, that for plasma protein binding displacement interactions, patient management may be best guided by the use of free (non-protein bound) plasma drug levels [23] (Fig. 2).

With some drug interactions, surrogate markers other than plasma drug levels are better suited as a guide to clinical management. For example, it is advisable to monitor the INR (international normalized ratio) with warfarin and dicoumarol whenever a significant change in therapy of a concomitant enzyme inducing AED is made. Also, the determination of the viral load of HIV patients prescribed AEDs and antiviral medication may provide an invaluable indicator of an underlying interaction.

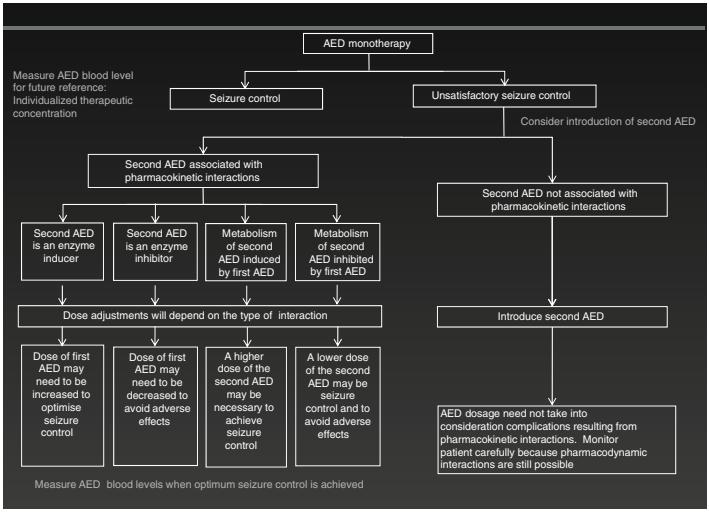

FIGURE 2 Strategies for managing interactions: dosage adjustments based on mechanism of drug interaction (Adapted from Patsalos et al. [3] with permission John Wiley and Sons)

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