Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs

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ABSTRACT – Interactions between antiepileptic drugs, or between antiepileptic drugs and other drugs, can be pharmacokinetic or pharmacodynamic in nature. Pharmacokinetic interactions involve changes in absorption, distribution or elimination, whereas pharmacodynamic interactions involve synergism and antagonism at the site of action. Most clinically important interactions of antiepileptic drugs result from induction or inhibition of drug metabolism. Carbamazepine, phenytoin, phenobarbital and primidone are strong inducers of cytochrome P450 and glucuronizing enzymes (as well as P-glycoprotein) and can reduce the efficacy of co-administered medications such as oral anticoagulants, calcium antagonists, steroids, antimicrobial and antineoplastic drugs through this mechanism. Oxcarbazepine, eslicarbazepine acetate, felbamate, rufinamide, topiramate (at doses ≥200 mg/day) and perampanel (at doses ≥8 mg/day) have weaker inducing properties, and a lower propensity to cause interactions mediated by enzyme induction. Unlike enzyme induction, enzyme inhibition results in decreased metabolic clearance of the affected drug, the serum concentration of which may increase leading to toxic effects. Examples of important interactions mediated by enzyme inhibition include the increase in the serum concentration of phenobarbital and lamotrigine caused by valproic acid. There are also interactions whereby other drugs induce or inhibit the metabolism of antiepileptic drugs, examples being the increase in serum carbamazepine concentration by erythromycin, and the decrease in serum lamotrigine concentration by oestrogen-containing contraceptives. Pharmacodynamic interactions between antiepileptic drugs may also be clinically important. These interactions can have potentially beneficial effects, such as the therapeutic synergism of valproic acid combined with lamotrigine, or adverse effects, such as the reciprocal potentiation of neurotoxicity observed in patients treated with a combination of sodium channel blocking antiepileptic drugs.

Key words: antiepileptic drugs, epilepsy, drug interactions, pharmacokinetics, pharmacodynamics, humans

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Up to one quarter of people with epilepsy take two or more antiepileptic drugs (AEDs) (Tsiropoulos *et al.*, 2006), and this proportion has been reported to increase to over 75% among medically refractory patients attending tertiary referral centres (Malerba *et al.*, 2010). Additionally, there is a high probability of AEDs being co-prescribed with other drugs at some point in life. Co-morbidities are particularly prevalent in elderly people with epilepsy, in whom AEDs are often used together with antihypertensive drugs, psychotropics, lipid lowering agents, and other drugs (Leppik, 2008).

Because most AEDs have a narrow therapeutic index and many affect the activity of drug metabolizing enzymes, in addition to being themselves substrates of the same enzymes (Patsalos and Perucca, 2003a, 2003b; Perucca, 2006), clinically relevant drug interactions are common and often lead to adverse effects (Perucca and Kwan, 2005; Brodie *et al.*, 2013; Patsalos, 2013a, 2003b).

Interactions can be pharmacokinetic or pharmacodynamic in nature. Pharmacokinetic interactions involve changes in drug metabolism or, less often, drug absorption, distribution and renal excretion, and are associated with a change in the serum concentration of the affected drug. In contrast, pharmacodynamic interactions occur at the site of action and do not involve changes in the serum concentration of the affected drug. Pharmacokinetic interactions are easier to document objectively, and therefore they are reported more frequently, but they are not necessarily more important than pharmacodynamic interactions.

Although some attempts have been made to classify drug interactions according to their clinical relevance (Johannessen and Johannessen Landmark, 2010), in practice it is difficult to generalize about the magnitude and clinical importance of any interaction, because consequences vary across patients depending on factors such as dosage and serum concentration of both the interacting and the affected drug, the clinical status of the patient (including his/her genetic profile, which may affect the expression of enzymes involved in drug metabolism and pharmacodynamic sensitivity to drug effects), and potential confounding factors such as associated diseases and other co-medications.

Mechanisms of interaction

Pharmacokinetic interactions

Enzyme induction
Carbamazepine, phenytoin, phenobarbital and primidone are broad-spectrum enzyme inducers because they stimulate the activity of many cytochrome P450 (CYP) enzymes, as well as uridin-glucuronyl trans-

ferases (UGT) and epoxide hydrolase (Patsalos *et al.*, 2002; Perucca, 2006; Brodie *et al.*, 2013). Oxcarbazepine, eslicarbazepine acetate, felbamate, rufinamide, topiramate (at doses ≥200 mg/day) and perampanel (at doses ≥8 mg/day) have weaker enzyme-inducing properties, and may stimulate a more restricted range of CYP and/or UGT isoenzymes (Perucca, 2006; Patsalos, 2013a, 2013b). Lamotrigine generally does not interfere with drug metabolizing enzymes, although at a dosage of 300 mg/day it has been reported to cause a decrease of about 20% in the serum concentration of levonorgestrel, a component of the contraceptive pill (Sidhu *et al.*, 2006a). A mean 40% increase of levonorgestrel clearance has also been observed with co-administration of perampanel 12 mg/day (but not with 4 and 8 mg/day) (Fycompa, 2013).

Enzyme induction involves the synthesis of new enzymes and may take many days before it is completely established. The typical consequence of enzyme induction is an increased metabolism of the affected drug, leading to a decrease in its serum concentrations and pharmacological effect. Conversely, if the inducer is withdrawn, the serum concentration of the affected drug will increase, possibly leading to adverse effects (Brodie *et al.*, 2013). For some drugs which are converted to active or toxic metabolites, enzyme induction may lead to an increased concentration of the active metabolite and, consequently, an enhancement of clinical effects. For example, evidence has been provided that the induction of cyclophosphamide and thiotepa metabolism by phenytoin can increase, to a clinically significant extent, the exposure to the active metabolites 4-hydroxy-cyclophosphamide and tepa, respectively, requiring a reduction in the dosage of both anticancer drugs (De Jonge *et al.*, 2005).

Enzyme induction can have drastic effects, particularly when the affected drug undergoes extensive first-pass metabolism, such as felodipine and nisoldipine. In the latter cases, increase in first-pass metabolism leads to markedly reduced oral bioavailability of the affected drug, the concentration of which can be decreased by 90% or even more with consequent loss of clinical efficacy (Perucca, 2006).

AED interactions caused by enzyme induction can be predicted by knowing which isoenzymes metabolize a given drug, and the effects of AEDs on those enzymes. For example, carbamazepine is a well known inducer of CYP3A4 (and other enzymes) and predictably stimulates the metabolism of other CYP3A4 substrates such as many statins, many dihydropyridine calcium antagonists, and many steroids (Patsalos and Perucca, 2003a, 2003b; Brodie *et al.*, 2013). As discussed above, however, the magnitude of these interactions is subject to considerable inter-patient variability, and is not easily predictable for individual patients.

Enzyme inhibition

Enzyme inhibition is the process by which a drug inhibits the activity of enzymes metabolizing other drugs. Among commonly used AEDs, valproic acid can be considered a broad-spectrum enzyme inhibitor as it inhibits the activity of UGT enzymes (UGT1A4 and UGT2B7) as well as CYP2C9, and, weakly, CYP2C19 and CYP3A4 (Zhou *et al*., 2007). Conversely, valproic acid does not inhibit CYP1A2, CYP2D6, and CYP2E1 (Patsalos and Perucca, 2003a; Perucca, 2006).

Weak enzyme inhibitors of CYP2C19 include oxcarbazepine, eslicarbazepine, and topiramate, all of which can cause a moderate increase (usually by <50%) in the serum concentration of phenytoin, a compound partly metabolised by CYP2C19 (Patsalos *et al*., 2002; McCormack and Robinson, 2009).

Among less commonly used AEDs, felbamate inhibits several enzymes, particularly CYP2C19 (Patsalos *et al*., 2002), whereas stiripentol potently inhibits CYP3A4, CYP1A2, CYP2D6, and CYP2C19, leading to clinically relevant increases in the serum concentrations of many concomitantly administered AEDs (Johannessen Landmark and Patsalos, 2010). Rufinamide may also increase slightly (usually by <20%) serum phenobarbital and phenytoin concentrations, but the mechanism of these interactions is unclear (Perucca *et al*., 2008). Finally, the newest AED, perampanel, has been shown to determine, on average, a 35% increase in oxcarbazepine concentrations, although the effect of perampanel on the concentration of the active metabolite licarbazepine (monohydroxycarbazepine) does not seem to have been investigated (Fycompa, 2013; Zaccara *et al*., 2013).

