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Clinically relevant drug interactions with antiepileptic drugs

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Some patients with difficult-to-treat epilepsy benefit from combination therapy with two or more antiepileptic drugs (AEDs). Additionally, virtually all epilepsy patients will receive, at some time in their lives, other medications for the management of associated conditions. In these situations, clinically important drug interactions may occur. Carbamazepine, phenytoin, phenobarbital and primidone induce many cytochrome P450 (CYP) and glucuronyl transferase (GT) enzymes, and can reduce drastically the serum concentration of associated drugs which are substrates of the same enzymes. Examples of agents whose serum levels are decreased markedly by enzyme-inducing AEDs, include lamotrigine, tiagabine, several steroidal drugs, cyclosporin A, oral anticoagulants and many cardiovascular, antineoplastic and psychotropic drugs. Valproic acid is not enzyme inducer, but it may cause clinically relevant drug interactions by inhibiting the metabolism of selected substrates, most notably phenobarbital and lamotrigine. Compared with older generation agents, most of the recently developed AEDs are less likely to induce or inhibit the activity of CYP or GT enzymes. However, they may be a target for metabolically mediated drug interactions, and oxcarbazepine, lamotrigine, felbamate and, at high dosages, topiramate may stimulate the metabolism of oral contraceptive steroids. Levetiracetam, gabapentin and pregabalin have not been reported to cause or be a target for clinically relevant pharmacokinetic drug interactions. Pharmacodynamic interactions involving AEDs have not been well characterized, but their understanding is important for a more rational approach to combination therapy. In particular, neurotoxic effects appear to be more likely with coprescription of AEDs sharing the same primary mechanism of action.

Introduction

Although monotherapy remains the mainstay for the treatment of epilepsy, combinations of antiepileptic drugs (AEDs) are used frequently in patients not responding to a single medication. AEDs may also be combined with drugs used to treat intercurrent or associated conditions. When multiple drug therapy is used, there is a possibility of clinically relevant drug interactions, which in patients with epilepsy are particularly common for a variety of reasons: (i) AEDs are administered for prolonged periods, often for a lifetime, thereby increasing the probability of coprescription; (ii) most AEDs have a narrow therapeutic index, and even relatively modest alterations in their pharmacokinetics can result in loss of response or toxic effects; (iii) the most widely used AEDs (carbamazepine, valproic acid, phenytoin and phenobarbital) have prominent effects on the activity of enzymes which metabolize the majority of existing medication; (iv) most of the old and new generation AEDs are substrates of the same enzymes [1, 2].

Comprehensive reviews of interactions involving AEDs have been published recently [1–5]. The purpose of the present review is to highlight those which, because of their frequency or magnitude, are especially likely to have adverse clinical consequences.

Mechanisms of AED interactions

The vast majority of clinically important AED interactions result from induction or inhibition of drug metabolizing enzymes. However, other mechanisms, including pharmacodynamic interactions, may be occasionally at play.

Enzyme induction

Carbamazepine, phenytoin, phenobarbital and primidone (henceforth referred to collectively as enzyme-inducing AEDs) stimulate the activity of a variety of cytochrome P450 (CYP) enzymes, including CYP1A2, CYP2C9, CYP2C19 and CYP3A4, as well as glucuronyl transferases (GT) and epoxide hydrolase [6–9]. Because these enzymes are involved in the biotransformation of the majority of therapeutic agents, patients taking enzyme inducing AEDs metabolize at a faster rate a wide range of concomitantly administered medications, whose dosage requirements may be consequently increased. For drugs which are converted to active or toxic metabolites, conversely, enzyme induction may result in enhancement of the activity of the affected drug: one example is represented by the induction of primidone metabolism by phenytoin, which results in increased serum concentrations of the active metabolite phenobarbital, with the attendant risk of phenobarbital-related adverse effects [1, 10].

None of the newer AEDs shares the broad spectrum enzyme-inducing activity of older generation agents [11]. However, oxcarbazepine, lamotrigine, felbamate and, at dosages $\geq$200 mg day^{-1}, topiramate stimulate the metabolism of oral contraceptive steroids, possibly by tissue-selective stimulation of CYP3A4 [12, 13], and oxcarbazepine has also a stimulating effect on the GT-mediated lamotrigine metabolism [14] and, to a lesser extent, the CYP3A4-mediated oxidation of felodipine [15]. In addition, most new generation AEDs are cleared fully or partly by inducible enzymes (Table 1), and they are therefore a target for interactions mediated by enzyme induction.