Enzyme inhibition typically results in decreased metabolism of the affected drug, with an increase in serum concentrations to a new steady state. Unlike enzyme induction, enzyme inhibition generally occurs immediately, although its magnitude may increase gradually in parallel with the increase in serum concentration of the inhibiting agent. The serum concentrations of the affected drug reach a new steady-state after four- to five times the new half-life of the affected drug. For example, because the half-life of lamotrigine after co-administration of valproic acid may be as long as 3 to 4 days, it may take up to 2 to 3 weeks for the increase in serum lamotrigine to stabilize when valproic acid is added (Perucca and Kwan, 2005). Likewise, the time for enzyme inhibition to disappear after withdrawal of the inhibitor will depend on the half-lives of both the inhibiting drug and the affected drug.

Like enzyme induction, enzyme inhibition can be predicted by knowing which isoenzymes metabolize a given drug, and the effects of other drugs on those enzymes. For example, valproic acid is an inhibitor of UGT1A4 and predictably increases the serum concentrations of the UGT1A4 substrate lamo-

trigine by up to twice the initial concentration, or even more (Patsalos and Perucca, 2003a). Likewise, erythromycin is an inhibitor of CYP3A4 and predictably can double or even treble the serum concentrations of carbamazepine, a CYP3A4 substrate (Patsalos and Perucca, 2003b). Interindividual variability in the magnitude of interaction, however, can be considerable.

Table 1 summarizes major routes of elimination of AEDs and the enzymes involved in their metabolism.

Other pharmacokinetic mechanisms

Absorption. Drug interactions affecting gastrointestinal absorption do not seem to be common. A clinically important example is the marked impairment in the absorption of phenytoin when this drug is given together with certain enteral tube feedings (Worden *et al*., 1984). The absorption of some AEDs may also be decreased by concomitant ingestion of some antacids. For example, serum phenytoin concentrations have been found to be reduced slightly (by less than 15%) after co-ingestion with an antacid mixture of magnesium trisilicate and aluminium hydroxide (Kulshrestha *et al*., 1978), whereas gabapentin bioavailability was reduced by about 40% through co-administration with magnesium oxide (Yagi *et al*., 2012).

Protein binding and distribution. Some AEDs, most notably phenytoin and valproic acid, are highly bound to serum proteins, and displacement from protein binding sites may occur when other highly protein-bound drugs are administered concurrently. The most common of these interactions is the displacement of protein-bound phenytoin by valproic acid (Perucca, 2006).

The implications of these interactions are often misunderstood. Although it is true that only the free (unbound) drug is available to cross the endothelium and reach target sites in the tissues, typically the amount of drug which is displaced from the bloodstream represents a very small proportion of the total amount of drug present in the body. Moreover, the displaced drug is eliminated more quickly. The overall consequence of plasma protein binding interactions is therefore a fall in total serum concentration of the displaced drug without any significant change in the concentration of unbound, pharmacologically active drug. Clinicians, however, must be aware of these interactions when interpreting serum drug concentration data. In fact, laboratories routinely measure total (not unbound) drug concentrations, and if a displacement interaction occurs, the total drug concentrations underestimate the amount of unbound, pharmacologically active drug. In particular, in patients co-medicated with phenytoin and valproic acid, therapeutic and toxic effects typically occur at total serum phenytoin concentrations which are lower than usual. Likewise, if a fall in total serum phenytoin

Table 1. Main routes of elimination of antiepileptic drugs (AEDs).

	Main routes of elimination and main enzymes involved	Other routes of elimination	Active metabolites
Carbamazepine	Oxidation (CYP3A4)	Oxidation and conjugation (CYP2C8, CYP1A2, UGT2B7)	Carbamazepine-10,11-epoxide
Clobazam	Oxidation (CYP3A4 and CYP2C19)	Oxidation (CYP2C18, CYP2B6)	Desmethyl-clobazam (norclobazam)
Clonazepam	Oxidation (CYP3A4)	----	----
Eslicarbazepine acetate[2]	Glucuronide conjugation (UGT1A4, UGT1A9, UGT2B4, UGT2B7, UGT2B17)	Renal excretion	----
Ethosuximide	Oxidation (CYP3A4)	Oxidation (CYP2E1), renal	
Felbamate	Oxidation (CYP 3A4) (> 50%)	Renal excretion (>30%), Oxidation (CYP2E1), Glucuronide conjugation	----
Gabapentin	Renal excretion	----	----
Lacosamide	Demethylation (CY3A4, CYP2C9, CYP2C19)	Renal excretion (about 40%)	----
Lamotrigine	Glucuronide conjugation (UGT1A4)	----	----
Levetiracetam	Renal excretion (75%)	Hydrolysis (25%)	----
Oxcarbazepine[1]	Glucuronide conjugation (>50%)	Renal excretion (< 30%)	Mono-hydroxy derivative (licarbazepine)
Perampanel	Oxidation (CYP3A4)	Glucuronide conjugation	----
Phenobarbital	Oxidation (CYP2C9) and N-glucosidation	Oxidation (CYP2C19, CYP2E1) and renal excretion (25%)	----
Primidone	Oxidation (CYP2C9)	Renal excretion, Oxidation (CYP2C19, CYP2E1), N-glucosidation	Phenobarbital
Phenytoin	Oxidation (CYP2C9 and CYP2C19)	Oxidation (CYP2C18, CYP3A4)	----
Pregabalin	Renal excretion	----	----
Retigabine	N-acetylation	N-glucuronide conjugation (UGT1A1, UGT1A3, UGT1A4, UGT1A9)	----
Rufinamide	Hydrolysis (carboxylesterases)	Glucuronide conjugation	

Table 1 (*Continued*).

	Main routes of elimination and main enzymes involved	Other routes of elimination	Active metabolites
Stiripentol	Oxidation (CYP1A2, CYP2C19, CYP3A4)	Glucuronide conjugation	----
Tiagabine	Oxidation (CYP3A4)	----	----
Topiramate	Renal excretion (40–80%)	Oxidation (inducible CYP isoforms: 20–60%)	----
Valproic acid	Oxidation (CYP2C9 and other CYPs: >50%) and glucuronide conjugation (several UGTs: 30–40%)	----	----
Vigabatrin	Renal excretion	----	----
Zonisamide	Oxidation (CYPA4), reduction and N-acetylation (> 50%)	Renal excretion (30%)	----

CYP: Cytochrome P450; UGT: Uridine Diphosphate Glucuronosyltransferases
[1]Oxcarbazepine is a prodrug, virtually entirely converted by cytosolic aryl-ketone-reductase to the active metabolite licarbazepine (a racemic mixture of eslicarbazepine and (R)-licarbazepine). The indicated routes of elimination and enzymes involved refer to licarbazepine.
[2]Eslicarbazepine acetate is a prodrug, extensively converted to eslicarbazepine by esterases. The indicated routes of elimination and enzymes involved refer to eslicarbazepine.

concentration is observed after adding valproic acid, the phenytoin dosage does not need to be increased. In fact, occasionally phenytoin dosage may need to be decreased to compensate for a concomitant inhibition of phenytoin metabolism by valproic acid which can cause a slight increase in unbound phenytoin concentrations.

The role of P-glycoprotein (P-gp) and other transporter proteins. Access of some drugs to the brain is regulated by transporter proteins such as P-gp and other transporters (Kim, 2002). Over-expression of these transporters has been reported in epileptogenic brain tissue of patients with refractory focal epilepsy, and may contribute to AED resistance (Rivers *et al.*, 2008; Löscher *et al.*, 2011). The presence of P-gp in other organs may have a role in the absorption, distribution and excretion of a wide variety of drugs and the suggestion has been made that over-expression of this protein could lead to subtherapeutic serum concentrations of some AEDs (Lazarowski *et al.*, 2007). Similar to drug metabolizing enzymes, P-gp can be inhibited or induced by other agents, resulting in altered concentrations of substrate drugs in the blood and brain (Löscher and Schmidt, 2006). For example, the ability of carbamazepine to decrease the serum concentrations of the antihistamine fexofenadine (Akamine *et al.*, 2012) and of the selective beta-blocker talinolol (Giessmann *et al.*, 2004) can be explained, at least in part, by increased expression of P-gp and/or other transporters. In fact, some pharmacokinetic interac-

tions currently attributed to enzyme induction may well be due to over-expression of transporter proteins, causing reduced gastrointestinal absorption of the affected drug, or enhancing its elimination in bile and urine (Perucca, 2006).

Pharmacodynamic interactions

Two drugs can interact at the site of action by potentiating each other's effects (synergistic interactions) or by antagonizing each other's effects (antagonistic interactions). Importantly, such interactions may influence therapeutic and toxic effects in different ways: for example, two drugs could have synergistic (or additive) efficacy, but antagonistic or less than additive (infra-additive) toxicity, resulting in an improved therapeutic index of the combination. Conversely, combining two drugs can also lead to increased toxicity and little or no gain in efficacy. Usually, pharmacodynamic interactions are inferred from empirical observations and are difficult to document objectively because efficacy and tolerability can be assessed conclusively only in the setting of randomized controlled trials. However, as discussed later in this article, evidence is accumulating that knowledge of the mechanism of action of individual AEDs can help in predicting both favourable and adverse pharmacodynamic interactions (Perucca, 2011).

Pharmacodynamic interactions can also occur between AEDs and other drugs. Examples are the

additive (or synergistic) therapeutic effects between valproic acid and some new-generation antipsychotics used for the treatment of mania such as quetiapine (Ketter, 2008), or worsening of adverse metabolic effects when valproic acid is combined with olanzapine (Meltzer *et al.*, 2011).

Interactions between AEDs

Interactions resulting in decreased serum concentration of the affected drug

The four major enzyme-inducing AEDs (carbamazepine, phenytoin, phenobarbital and primidone) stimulate the metabolism and reduce the serum concentration of most other concurrently administered AEDs (*table 2*). This can result in decreased efficacy of the affected drug. Sometimes, this is compensated for by the added therapeutic effect of the interacting AED, but in other cases, an adjustment in the dosage of the affected drug will be required. For example, the dosage requirement of valproic acid, lamotrigine, and tiagabine are significantly increased in patients taking carbamazepine, barbiturates (a term used henceforth to indicate collectively phenobarbital and primidone) and phenytoin (Patsalos and Perucca, 2003a). The clearance of perampanel has also been reported to be increased threefold and twofold by carbamazepine and phenytoin, respectively (Fycompa, 2013), suggesting that its dose requirements may also be impacted by type of co-medication. For some AEDs such as carbamazepine and tiagabine, which exhibit considerably shorter half-lives in the presence of enzyme inducers, enzyme induction also increases fluctuations in serum drug concentrations during a dosing interval, potentially leading to intermittent adverse effects at the time of peak concentration and breakthrough seizures at the time of trough (Riva *et al.*, 1985; Zaccara *et al.*, 2004; Tothfalusi *et al.*, 2008). In these cases, more frequent daily dosing, or the use of extended release formulations, can improve clinical response (Canger *et al.*, 1990).

Oxcarbazepine, eslicarbazepine acetate, rufinamide and felbamate also decrease the serum concentrations of some concomitantly administered AEDs (*table 2*), but these interactions are typically small in magnitude and of limited clinical significance (Patsalos, 2013a).

Caution is needed when an enzyme-inducing AED is discontinued, or substituted with a drug which does not have enzyme-inducing effects, because the serum concentration of the affected AEDs may increase, leading to potentially toxic concentrations if dose is not adjusted appropriately.

Interactions resulting in increased serum concentration of the affected drug

The best example of clinically relevant AED interactions associated with increased serum concentrations of the affected drug (*table 2*) is provided by the inhibition of the metabolism of lamotrigine and phenobarbital by valproic acid (Patsalos and Perucca, 2003a; Perucca, 2006).

The half-life of lamotrigine is increased two- to three-fold by valproic acid, resulting in a corresponding increase in serum lamotrigine concentrations (Yuen *et al.*, 1992). At least in adults, lamotrigine metabolism is inhibited maximally at a valproic acid dose of about 500 mg/day, and no further inhibition occurs at higher doses (Gidal *et al.*, 2003). This interaction has major clinical relevance. To minimize the risk of potentially life-threatening skin rashes, lamotrigine should be started at much lower doses and up-titrated more slowly in patients co-medicated with valproic acid (Messenheimer, 1998). The recommended maintenance doses of lamotrigine are also lower when used in combination with valproic acid. Although there is no risk of rash when valproic acid is added in patients already stabilized on lamotrigine, neurotoxic effects may occur if the dosage of the latter is not reduced by about 50% as soon as the dosage of valproic acid reaches, in an adult, about 250-500 mg/day (Messenheimer, 1998). Appropriate schemes have also been developed to adjust lamotrigine dose when valproic acid is discontinued. There are other important aspects in this interaction. In particular, valproic acid has been found to attenuate the prominent fall in lamotrigine concentration which occurs during pregnancy, or in association with use of oral contraceptives (Tomson and Hiilesmaa, 2007). Another important finding is that in patients receiving valproic acid in combination with enzyme inducing AEDs, the resulting enzyme induction and inhibition cancel out reciprocally, and lamotrigine pharmacokinetics are similar to those observed with lamotrigine monotherapy (Rambeck and Wolf, 1993). Finally, the interaction between valproic acid and lamotrigine can be bidirectional. A 25% decrease in valproic acid concentrations has been reported in patients in whom lamotrigine is added to valproic acid (Anderson *et al.*, 1996), although this interaction appears to be inconsistent (Patsalos and Perucca, 2003a).

Valproic acid also increases serum phenobarbital concentrations (May and Rambeck, 1985) and a reduction of the phenobarbital dose by 30-50% is necessary in most patients, with individual subjects requiring even larger adjustments (Henriksen and Johannessen, 1982). When valproic acid is added to carbamazepine, inhibition of the enzyme epoxide hydrolase may cause

an increase by up to 100% or even more in the serum concentration of the active epoxide metabolite of carbamazepine, potentially leading to CNS side effects (Perucca, 2006). Finally, valproic acid increases the serum concentration of rufinamide, and rufinamide dosage requirements are expected to be 50-60% lower in children co-medicated with valproic acid compared with children co-medicated with other AEDs (Perucca *et al.*, 2008). Interestingly, the increase in rufinamide concentrations caused by valproic acid seems to be greater in children than in adolescents and adults, probably because the degree of interaction is dependent on the concentration of valproic acid and children are typically exposed to higher valproic acid concentrations (Cloyd *et al.*, 2007; Brodie *et al.*, 2009; Luszczki, 2009).

Other clinically important interactions mediated by metabolic inhibition include the increase in plasma concentrations of phenobarbital, phenytoin and valproic acid caused by felbamate (Wagner *et al.*, 1991; Wagner *et al.*, 1994; Reidenberg *et al.*, 1995; Sachdeo *et al.*, 1999) and the increase in plasma concentration of clobazam, N-desmethyl-clobazam, valproic acid, phenytoin, carbamazepine, and phenobarbital caused by stiripentol (Tran *et al.*, 1996; Trojnar *et al.*, 2005). Sulthiame also increases the serum concentration of phenytoin, N-desmethyl-clobazam and, possibly, phenobarbital to a potentially clinically important extent (Perucca, 1982; Yamamoto *et al.*, 2014), although these interactions are uncommon nowadays since sulthiame is rarely used in the management of epilepsy.

Less important interactions mediated by metabolic inhibition include an increase in serum phenytoin concentration (by up to 40%) after administration of oxcarbazepine (Barcs *et al.*, 2000) or eslicarbazepine acetate (Fattore and Perucca, 2011), and an inconsistent increase in serum phenytoin after addition of topiramate (Bialer *et al.*, 2004).

Pharmacodynamic interactions

When AEDs are combined, reciprocal interactions at the site of action may occur, which can influence both their efficacy and tolerability. The best documented of these interactions is that occurring between valproic acid and lamotrigine. Several studies have now indicated that the combination of these two AEDs can produce seizure control in a variety of seizure types which are not fully responsive to maximally tolerated doses of either agent given alone (Patsalos and Perucca, 2003a; Perucca, 2006). As a result of concurrent pharmacokinetic interactions (see section above), however, use of valproic acid and lamotrigine in combination requires special caution, and careful dosage adjustments (often with a reduction in dose of both drugs) need to be made to minimize

potential adverse effects. Other potentially favourable pharmacodynamic interactions have been suggested to occur between valproic acid and ethosuximide in patients with absence seizures and between valproic acid and carbamazepine in patients with focal seizures (Patsalos and Perucca, 2003a). It is interesting to note that these reports which are suggestive of additive or synergistic efficacy involve combinations of AEDs with different mechanisms of action.