Enzyme inhibition

Valproic acid differs from other older generation AEDs in being an inhibitor rather than an inducer of drug metabolizing enzymes, including those involved in the oxidation of phenobarbital, the glucuronidation of lamotrigine and the conversion of carbamazepine-10,11-epoxide to the corresponding diol (epoxide hydrolase) [1]. Oxcarbazepine is a weak inhibitor of CYP2C19, and may increase by this mechanism the plasma levels of phenytoin and, to a lesser extent, phenobarbital [1]. Felbamate, an AED rarely used because of serious haematological and hepatic toxicity, is a more potent metabolic inhibitor, and it causes important elevations in the serum levels of phenytoin, phenobarbital, valproic acid, carbamazepine-10,11-epoxide, and N-desmethylclobazam [1, 11]. Other clinically important interactions mediated by enzyme inhibition are those whereby the metabolism of an AED is inhibited by drugs used for other indications.

Other pharmacokinetic mechanisms

Clinically important AED interactions mediated by inhibition of gastrointestinal absorption have been reported rarely. In recent years, however, evidence has been provided that medications which induce or inhibit CYP enzymes may also modulate the expression of drug transporters, including P-glycoprotein (P-gp) and multiple drug resistance proteins 2 and 3 (MRP2 and MRP3), in the gastrointestinal tract, in the kidney and in other tissues [16, 17]. These observations raise the possibility that some AED interactions currently ascribed to enzyme induction may in fact be mediated by reduced gastrointestinal absorption or enhanced renal elimination of the affected drug, as shown in a recent elegant study of the interaction between carbamazepine and the β_1-blocker talinolol [18].

Valproic acid, phenytoin and tiagabine are highly bound to plasma proteins and may be involved in displacement from protein binding sites. The most common of these interactions is the displacement of plasma protein-bound phenytoin by valproic acid [19, 20]. Unless additional mechanisms are at work, these interactions are not clinically important, because the displaced drug is diluted into a large volume of distribution and/or is rapidly cleared, resulting in a new state in which the total serum concentration of the affected drug is decreased but the unbound (pharmacologically active) concentration is unchanged [21]. Nevertheless, clinicians must be aware of these interactions when interpreting serum drug concentration data. In particular, in patients taking phenytoin in combination with valproate, therapeutic and toxic effects will occur at total serum phenytoin concentrations which are lower than those required to produce equivalent effects in patients not taking valproate [19].

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

Drug	Main route(s) of elimination	Main enzyme system involved
Old generation AEDs		
Carbamazepine	Oxidation	CYP3A4 (active 10,11-epoxide metabolite cleared by epoxide hydrolase)
Ethosuximide	Oxidation	CYP3A4
Phenobarbital	Oxidation + N-glucosidation (75% of the dose) and renal excretion (25%)	CYP2C9 and CYP2C19
Phenytoin	Oxidation	CYP2C9 and CYP2C19
Valproic acid	Oxidation (>50%) and glucuronide conjugation (30–40%)	Mitochondrial oxidases, CYPs and glucuronyl transferases
New generation AEDs		
Felbamate	Oxidation (>50%) and renal excretion (>30%)	Inducible CYP isoforms
Gabapentin	Renal excretion	None
Lamotrigine	Glucuronide conjugation	Glucuronyl transferase type 1A4
Levetiracetam	Renal excretion (75%) and hydrolysis (25%)	Hydrolase
Oxcarbazepine[1]	Glucuronide conjugation (>50%) and renal excretion (<30%)	Glucuronyl transferases
Pregabalin	Renal excretion	None
Tiagabine	Oxidation	CYP3A4
Topiramate	Oxidation (20–60%) and renal excretion (40–80%)	Inducible CYP isoforms
S-Vigabatrin	Renal excretion	None
Zonisamide	Oxidation + reduction + N-acetylation (>50%) and renal excretion (30%)	CYP3A4 and N-acetyl-transferases

[1]*Oxcarbazepine is a prodrug, virtually entirely converted by cytosolic aryl-ketone-reductase to the active metabolite monohydroxycarbazepine (MHD). The indicated routes of elimination and enzymes involved refer to MHD.*

Pharmacodynamic interactions

Pharmacodynamic interactions are usually inferred by default when a change in clinical response apparently due to a drug interaction is not reflected in any identifiable pharmacokinetic change [1]. Pharmacodynamic interactions involving AEDs are difficult to document objectively, given the complexity of quantifying dose–response relationships in the clinical setting. Clinical observations, however, suggest that these interactions may be more common than previously thought, and their characterization would be important for a more rational approach to the use of AED combinations in epilepsy [22].