Conversely, experimental and clinical studies suggest that combinations of sodium channel blockers are often associated with an increased incidence of CNS adverse effects, rather than additive efficacy. Indeed, data suggesting adverse pharmacodynamic interactions have been reported for the combination of oxcarbazepine with carbamazepine, eslicarbazepine acetate with carbamazepine, lamotrigine with carbamazepine, and lacosamide with a variety of other sodium channel blocking AEDs (Besag *et al.*, 1998; Sake *et al.*, 2010; Fattore and Perucca, 2011; Perucca, 2011; Zaccara *et al.*, 2012). Although, mechanistically, these findings make sense, clinical evidence is based on uncontrolled observations or post-hoc analyses, and should be interpreted with caution.

Interactions between AEDs and other drugs

A large number of such interactions have been reported (Patsalos and Perucca, 2003b; Patsalos, 2013b). Those involving antidepressants and antipsychotic drugs are summarized in *box 1*, those involving oral anticoagulants are listed in *box 2*, and those involving antimicrobials are listed in *box 3*. Other important interactions are discussed in the sections below.

Interactions resulting in decreased serum concentration of AEDs

Administration of the combined contraceptive pill may decrease serum lamotrigine concentrations by about 50% or even more (Sabers *et al.*, 2003), leading to loss of seizure control in some women (Sabers *et al.*, 2001; Reddy, 2010). The interaction is mediated by the induction of lamotrigine glucuronidation by ethinylestradiol, whereas the progestagen component of the pill plays no contributory role (Reimers *et al.*, 2005). This interaction also follows a cyclic pattern, with a marked decrease in serum lamotrigine concentrations during the 21 days when the pill is taken, and a twofold rebound increase in lamotrigine concentration during the pill-free week (Sidhu *et al.*, 2006a). Oral contraceptives can also cause a similar, but less pronounced, cyclic interaction leading to a decrease in serum valproic acid concentrations (Herzog *et al.*,

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Table 2. Pharmacokinetic interactions between AEDs[1]. The vertical column refers to the AED which is added. The boxes on each line illustrate the expected changes in serum concentrations of the pre-existing drug. The magnitude of each interactions and its clinical relevance reflects the authors' judgment and need to be interpreted flexibly because intersubject variability in magnitude and consequences can be considerable.

Pre-existing AED	First generation AEDs								Second-generation AEDs															
AED added	CBZ	CLB	CNP	ETS	PB	PHT	PRM	VPA	ESL	FBM	GBP	LEV	LTG	LCM	PER	PGB	OXC	RTG	RFN	STP	TGB	TPM	VGB	ZNS
CBZ		2	3			4						5		6				7						
CLB[viii]			9																					
CNP[x]		11																						
ETS[xii]						13		14																
PB		15	16			17	18					19		20										
PHT		21					22					23		24					25					
PRM		26		27	28							29												
VPA	30					31												34						35
ESL																	36							
FBM	37	38																						
GBP																								
LEV																								
LTG			39					40																
LCM																								
PER[xlii]																								
PGB															43									
OXC	44								45															
RTG xlvi													47											
RFN																								
STP xlviii																								
TGB																								
TPM																								
VGB																								
ZNS																								

🟥	Marked increase in serum concentration
🟧	Slight to moderate increase in serum concentraion
⬜	No change
◻	No change anticipated
🟦	Mild to moderate decrease in serum concentration
🟦	Marked decrease in serum concentration
🟨	Not known
🟩	Complex or variable interaction (see note)

Abbreviations: CBZ: carbamazepine; CLB: clobazam, CNP: clonazepam; ETS: ethosuximide; PB: phenobarbital; PHT: phenytoin; PRM: primidone; VPA: valproic acid (valproate); ESL: eslicarbazepine acetate (serum concentrations refer to active metabolite eslicarbazepine); FBM: felbamate; GBP: gabapentin; LEV: levetiracetam; LTG: lamotrigine; LCM: lacosamide; PGB: pregabalin; OXC: oxcarbazepine (serum concentrations refer to active metabolite licarbazepine); RTG: retigabine (ezogabine); STP: stiripentol; TGB: tiagabine; TPM: topiramate; VGB: vigabatrin; ZNS: zonisamide.

[1]Unless otherwise specified, reported information is based on Johannessen Landmark and Patsalos (2010); Perucca (2006); Patsalos and Perucca (2003a); Fattore and Perucca (2011), Patsalos (2013a) and Tompson and Crean (2014).

[2]Carbamazepine decreases the serum concentrations of clobazam and increases the concentrations of its active metabolite N-desmethylclobazam.

[3]Lai *et al.* (1978).

[4]Carbamazepine may decrease or increase serum phenytoin concentrations. *et al.* (2011).

[5]Freitas-Lima *et al.* (2011).

[6]Contin *et al.* (2013).

[7]Observations from Phase II studies suggest that phenytoin and carbamazepine may cause a moderate reduction in serum retigabine (ezogabine) concentrations (Fattore and Perucca, 2011).

[8]Information on the effect of clobazam on other AEDs is based mainly on Walzer *et al.* (2012).

Table 2 (*Continued*).

[9]Not commonly coprescribed.

[10]Information on the effect of clonazepam on other AEDs is based mainly on Greenblatt *et al.* (1987).

[11]Not commonly co-prescribed.

[12]Information on the effect of ethosuximide on other AEDs is based mainly on Glauser *et al.* (2004).

[13]Dawson *et al.* (1978).

[14]Sälke-Kellermann *et al.* (1997).

[15]Phenobarbital decreases the serum concentrations of clobazam and increases the concentrations of its active metabolite N-desmethylclobazam.

[16]Lai *et al.* (1978).

[17]Phenobarbital may decrease or increase serum phenytoin concentrations.

[18]Not commonly co-prescribed.

[19]Freitas-Lima *et al.* (2011).

[20]Contin *et al.* (2013).

[21]Phenytoin decreases the serum concentrations of clobazam and increases the concentrations of its active metabolite N-desmethylclobazam.

[22]Phenytoin decreases serum primidone concentrations and increases the concentrations of its active metabolite phenobarbital.

[23]Freitas-Lima *et al.* (2011).

[24]Contin *et al.* (2013).

[25]Observations from Phase II studies suggest that phenytoin abd carbamazepine may cause a moderate reduction in serum retigabine (ezogabine) concentrations (Fattore and Perucca, 2011).

[26]Primidone decreases the serum concentrations of clobazam and increases the concentrations of the active metabolite N-desmethylclobazam.

[27]Not commonly co-prescribed

[28]Primidone may decrease or increase serum phenytoin concentrations

[29]Freitas-Lima *et al.* (2011).

[30]Valproic acid increases the serum concentration of the active metabolite carbamazepine-10,11-epoxide

[31]Valproic acid has variable effects on ethosuximide concentrations, which can be slightly increased, decreased or unchanged (Battino *et al.*, 1995)

[32]Valproic acid displaces phenytoin from plasma protein binding sites. As a consequence of this interaction, the total serum concentration of phenytoin is usually decreased, whereas the free phenytoin concentration is unchanged or slightly increased.

[33]Marked increase in the serum concentrations of metabolically derived phenobarbital.

[34]Fattore and Perucca (2011).

[35]Ragueneau-Majlessi *et al.* (2001).

[36]Not commonly co-prescribed

[37]Felbamate increases the serum concentration of the active metabolite carbamazepine-10,11-epoxide.

[38]Felbamate decreases the serum concentrations of clobazam and increases the concentrations of its active metabolite N-desmethylclobazam

[39]Eriksson *et al.* (1996).

[40]Interaction seems to be inconsistent (see text).

[41]Interaction seems to be inconsistent (see text).

[42]iFycompa. Summary of product characteristics [online]. www.ema.europa.eu/ema/docs/en_GB/document_library/EPASR_-_Product_Infromation/human/002434/WC500130815.pdf (Accessed 23 January 2014).

[43]Interaction seems to be inconsistent (see text).

[44]Oxcarbazepine decreases by 0-20% the serum concentrations of carbamazepine and increases by about 30% the concentrations of carbamazepine-10,11-epoxide.

[45]Not commonly co-prescribed.

[46]Information on the effect of retigabine (ezogabine) on other AEDs is based mainly on Fattore and Perucca (2011).

[47]Hermann *et al.* (2003).

[48]Information on the effect of stiripentol on other AEDs is based mainly on Trojnar *et al.* (2005).

[49]Serum concentrations of clobazam and active metabolite N-desmethylclobazam) are both increased. However, the increase in N-desmethylclobazam concentrations is far more prominent.

2005; Galimberti *et al*., 2006) and possibly oxcarbazepine might be affected in a similar way because its active metabolite licarbazepine (monohydroxycarbazepine) is also cleared by glucuronidation, the metabolic pathway stimulated by oestrogens (Aguglia *et al*., 2009).

Other drugs can stimulate the metabolism of AEDs. In particular, serum lamotrigine concentrations can be reduced by about 50% by rifampicin (Ebert *et al*., 2000). The antiretroviral combination of lopinavir/ritonavir has been found to reduce serum lamotrigine concentrations by about 50% (van der Lee *et al*., 2006) and phenytoin concentrations by about 30% (Lim *et al*., 2004), whereas atazanavir/ritonavir reduces serum lamotrigine levels by about 30% (Burger *et al*., 2008) and efavirenz reduces serum carbamazepine concentrations by 27% on average (Okulicz *et al*., 2011; Birbeck *et al*., 2012).

Cisplatin and some other antineoplastic drugs may decrease serum phenytoin concentrations (Vecht *et al*., 2003) and carbapenem antibiotics such as imipenem, meropenem, ertapenem and panipenem can cause a prominent, clinically important decrease in the serum concentrations of valproic acid (De Turck *et al*., 1998; Mori *et al*., 2007; Park *et al*., 2012). The mechanisms responsible for the latter interactions are unclear, but are probably unrelated to enzyme induction.

Interactions resulting in increased serum concentration of AEDs

Many therapeutic drugs are inhibitors of CYP3A4, the primary enzyme responsible for carbamazepine metabolism. In view of the wide utilization of carbamazepine, it is not therefore surprising that many interactions leading to clinically important elevations in carbamazepine concentrations and consequent manifestations of carbamazepine toxicity have been described (Patsalos and Perucca, 2003a, 2003b; Perucca, 2006). Clinicians should be aware of the most common of these interactions and choose, within specific drug classes, those agents that are least likely to cause troublesome effects. For example, among macrolide antibiotics, erythromycin, clarithromycin and triacetyloleandomycin are the most potent CYP3A4 inhibitors and are best avoided in carbamazepine-treated patients, whereas azithromycin, rokitamycin, dirithromycin and spiramycin do not interact with CYP3A4 and therefore do not affect carbamazepine concentrations (see *box 3*).

Phenytoin is a substrate of CYP2C9 and CYP2C19 and its serum concentrations can be increased by drugs which inhibit these enzymes (Nelson *et al*., 2001). A list of drugs which can inhibit the metabolism of specific AEDs is reported in *table 3*. The list is not exhaus-

tive and clinicians are advised to review the relevant prescribing information of any agent which they may consider adding to (or removing from) the treatment regimen of AED-treated patients.

Interactions resulting in decreased serum concentration of other drugs

A list of drugs whose metabolism can be stimulated by strong enzyme-inducing AEDs (carbamazepine, phenytoin, phenobarbital and primidone) is reported in *table 4*. This list is not exhaustive, and additional information can be found in more comprehensive reviews (Patsalos and Perucca, 2003b; Perucca, 2006; Johannessen and Johannessen Landmark, 2010; Patsalos, 2013b) and in the prescribing information of specific drugs. In general, these interactions lead to decreased efficacy of the affected drug, which in many cases can be compensated for by an appropriate increase in the dosage of the latter. Likewise, a reduction in dosage of the affected drug may be required when the enzyme-inducing agent is discontinued.

Many of these interactions are clinically significant and some can lead to virtually complete loss of efficacy of the affected drug, which cannot be easily compensated for by dose adjustment. For example, the serum concentration of many dihydropyridine calcium antagonists (Capewell *et al*., 1988; Tartara *et al*., 1991; Michelucci *et al*., 1996; Flockart and Tanus-Santos, 2002) can be decreased by more than 80-90% in patients taking enzyme-inducing AEDs, and the combination of these drugs should best be avoided. For some drug classes such as antineoplastic drugs, antiretroviral agents (see *box 3*), oral anticoagulants (see *box 2*), and immunosuppressants, the consequences of loss of efficacy due to enzyme induction can be serious and even fatal. Caution, however, should be exercised in generalizing these findings. For example, while some studies reported decreased efficacy of some antineoplastic drugs in patients taking enzyme-inducing AEDs (Vecht and Wagner, 2003; Oberndorfer *et al*., 2005), other investigations do not confirm these results (Jaeckle *et al*., 2009). These discrepancies might be related, at least in part, to differences in the specific type of antineoplastic therapy being applied (Perucca, 2013). For antineoplastic drugs which exert their effects through conversion to active metabolites, such as cyclophosphamide, enzyme induction can actually potentiate rather than attenuate pharmacological and toxic effects (De Jonge *et al*., 2005).

Oral contraceptive steroids are among the compounds most sensitive to enzyme induction. As a result, loss of contraceptive activity is expected when the pill is used in women taking old-generation enzyme-inducing AEDs. A prominent reduction in serum concentrations of oestrogens and progestagens is

Table 3. Examples of interactions whereby other drugs increase the serum concentration of antiepileptic drugs.

Affected drug	Class of inhibiting drug	Interfering drug
Carbamazepine	Antidepressants: Antimicrobials	Fluoxetine, Fluvoxamine, Trazodone, Viloxazine Clarithromycin, Erythromycin, Fluconazole, Isoniazid, Itraconazole, Ketoconazole, Metronidazole, Ritonavir, Troleandomycin, Voriconazole
	Other drugs:	Cimetidine, Danazol, Dextropropoxyphene, Diltiazem, Omeprazole, Risperidone, Quetiapine, Ticlopidine, Verapamil
Clobazam	Antimicrobials: Other drugs:	Ketoconazole Omeprazole (increases levels of N-desmethly-clobazam only)
Phenytoin	Antidepressants: Antimicrobials: Other drugs:	Fluoxetine, Fluvoxamine, Imipramine, Sertraline, Trazodone, Viloxazine Chloramphenicol, Fluconazole, Isoniazid, Miconazole, Sulfaphenazole Allopurinol, Amiodarone, Azapropazone, Cimetidine, Chlorpheniramine, Dextropropoxyphene, Diltiazem, Disulfiram, Doxifluridine, 5-Fluorouracil, Omeprazole, Phenylbutazone, Sulfinpyrazone, Tacrolimus, Tamoxifen, Ticlopidine, Tolbutamide
Phenobarbital	Antimicrobials: Analgesics:	Chloramphenicol Dextropropoxyphene
Ethosuximide	Antimicrobials:	Isoniazid
Valproic acid	Antidepressants: Antimicrobials: Other drugs:	Sertraline Erythromycin, Isoniazid Cimetidine
Lamotrigine	Antidepressants:	Sertraline
Perampanel	Antimicrobials	Ketoconazole
Topiramate	Diuretics	Hydrochlorothiazide

Sources: Patsalos and Perucca (2003b); Perucca (2006); Fycompa (2013), Walzer *et al.* (2012) and other currently available Prescribing Information.

also caused by oxcarbazepine and eslicarbazepine acetate, whereas a smaller magnitude of interaction (not necessarily involving both components of the combined contraceptive) has been reported for lamotrigine (300 mg/day), topiramate (at doses ≥200 mg/day), felbamate and rufinamide (Johnston and Crawford, 2014). A high dose of perampanel also increases the clearance of levonorgestrel by approximately 40%, but this interaction is not found at lower doses (4-8 mg/day) (Fycompa, 2013). Contraceptive formulations which can be affected by enzyme-inducing AEDs include not only the combined oral contraceptive pill, but also the combined contraceptive patch, the combined contraceptive vaginal ring, the progestogen-only pill (minipill), the progestagen implant, and postcoital contraceptives (O'Brien and Guillebaud, 2010). Conversely, medroxyprogesterone acetate-depot, levonorgestrel-releasing intrauterine devices, and copper-containing intrauterine devices are not affected by enzyme inducers. If one of the latter methods of contraception is not acceptable, O'Brien and Guillebaud (2010) suggest to consider using a combined oral contraceptive with a high dose of ethinylestradiol (50-60 μg), given in a continuous manner or in a tricycling regimen. Tricycling involves taking three or four cycles of the combined

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Table 4. A list of drugs whose metabolism can be stimulated by concurrent treatment with enzyme inducing AEDs, most notably carbamazepine phenytoin, phenobarbital and primidone. The list should not be regarded as exhaustive.