Interactions between AEDs

Interactions resulting in decreased 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, most notably valproic acid [23, 24], tiagabine [25], ethosuximide [26], lamotrigine [27, 28], topiramate [29], oxcarbazepine and its active monohydroxy-derivative (MHD) [30], zonisamide [31], felbamate [32] and many benzodiazepine drugs [33, 34]. The metabolism of carbamazepine itself is subject not only to autoinduction, but also to heteroinduction by phenytoin and barbiturates [35].

The clinical significance of these interactions is usually relatively modest, because the partial loss of efficacy resulting from the decreased serum concentration of the affected drug tends to be compensated for by the antiepileptic effect of the added drug. However, when the decrease in AED concentration is particularly prominent, the interaction may result in worsened seizure control, unless the dosage of the affected drug is adjusted accordingly [36]. AEDs whose dosage requirements are particularly increased in the presence of enzyme-inducing comedication include valproic acid, carbamazepine, lamotrigine and tiagabine. For example, the plasma con-

centration of valproic acid can be reduced on average by 50–75% in patients comedicated with enzyme inducers [24], and the concentration of lamotrigine is also reduced by over 50% [28]. Conversely, the plasma concentrations of levetiracetam, gabapentin, pregabalin and vigabatrin are not affected to any important extent by comedication with other AEDs [11].

Since enzyme induction is a reversible phenomenon, particular caution is required when an enzyme-inducing agent is discontinued, because the serum concentration of concurrently administered AEDs may increase to potentially toxic levels. For example, in patients comedicated with valproic acid, discontinuation of carbamazepine, or substitution of carbamazepine with another AED devoid of enzyme-inducing activity, may result in a prominent rebound increase of serum valproic acid concentrations, with the attendant risk of toxicity [37]. Likewise, clinically important increases in the serum concentration of tiagabine and lamotrigine may be observed after withdrawal of enzyme-inducing comedication, or substitution of the latter with other AEDs which do not have enzyme-inducing effects.

Interactions resulting in increased concentration of the affected drug

Two clinically important interactions stand out in this category: the inhibition of the metabolism of lamotrigine and phenobarbital by valproic acid. Inhibition of lamotrigine metabolism is already maximal at dosages of valproate around 500 mg day^{-1}, and results in an approximate twofold increase in serum lamotrigine levels [38–40]. Because the risk of lamotrigine-induced skin rashes is dependent on the rate of rise of serum lamotrigine concentration, in patients comedicated with valproate lamotrigine should be initiated at reduced dosages (in adults, 25 mg on alternate days) and titrated more slowly to target dosages which are lower than those used in patients not taking valproate. Although there is no risk of rash when valproate is added on in a patient 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 valproate reaches, in an adult, about 250–500 mg day^{-1}.

The second clinically important interaction caused by valproic acid is an elevation in serum phenobarbital levels, which is probably secondary to inhibition of CYP2C9 and/or CYP2C19 [41]. Although today phenobarbital is used infrequently in Europe and the USA, it remains the most commonly prescribed AED in developing countries, and therefore its interaction with valproate is particularly important. After adding valproate, serum phenobarbital concentrations increase over several weeks by about 30–50% in most patients, but individual patients may show a greater interaction. A reduction in phenobarbital (or primidone) dosage by up to 80% may be required to avoid adverse effects.

Less important interactions mediated by metabolic inhibition include an increase in serum phenytoin (by up to 40%) after administration of oxcarbazepine [42], and an inconsistent increase in serum phenytoin after addition of topiramate [43]. In carbamazepine-treated patients started on valproate comedication, neurotoxic signs may occasionally be caused by an increase in serum carbamazepine-10,11 epoxide levels, secondary to inhibition of epoxide hydrolase by valproic acid [44]. Interactions caused by sulthiame and felbamate, while clinically relevant (Table 2), are uncommon because these agents are rarely used in the current management of epilepsy.