Analgesics	Buprenorphine, Fentanyl, Methadone, Paracetamol (Acetaminophen), Pethidine (Meperidine), Tramadol
Antimicrobials	Albendazole, Chloramphenicol, Doxycycline, Efavirenz, Indinavir, Itraconazole, Lopinavir, Metronidazole, Nevirapine, Posiconazole, Praziquantel, Rifampicin, Ritonavir, Saquinavir, Voriconazole
Antineoplastic drugs[1]	9-Aminocampthotecin, Busulfan, Cyclophosphamide, Etoposide, Ifosfamide, Imatinib, Irinotecan, Methotrexate, Misonidazole, Nitrosureas, Paclitaxel, Procarbazine, Tamoxifen, Teniposide, Thiotepa, Topotecan, Vinca Alkaloids
Cardiovascular drugs	Acenocoumarol, Alprenolol, Amiodarone, Apixaban, Atorvastatin, Dicoumarol, Digoxin, Diltiazem, Disopyramide, Felodipine, Isradipine, Lovastatin, Metoprolol, Mexiletine, Nifedipine, Nimodipine, Nisoldipine, Propranolol, Quinidine, Simvastatin, Talinolol, Timolol, Verapamil , Warfarin
Immunosuppressants	Cyclosporin A , sirolimus, tacrolimus
Psychoactive drugs	Amitriptyline, Aripiprazole, Benzodiazepines, Bupropion, Citalopram, Chlorpromazine, Clomipramine, Clozapine, Desipramine, Desmethylclomipramine, Doxepin, Flupenthixol, Haloperidol, Imipramine, Mesoridazine (active metabolite of thioridazine), Mianserin, Mirtazepine, Nefazodone, Nortriptyline, Olanzapine, Paroxetine, Protriptyline, Quetiapine, Sertraline, Risperidone, Trazodone, Ziprasidone, Zuclopenthixol
Steroids	Cortisol, Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisone, Prednisolone, Contraceptive Steroids
Other drugs	Metyrapone, Theophylline, Thyroxine, Vecuronium (and some other non-depolarizing neuromuscular blocking agents)

Not all interactions listed are clinically significant, and they do not necessarily occur with all enzyme inducers. For example, while carbamazepine consistently stimulates warfarin metabolism, phenytoin may either stimulate or inhibit warfarin metabolism, In most situations, stimulation of metabolism results in decreased serum concentration and decreased effect of the affected drug, but potentiation of effect may be seen when metabolic stimulation leads to accumulation of active metabolites. For further information, please refer to specific prescribing information.
Sources: Patsalos and Perucca (2003b); Perucca (2006); Patsalos (2013a,b) and currently available Prescribing Information.

pill consecutively, without a break, followed by a four-day pill-free interval. If a combined pill containing high-dose ethinylestradiol is not available, an alternative consists in using two tablets of a contraceptive containing 30 μg ethinylestradiol and 150 μg levonorgestrel in a tricycling regimen. Because lamotrigine has a lower impact on contraceptive steroids than most enzyme-inducing AEDs, a possibility for women taking lamotrigine without enzyme inducers is to use a combined pill at normal doses, but with tricycling or continuous use (O'Brien and Guillebaud, 2010). In patients in whom interacting AEDs are withdrawn while taking oral contraceptives, the physician should wait two months before reducing the dose of the combined hormonal contraceptive (Johnston and Crawford, 2014). Valproic acid, benzodiazepine drugs and some newer-generation AEDs, most notably levetiracetam, gabapentin, pre-gabalin, tiagabine, lacosamide, retigabine (ezogabine) and vigabatrin, do not appear to affect the serum concentrations of contraceptive steroids (Johnston and Crawford, 2014). There is evidence, however, of clobazam having a weak inducing effect on CYP3A4 activity (Walzer *et al.*, 2012), and its potential interaction with steroid oral contraceptives does not appear to have been investigated.

As discussed in section above, oxcarbazepine, eslicarbazepine acetate, felbamate, rufinamide and high-doses of topiramate or perampanel have weaker enzyme-inducing properties, and these drugs appear to be less likely to cause a clinically significant decrease in the concentration of other drugs (Patsalos, 2013b). However, there can be exceptions, such as the 50% reduction in serum simvastatin concentrations caused by eslicarbazepine acetate (Fattore and Perucca, 2011).

Interactions resulting in increased serum concentration of other drugs

Because of its enzyme inhibiting activity, valproic acid may increase the serum concentrations of a variety of drugs, including zidovudine, lopinavir (Di Cenzo *et al.*, 2004), lorazepam, nimodipine, paroxetine, amitriptyline, nortriptyline, nitrosureas and etoposide (Patsalos and Perucca, 2003b). In some cases, these interactions may result in increased efficacy and/or toxicity of the affected drug. For example, co-administration of valproic acid and antineoplastic agents in patients with brain tumours has been reported to result in increased haematological toxicity of the chemotherapeutic agents, but also, possibly, in increased survival (Oberndorfer *et al.*, 2005; Weller *et al.*, 2011). Whether the latter is related to increased serum concentrations of antineoplastic agents or to an independent pharmacodynamic effect of valproic acid, such as inhibition of histone deacetylatase, however, remains to be determined (Weller *et al.*, 2011).

Felbamate, another enzymatic inhibitor, reduces the metabolic elimination of warfarin, whose dosage may need to be adjusted to avoid excessive anticoagulant activity (Tisdel *et al.*, 1994). Likewise, stiripentol inhibits several CYP enzymes and dosage adjustments of other medications should be considered when this compound is used concomitantly (Chiron, 2007).

Conclusions

Many AEDs have a high potential for being the cause or the target of clinically important drug interactions. Most of these interactions involve induction or inhibition of drug metabolizing enzymes, and can be predicted through knowledge of the relevant mechanisms. In general, interactions between AEDs can be managed by dosage adjustment, aided by serum drug level monitoring and careful assessment of clinical response. Some interactions with non-AEDs can have serious consequences, and cannot always be managed with dosage adjustments.

Many of the newer-generation AEDs are devoid of enzyme-inducing and inhibiting activity, and are less prone to cause clinically important interactions. Because of this, their use can be especially advantageous in patients who require other medications because of concurrent medical conditions. □

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Box 1. Interactions between AEDs and antidepressant /antipsychotic drugs

1 Interactions between AEDs and antidepressants

Co-morbid depression is frequent in people with epilepsy and a common pathophysiological basis for these disorders is suggested by several lines of evidence (Kanner, 2011). Because of their enzyme-inducing properties, carbamazepine, phenytoin, and barbiturates stimulate the metabolism of many antidepressants. Conversely, valproic acid may act as an enzyme inhibitor and may increase serum antidepressant concentrations.
With respect to effects of AEDs on the pharmacokinetics of antidepressants:
• Enzyme-inducing AEDs may decrease the serum concentration of tricyclic antidepressants such as amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, desmethylclomipramine, protriptyline, and doxepin (Spina and Perucca, 2002). This may lead to higher dose requirements of these antidepressants (Brosen and Kragh-Sorensen, 1993).
• Enzyme-inducing AEDs may decrease the serum concentrations of mirtazepine (Sitsen *et al*., 2001; Spaans *et al*., 2002) mianserin and desmethyl-mianserin (Nawishy *et al*., 1981), possibly leading to increased mirtazepine and mianserin dose requirements.
• Carbamazepine reduces the serum concentrations of bupropion by 84%. However, exposure to the active metabolite hydroxy-bupropion is increased by 50% by carbamazepine, which makes the clinical relevance of this interaction unclear (Perucca, 20069).
• Phenobarbital and phenytoin decrease the plasma concentrations of paroxetine and sertraline by about 25% (Pihlsgård and Eliasson, 2002). The clinical relevance of these interactions is probably modest.
• Other antidepressants whose metabolism can be stimulated by enzyme-inducing AEDs are listed in *table 4*.
• Valproic acid and its amide derivative valpromide may cause a moderate elevation in serum amitriptyline and nortriptyline concentrations (Vandel *et al*., 1988; Bertschy *et al*., 1990; Wong *et al*., 1996). Valproic acid may also increase the serum concentration of clomipramine and its metabolites (DeToledo *et al*., 1997). These interactions might require a decrease in the dosage of these antidepressants. However, in one study, desipramine concentrations were reported to be increased after discontinuation of valproic acid (Joseph and Wroblewsky, 1993).
• Valproic acid may increase serum paroxetine concentrations (Andersen *et al*., 1991) but this interaction has not been found to be associated with obvious alterations in clinical effect.
• Most newer-generations AEDs are not expected to modify the pharmacokinetics of antidepressants (Reimers *et al*., 2005).
Some antidepressants may also affect serum AEDs concentrations:
• Fluoxetine may increase, by a potentially clinically relevant extent, the serum concentration of phenytoin (Nelson *et al*., 2001) and carbamazepine (Grimsley *et al*., 1991).
• Fluvoxamine can increase serum phenytoin (Perucca, 2006) and carbamazepine concentrations (Cottencin *et al*., 1995).
• There are anecdotal reports suggesting that sertraline can increase the serum concentrations of phenytoin (Haselberger *et al*., 1997) and lamotrigine (Kaufman and Gerner, 1998).
• Imipramine, trazodone and viloxazine can increase serum phenytoin concentrations, potentially to a clinically important extent (Perucca, 2006).

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Box 1 (*Continued*).

2 Interactions between AEDs and antipsychotics

Co-prescription of AEDs and antipsychotics is relatively frequent because the prevalence of psychotic symptoms is increased in people with epilepsy. Moreover, combinations of antipsychotics and AEDs are increasingly used in the management of bipolar disorder (Nivoli *et al.*, 2012). Interactions between these drugs are common (Spina and Perucca, 2002; Kennedy *et al.*, 2013).

Most of the interactions described involve carbamazepine, which can induce the metabolism of many antipsychotics and reduce their serum concentration. Unless the dosage of the antipsychotic is carefully adjusted, these interactions can result in exacerbation of psychotic symptoms. In particular, carbamazepine has been found to cause:

- A decrease in serum haloperidol concentrations by 20 to 80% (Kidron *et al.*, 1985), with possible worsening of therapeutic response (Kahn, 1990).
- A decrease in the serum concentration of chlorpromazine (Raitasuo *et al.*, 1994) and mesoridazine, the active metabolite of thioridazine (Tiihonen *et al.*, 1995; Spina and Perucca, 2002).
- A decrease in the serum concentration of aripiprazole by 71% (Citrome *et al.*, 2007) to 88% (Castberg and Spigset, 2007) on average, and a mean decrease in the concentrations of the metabolite dehydroaripiprazole by 69% (Castberg and Spigset, 2007).
- A decrease in the serum concentration of clozapine by 50% (Jerling *et al.*, 1994).
- A decrease in serum olanzapine concentrations by 36-71% (Olesen and Linnet, 1999; Haslemo *et al.*, 2012).
- A decrease in serum quetiapine concentrations by over 85% (Grimm *et al.*, 2006).
- A prominent decrease in the serum concentration of risperidone and 9-hydroxy-risperidone (Spina *et al.*, 2000; Ono *et al.*, 2002).
- A decrease in serum ziprasidone concentration by 36% (Miceli *et al.*, 2000).

Phenobarbital and phenytoin are expected to cause similar interactions. Indeed, phenobarbital has been found to reduce the serum concentrations of chlorpromazine (Forrest *et al.*, 1970; Curry *et al.*, 1970) and clozapine (Lane *et al.*, 1998; Facciola *et al.*, 1998), whereas phenytoin has been reported to cause prominent reductions in the serum concentrations of clozapine (Miller, 1991) and quetiapine (Wong *et al.*, 2001). A larger list of antipsychotic drugs, the serum concentration of which can be reduced by enzyme inducing AEDs, is given in *table 4*.

Valproic acid is also frequently used in combination with antipsychotic agents, but its interactions are far less prominent than those caused by enzyme inducers. Specifically, interactions caused by valproic acid may include:

- A decrease, by about 25%, in the serum concentrations of aripiprazole (Citrome *et al.*, 2005; Castberg and Spigset, 2007).
- Inconsistent changes in clozapine concentrations. While some studies suggested that valproic acid might inhibit the conversion of clozapine to norclozapine (Centorrino *et al.*, 1994; Wong *et al.*, 2006), others found a 41% decrease in clozapine concentrations after the addition of valproic acid (Finley and Warner, 1994).
- Little or no changes in serum olanzapine concentrations. Some studies found no significant interaction (Gex-Fabry *et al.*, 2003; Botts *et al.*, 2008), while others reported a modest decrease (<35%) in serum olanzapine concentrations of doubtful clinical relevance (Spina *et al.*, 2009; Haslemo *et al.*, 2012).
- No clinically significant changes in serum quetiapine concentrations (Castberg *et al.*, 2007; Winter *et al.*, 2007).

Some newer-generation AEDs are also used in the management of psychiatric disorders, although their interaction potential is generally modest. Specifically:

- Oxcarbazepine does not appear to significantly modify serum risperidone and olanzapine concentrations in psychotic patients stabilized on these drugs (Muscatello *et al.*, 2005).
- Topiramate does not affect, to a clinically significant extent, the serum concentrations of clozapine, olanzapine, total risperidone active moiety, and haloperidol (Migliardi *et al.*, 2007; Topamax, 2014). However, it decreases the serum concentrations of the reduced haloperidol metabolite by about 30%. Topiramate at high doses (600 mg/day) increases the serum concentration of lithium by about 25% (Topamax, 2014).
- Lamotrigine may cause modest (≤35%) changes (either increase or decrease) in the serum concentrations of olanzapine (Spina *et al.*, 2006; Botts *et al.*, 2008; Haslemo *et al.*, 2012), and does not affect the serum concentrations of clozapine, risperidone and their active metabolites (Tiihonen *et al.*, 2003). On the other hand, olanzapine reduces serum lamotrigine concentrations by about 25% (Sidhu *et al.*, 2006b).

Box 2. Interactions between AEDs and oral anticoagulants

Oral anticoagulants, which are used for the prevention and treatment of thromboembolic disorders, have a narrow therapeutic window. Interactions affecting their pharmacokinetics or pharmacodynamics may therefore have serious consequences (Harder and Thürmann, 1996).

● Barbiturates and carbamazepine induce the metabolism of warfarin and other coumadin drugs, thereby increasing their dosage requirements (Harder and Thurmann 1996; Cropp and Bussey, 1997). The degree of interaction and the consequent increase in anticoagulant dose requirement vary from one patient to another: warfarin dose may need to be increased as much as tenfold (Breckenridge, 1974). Repeated determinations of the International Normalized Ratio (INR) are indicated to adjust dose to individual need. Discontinuation or reduction in dose of the inducing agent is even more dangerous, because the metabolism of the anticoagulant will slow with the attendant risk of increased anticoagulant effect and massive haemorrhage, if dosage is not reduced accordingly (McDonald and Robinson, 1968).

● The effect of phenytoin on the anticoagulant activity of warfarin is more complex. In fact, the effect of warfarin may be increased or decreased (Cropp and Bussey, 1997), making possible adjustments in anticoagulant dosage even more difficult (Hassan *et al.*, 2005).

● Valproic acid also has complex interactions with anticoagulants. It may inhibit the metabolism of warfarin and may also increase the risk of bleeding by interfering directly with platelet function and coagulation processes (Stephen, 2003). Intravenous loading with valproic acid could also determine transient INR changes by displacing warfarin from protein binding sites (Yoon *et al.*, 2011).