Pharmacodynamic interactions

Clinical observations suggest that certain AED combinations may be associated with adverse or beneficial interactions at pharmacodynamic level [22]. In particular, it has been shown repeatedly that the combination of valproate with lamotrigine [45], or valproate with ethosuximide [46], may produce seizure control in patients who did not respond to the highest tolerated dose of either drug given alone: this may be explained by a pharmacodynamic interaction resulting in synergistic efficacy and/or infra-additive neurotoxicity. Conversely, the combinations of lamotrigine with carbamazepine [47], or oxcarbazepine with carbamazepine [42], have been more commonly associated with neurotoxic effects compared with combinations of the same drugs with other agents, an observation which may be explained by the common action of carbamazepine, lamotrigine and oxcarbazepine in blocking voltage-dependent sodium channels. Indeed, combinations of drugs acting by different mechanisms would be expected to be more beneficial than combinations of drugs sharing the same mode of action, even though current knowledge of the pharmacology of AEDs is still insufficient to allow a mechanistic approach to AED therapy [22].

Interactions between AEDs and other drugs

Interactions resulting in decreased AED concentration

Serum lamotrigine levels are decreased by about 50% of oral contraceptive steroids, an interaction which is likely to be caused by stimulation of uridine GT type 1A4 (UGT1A4) activity by the steroids [48]. This interaction can result in reduced seizure control in some women [49]. Interestingly, the interaction follows a

cyclic pattern, with a marked decrease in serum lamotrigine levels during the 21 days of intake of the oestroprogestinic pill, and a twofold rebound increase in AED concentration during the pill-free week [13].

Other interactions resulting in a clinically important decrease in serum AED concentration have been rarely reported, but they can be important in individual cases. Notable examples include the marked inhibition of the gastrointestinal absorption of phenytoin given concurrently with some nasogastric feeds [50, 51], the decrease in serum phenytoin concentrations caused by cisplatin and some other antineoplastic drugs [52], and the dramatic fall in serum valproic acid concentration after addition of some antibiotics of the carbapenem class [53, 54].

Interactions resulting in increased AED concentration

Only extensively metabolized AEDs are affected by these interactions, which are mediated by metabolic inhibition [2]. Interactions resulting in elevated serum AED concentrations have been reported mostly with carbamazepine, phenytoin and phenobarbital, while new AEDs appear to be rarely affected (Table 2). This is partly explained by the fact that many new AEDs undergo little or no biotransformation (Table 1), but it is also possible that interactions affecting new AEDs are under-recognized due to limited clinical experience and lack of routine application of therapeutic drug monitoring [11].

Theoretically, any of the interfering drugs listed in Table 2 can precipitate clinical signs of intoxication with the affected drug, although the magnitude of interaction varies from drug to drug and from patient to patient. Potentially serious adverse consequences can be minimized by careful clinical observation and monitoring of the serum concentration of the potentially affected drug. Most interactions mediated by metabolic inhibition can be predicted based on the contribution of

Table 2
Drugs which have been found to increase the serum concentration of antiepileptic drugs, presumably by inhibiting their metabolism

Affected drug		Interfering drug
Carbamazepine	*Antiepileptic drugs:*	Felbamate[1], valproic acid[1], valpromide[1]
	Antidepressants:	Fluoxetine, fluvoxamine, nefazodone, trazodone, viloxazine
	Antimicrobials:	Clarithromycin, erythromycin, fluconazole, isoniazid, ketoconazole, metronidazole, ritonavir, troleandomycin
	Miscellaneous:	Cimetidine, danazol, dextropropoxyphene, diltiazem, risperidone, quetiapine[1], ticlopidine, verapamil
Ethosuximide	*Antimicrobials:*	Isoniazid
Lamotrigine	*Antiepileptic drugs:*	Valproic acid
	Antidepressants:	Sertraline
Phenobarbital	*Antiepileptic drugs:*	Felbamate, phenytoin, sulthiame, valproic acid
	Antimicrobials:	Chloramphenicol
	Miscellaneous:	Dextropropoxyphene
Phenytoin	*Antiepileptic drugs:*	Felbamate, oxcarbazepine, sulthiame, valproic acid[2]
	Antidepressants:	Fluoxetine, fluvoxamine, imipramine, sertraline, trazodone, viloxazine
	Antimicrobials:	Chloramphenicol, fluconazole, isoniazid, miconazole, sulfaphenazole
	Antineoplastic drugs:	Doxifluridine, fluorouracil, tamoxifen, tegafur, UFT
	Miscellaneous:	Allopurinol, amiodarone, azapropazone, cimetidine, chlorpheniramine, dextropropoxyphene, diltiazem, disulfiram omeprazole, phenylbutazone, sulfinpyrazone tacrolimus, ticlopidine, tolbutamide
Valproic acid	*Antiepileptic drugs:*	Felbamate
	Antidepressants:	Sertraline
	Antimicrobials:	Isoniazid
	Miscellaneous:	Cimetidine