● Warfarin metabolism can also be inhibited by felbamate. Patients treated with both drugs need a reduction in warfarin dose to maintain adequate anticoagulant efficacy (Tisdel *et al.*, 1994).

● Oxcarbazepine, at a dose of 900 mg/day, does not affect warfarin pharmacokinetics (Krämer *et al.*, 1992); although an interaction at higher doses cannot be excluded (Perucca and Kwan, 2005). In a study of healthy subjects, the structural analogue eslicarbazepine acetate, at a dose of 1200 mg/day, caused a small, but statistically significant reduction in serum S-warfarin concentrations, but there were no changes in R-warfarin pharmacokinetics or INR values (Vaz-da-Silva *et al.*, 2010).

● Newer oral anticoagulants include the direct thrombin inhibitor dabigatran etexilate and the anti-factor Xa inhibitors, rivaroxaban and apixaban. Compared with coumadin anticoagulants, these agents have a wider therapeutic window and lower susceptibility to pharmacokinetic interactions (Nutescu *et al.*, 2011). Strong inducers of P-gp and CYP3A4 such as carbamazepine, phenytoin and barbiturates, however, are expected to decrease apixaban and rivaroxaban concentrations and, according to prescribing information, their use should be preferably avoided in patients taking these anticoagulants (Predaxa, 2014; Xarelto, 2014). Serum apixaban concentrations may also be reduced by strong enzyme inducing AEDs and, although no changes in dose requirements are anticipated, caution is recommended if these medications are co-administered (Eliquis, 2014).

● New-generation AEDs devoid of enzyme-inducing and inhibiting properties are not expected to interfere with anticoagulants, and should be preferred for the treatment of seizure disorders in patients requiring anticoagulation. A study conducted on healthy volunteers showed no interaction between levetiracetam and warfarin (Ragueneau-Majlessi *et al.*, 2001).

Box 3. Interactions between AEDs and anti-infectious agents

1 Interactions between AEDs and antibacterials/antimicotics

Several antibacterials/antimicotics interfere with the metabolism of AEDs, resulting in either increased or decreased plasma AED concentrations with consequent possible toxicity or loss of efficacy. Less frequently, enzyme-inducing AEDs can modify the pharmacokinetics of chemotherapeutic agents with consequent loss of efficacy.

● Carbamazepine metabolism is inhibited, with consequent risk of toxicity, by several antibacterials (Patsalos and Perucca, 2003b), including isoniazid (Valsalan and Cooper, 1982) and the macrolide antibiotics clarithromycin, erythromycin, and troleandomycin (Pauwels, 2002). Macrolides with reduced or absent interaction potential (azithromycin, dirithromycin, rokitamycin, spiramycin) are recommended for the treatment of infections in patients receiving carbamazepine. Some antifungal drugs (ketoconazole, fluconazole and other azoles)

Box 3 (*Continued*).

are also inhibitors of the CYP3A4-mediated metabolism of carbamazepine and increase serum carbamazepine concentration through this mechanism. Conversely, rifampicin, which has inducing properties on CYP3A4, reduces serum carbamazepine concentrations (Tucker *et al.*, 1992).

● Phenytoin metabolism is inhibited by several antimicrobials. Isoniazid, chloramphenicol, some fluoro-quinolones (clinafloxacin and possibly ciprofloxacin), some antifungal drugs (miconazole and fluconazole), sulfaphenazole and, to a lesser extent, other sulfonamides, can substantially increase the serum concentration of phenytoin and lead to possible toxicity. In contrast, rifampicin induces phenytoin metabolism (Patsalos and Perucca, 2003b).

● Phenobarbital metabolism is inhibited by chloramphenicol (Patsalos and Perucca, 2003b).

● Serum valproic acid concentrations are markedly reduced by carbapenem antibiotics (imipenem, meropenem, ertapenem), due to a combination of mechanisms affecting absorption, distribution, and metabolism (Mancl and Gidal, 2009). Coadministration of these drugs with valproic acid should be avoided or, when avoidance is not possible, valproic acid concentrations should be frequently monitored. Doripenem, a new carbapenem antibiotic, also has the potential for decreasing serum valproic acid concentrations (Hellwig *et al.*, 2011). Finally, serum valproic acid concentrations can be increased by isoniazid (Perucca, 2006) and erythromycin (Santucci *et al.*, 2010).

● Interactions between antibiotics and new AEDs are much less frequent. Lamotrigine metabolism is stimulated by rifampicin (Ebert *et al.*, 2000). The metabolism of oxcarbazepine, tiagabine, and felbamate does not appear to be affected by erythromycin. A single case of oxcarbazepine toxicity after starting clarithromycin has been reported, possibly due to an interaction involving transport proteins at the blood-brain barrier (Santucci *et al.*, 2010).

● Enzyme-inducing AEDs accelerate the elimination of doxycycline, thereby reducing its effectiveness (Penttila *et al.*, 1974). The serum concentration of itraconazole can be reduced more than tenfold by enzyme-inducing AEDs. Phenobarbital increases the metabolism of chloramphenicol, and decreases the effectiveness of griseofulvin probably by impairing its absorption (Riegelman *et al.*, 1970). Other interactions resulting in induced metabolism of antimicrobials are listed in *table 4*.

2 Interactions between AEDs and antiretroviral therapies used for treatment of HIV/AIDS

A variety of interactions between AEDs and antiretroviral drugs (ARV) have been reported, Those which are most clinically relevant involve induction of ARV metabolism, resulting in loss of antiviral efficacy as measured by CD4+ T-cell decline and progression of the disease (L'Homme *et al.*, 2006; Burger *et al.*, 2008; Okulicz *et al.*, 2011; Birbeck *et al.*, 2012; Okulicz *et al.*, 2013).

● Phenytoin has moderate inducing effects on the metabolism of lopinavir, ritonavir, and possibly nevirapine (Birbeck *et al.*, 2012; Lim *et al.*, 2004). Carbamazepine reduces the serum concentrations of the non-nucleoside reverse transcriptase inhibitors efavirenz, and possibly, nevirapine (Penttila *et al.*, 1974).

● Valproic acid increases mean zidovudine concentrations by 80% (Di Cenzo *et al.*, 2004; Hirata-Koizumi *et al.*, 2007), and may also increase lopinavir concentrations (Di Cenzo *et al.*, 2004). On the other hand, valproic acid does not seem to modify the serum concentrations of ritonavir, atazanavir and efavirenz (Birbeck *et al.*, 2012).

● Atazanavir/ritonavir (but not atazanavir alone) reduce mean serum lamotrigine concentrations by 32%, whereas lopinavir/ritonavir reduce mean serum lamotrigine concentrations by 50% (van der Lee *et al.*, 2006; Birbeck *et al.*, 2012) and mean serum phenytoin concentrations by 31% (Okulicz *et al.*, 2011). In another study, efavirenz reduced mean serum carbamazepine concentrations by 27% (Ji *et al.*, 2008).

● When possible, enzyme-inducing AEDs should be avoided in patients treated with antiretroviral drugs. AEDs with minimal or no effect on drug metabolism should be preferred in HIV-positive patients (Okulicz *et al.*, 2013). Physicians should also be aware that some antiretroviral drugs affect the metabolism of AEDs.

TEST YOURSELF

(1) Which of the following AEDs are NOT inducers of cytochrome CYP3A4?
A. Levetiracetam
B. Phenytoin
C. Rufinamide and levetiracetam
D. Rufinamide

(2) When valproic acid is added to carbamazepine
A. Serum carbamazepine levels will increase, potentially leading to CNS side effects
B. Serum carbamazepine levels are generally unaffected but the levels of the active metabolite carbamazepine-10,11-epoxide may increase
C. Total serum carbamazepine levels are unchanged, but the levels of free (unbound) carbamazepine may increase, leading to clinical signs of toxicity
D. There is no pharmacokinetic interaction between these drugs

(3) The combined contraceptive pill, when given to AED-treated women with epilepsy:
A. May decrease serum lamotrigine concentrations, potentially leading to loss of seizure control unless lamotrigine dose is adjusted appropriately
B. May decrease serum valproic acid concentrations
C. Both A and B
D. Does not affect the levels of commonly administered AEDs

Note: Reading the manuscript provides an answer to all questions. You can check for the correct answer by visiting the Educational Centre section of www.epilepticdisorders.com