The list should not be regarded as exhaustive. For further information and a list of references, see Patsalos and Perucca [1, 2].
[1]These drugs increase the concentration of the active metabolite carbamazepine-10,11-epoxide, the effect being most clinically relevant with valpromide. The concentration of carbamazepine is not affected by valproic acid and valpromide, ands it is decreased by felbamate. [2]Interaction inconsistent and limited to an increase in unbound phenytoin concentration. Total serum phenytoin concentration usually decreases due to displacement from plasma protein binding sites.

specific isozymes to the clearance of the affected drug (Table 1) and knowledge of the influence of the comedication of interest on these isozymes [55]. For example, precipitation of serious carbamazepine toxicity by clarithromycin, erythromycin and troleandomycin can be predicted by the ability of the latter to inhibit CYP3A4 activity [54–57]. Azithromycin, dirithromycin, rokitamycin and spiramycin are macrolide antibiotics which do not inhibit CYP3A4 and therefore are not expected to affect carbamazepine metabolism.

Interactions resulting in decreased concentration of other drugs

A large proportion of patients with epilepsy are treated with enzyme-inducing AEDs, and therefore they represent a unique population in terms of vulnerability to interactions mediated by enzyme induction [11]. The list of such interactions is impressive (Table 3), and most are clinically significant. In terms of magnitude, the interaction is greatest with drugs subject to extensive first-pass metabolism such as itraconazole [58], praziquantel [59], indinavir [60–62], and most dihydropyridine calcium antagonists [63–65], whose plasma concentration may be decreased over five- to 10-fold in enzyme induced patients. Because of practical difficulties in compensating for such interactions, effective use of some of these drugs may not feasible in enzyme-induced patients. Apart from the magnitude of the pharmacokinetic change, the clinical implications also vary depending on the therapeutic index of the affected drug. Serious and even irreversible consequences may be observed, as in the case of oral contraceptives (Box 1), oral anticoagulants (Box 2), immunosuppressants and chemotherapeutic agents. In some categories of patients, e.g. those requiring anticancer therapy, the use of AEDs devoid of enzyme-inducing properties is clearly preferred [2, 52].

Interactions resulting in increased concentration of other drugs

Interactions whereby AEDs increase the serum concentrations of drugs used for other indications are observed

Table 3

Drugs whose serum concentration has been reported to be decreased by coadministration of enzyme-inducing antiepileptic drugs (AEDs) (carbamazepine, phenobarbital, phenytoin and primidone)

Antidepressants[1]	Amitriptyline, bupropion, citalopram, clomipramine, desipramine, desmethylclomipramine, doxepin, imipramine, mianserin, mirtazepine, nefazodone, nortriptyline, paroxetine, protriptyline
Antimicrobials	Albendazole, doxycycline, griseofulvin[2], indinavir[3], itraconazole, metronidazole, praziquantel
Antineoplastic drugs[1]	9-aminocampthotecin, busulfan, cyclophosphamide, etoposide, ifosfamide, irinotecan, methotrexate, nitrosureas, paclitaxel, procarbazine, tamoxifen, teniposide, thiotepa, topotecan, vinca alkaloids
Antipsychotic drugs	Chlorpromazine, clozapine, haloperidol, mesoridazine (active metabolite of thioridazine), olanzapine, quetiapine, risperidone, ziprasidone
Benzodiazepines	Alprazolam, clobazam, clonazepam, desmethyldiazepam, diazepam, midazolam
Cardiovascular drugs[1]	Alprenolol, amiodarone, atorvastatin, dicoumarol, digoxin, disopyramide, felodipine, metoprolol, mexiletine, nifedipine, nimodipine, nisoldipine, propranolol, quinidine, simvastatin, verapamil[4], warfarin[5]
Immunosuppressants	Cyclosporin A[6], sirolimus, tacrolimus
Steroids	Cortisol, dexamethasone, hydrocortisone, methylprednisolone, prednisone, prednisolone, steroid oral contraceptives[7]
Miscellaneous	Fentanyl, metadone, metyrapone, misonidazole, paracetamol, pethidine, theophylline, thyroxine, vecuronium (and some other nondepolarizing neuromuscular blocking agents)

These interactions have not necessarily been shown with all enzyme inducers, and there can be differences in the enzyme-inducing and inhibiting spectrum of carbamazepine, phenobarbital, phenytoin and primidone. The list should not be regarded as exhaustive. For further information and a list of references, see Patsalos and Perucca [2] and Vecht et al. *[52].* [1]*Some of these drugs (for example, bupropion, procarbazine, ifosfamide, amiodarone, disopyramide) have active metabolites. Therefore, a reduced concentration of parent drug does not necessarily imply a reduced pharmacological effect.* [2]*Interaction reported with phenobarbital and probably due to impaired griseofulvin absorption.* [3]*Interaction likely to be extended to other CYP3A4 substrates such as nevirapine, efavirenz, delavirdine, ritonavir and saquinavir.* [4]*Interaction only relevant after oral administration of verapamil.* [5]*Phenytoin may cause an initial decrease in anticoagulant effect, followed by an increase in warfarin concentration.* [6]*There is suggestive evidence that oxcarbazepine may also decrease serum cyclosporin A levels.* [7]*Other AEDs which have been found to decrease the concentration of the oestrogen and/or progestagen component of oral contraceptive steroids include felbamate, lamotrigine, oxcarbazepine and, at dosages >200 mg day*$^{-1}$*, topiramate.*

Box 1
Antiepileptic drugs and oral contraceptives

Despite the fact that prescription of oral contraceptives in women with epilepsy is relatively common, knowledge of the interactions occurring between these agents and antiepileptic drugs (AEDs) is unsatisfactory. In a 1996 survey conducted in the USA, only 4% of neurologists and none of the obstetricians were correct in identifying the interactions between the combined oral contraceptive pill and six major older generation AEDs [69]. It is no surprise,therefore, that surveys also found women to be poorly informed on this issue [70].

The following AEDs have been shown to induce the metabolism of the oestrogen and/or progestagen components of the contraceptive pill [2, 12]:

- Carbamazepine
- Felbamate
- Oxcarbazepine
- Lamotrigine
- Phenobarbital
- Phenytoin
- Primidone
- Topiramate

In women taking the above AEDs, the efficacy of the pill may be reduced [12]. The magnitude of interaction may vary with type and dose of AED. In particular, topiramate does not affect serum norethisterone and ethinylestradiol levels at dosages up to 100 mg day^{-1}, has little or no effects at 200 mg day^{-1}, and decreases serum norethisterone consistently at higher doses [71, 72]. Lamotrigine 300 mg day^{-1} has been found to cause only a modest reduction (19%) in levonorgestrel levels [13]. In comparison, the reduction in ethinylestradiol and progestagen levels with carbamazepine 600 mg day^{-1} is in the order of 50% [12, 71, 73]. Gabapentin, levetiracetam, pregabalin, tiagabine, valproate, vigabatrin and zonisamide have been reported not to interact with steroid oral contraceptives. Benzodiazepines and ethosuximide are also considered not to interact [2, 12].

In general, AEDs not interacting with oral contraceptives are a preferable treatment choice for women with epilepsy in whom contraception is contemplated. If oral contraceptives are combined with AEDs which induce their metabolism, ethinylestradiol dose should be increased from between 20 and 35 μg to 50 μg. If breakthrough bleeding occurs, some authors recommend increasing ethinylestradiol dose further to 75 or 100 μg [12]. Although even high-dosage pills may not provide full protection, pregnancy rates are still much lower compared with barrier methods; moreover, a spermicidal gel or a barrier method could be used in addition to the pill to increase the level of protection. With respect to alternative methods of contraception, intrauterine contraceptives releasing levonorgestrel directly into the uterine cavity are considered to act mainly through a local effect and their efficacy is considered not be be affected in a major way by enzyme-inducing AEDs [12], even though more data are needed [74].

Reciprocal interactions may occur whereby oral contraceptives affect serum AED concentrations. Administration of the combined contraceptive pill causes a decrease in serum lamotrigine levels by about 50% [48], which may lead to loss of seizure control in some women [49]. Conversely, a rebound increase in serum lamotrigine levels with possible signs of toxicity may be observed when the contraceptive pill is discontinued. This interaction follows a cyclic pattern, with a marked decrease in serum lamotrigine levels during the 21 days of intake of the pill, and an increase in lamotrigine concentration during the pill-free week [13]. A similar cyclic interaction resulting in markedly decreased serum AED concentration during the 21 days of pill intake has been described for valproate in a single case report, and requires confirmation [75].

rarely. By virtue of its enzyme-inhibiting properties, valproic acid may increase the plasma levels of a variety of drugs, including zidovudine, lorazepam, nimodipine, paroxetine, amitryptiline, nortriptyline, nitrosureas and etoposide [2]. At least for amitriptyline and nortriptyline [66, 67], and for some antineoplastic drugs [52], these interactions may cause signs of toxicity.

Pharmacodynamic interactions

Pharmacodynamic interactions between AEDs and other drugs are poorly characterized. A well-documented example is the potentiation of the effects of nondepolarizing neuromuscular blockers (NDNMBs) by acutely administered AEDs [68]. Conversely, chronic AED therapy may cause resistance to NDNMBs, due to a combination of effects such as enzyme induction and upregulation of acetylcholine receptors.

Conclusions

Clinically important AED interactions are frequently observed in clinical practice, and often they can be anticipated by knowledge of the underlying mechanism. Whenever possible, these interactions should be prevented by avoiding the unnecessary use of polytherapy, and by selecting comedications which are less likely to interact. If the use of potentially interacting drugs cannot be avoided, adverse clinical consequences may be minimized, as appropriate, by individualized dose adjustments guided by careful monitoring of clinical response and measurement of serum drug concentrations.

Competing interests: None declared.

Box 2
Antiepileptic drugs and oral anticoagulants

Oral anticoagulants have an important role in the prevention and treatment of thromboembolic disorders. These drugs, however, have a narrow therapeutic window, and interactions affecting their pharmacokinetics or pharmacodynamics may result in serious complications [76].

There is a large body of evidence indicating that older generation enzyme-inducing AEDs, most notably barbiturates and carbamazepine, stimulate the metabolism of warfarin and other coumarin drugs, thereby increasing their dosage requirements [76, 77]. The size of the required increase in anticoagulant dosage varies from one patient to another: for warfarin, it may range from virtually nil to as much as 10-fold [78], and repeated International Normalized Ratio (INR) determinations are necessary to tailor dose adjustments to individual needs. A most dangerous situation comes when barbiturates or carbamazepine are discontinued, or substituted with other AEDs devoid of enzyme-inducing properties. Under these circumstances, the metabolism of the antocoagulant will slow and, if dosage is not reduced, there is a serious risk of massive haemorrhage [79].

Phenytoin's interactions with warfarin are more complex and unpredictable, and may involve a decrease or an increase in anticoagulant activity, or even biphasic responses [76, 77]. As a result of this, achieving a stable level of anticoagulation may be difficult when warfarin and phenytoin are combined [80]. Valproic acid may also increase serum warfarin concentrations, and facilitate bleeding by interfering directly with platelet function and coagulation processes [81].

Of the newer AEDs, oxcarbazepine 900 mg day^{-1} has not been found to affect the anticoagulant effect of warfarin, but the possibility of interaction at higher dosages has not been tested [2]. Levetiracetam 2000 mg day^{-1} and tiagabine 12 mg day^{-1} have also been reported not to interfere with the anticoagulant effect or the pharmacokinetics of warfarin [2].

Overall, newer generation AEDs with low interaction potential appear to be a preferable choice in patients who take oral anticoagulants. In any case, careful monitoring of the INR is recommended whenever comedication is changed in these patients.

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