EXPERT REVIEWS

Drug interactions involving the new second- and third-generation antiepileptic drugs

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During the period 1989–2009, 14 new antiepileptic drugs (AEDs) were licensed for clinical use and these can be subdivided into new second- and third-generation AEDs. The second-generation AEDs comprise felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide. The third-generation AEDs comprise eslicarbazepine acetate and lacosamide. The interaction propensity of AEDs is very important because all new AEDs are licensed, at least in the first instance, as adjunctive therapy. The present review summarizes the interactions (pharmacokinetic and pharmacodynamic) that have been reported with the newer AEDs. The pharmacokinetic interactions include those relating to protein-binding displacement from albumin in blood, and metabolic inhibitory and induction interactions occurring in the liver. Overall, the newer AEDs are less interacting because their pharmacokinetics are more favorable and many are minimally or not bound to blood albumin (e.g., eslicarbazepine, felbamate, gabapentin, lacosamide levetiracetam, rufinamide, topiramate and vigabatrin) and are primarily renally excreted or metabolized by noncytochrome P450 or uridine glucoronyl transferases (e.g., gabapentin, lacosamide levetiracetam, rufinamide, topiramate and vigabatrin) as opposed to hepatic metabolism which is particularly amenable to interference. Gabapentin, lacosamide, levetiracetam, pregabalin and vigabatrin are essentially not associated with clinically significant pharmacokinetic interactions. Of the new AEDs, lamotrigine and topiramate are the most interacting. Furthermore, the metabolism of lamotrigine is susceptible to both enzyme inhibition and enzyme induction. While the metabolism of felbamate, tiagabine, topiramate and zonisamide can be induced by enzyme-inducing AEDs, they are less vulnerable to inhibition by valproate. Noteworthy is the fact that only five new AEDs (eslicarbazepine, felbamate, oxcarbazepine, rufinamide and topiramate) interact with oral contraceptives and compromise contraception control. The most clinically significant pharmacodynamic interaction is that relating to the synergism of valproate and lamotrigine for complex partial seizures. Compared with the first-generation AEDs, the new second- and third-generation AEDs are less interacting, and this is a desirable development because it allows ease of prescribing by the physician and less complicated therapeutic outcomes and complications for patients.

Keywords: interactions • pharmacodynamics • pharmacokinetics • second-generation antiepileptic drugs • third-generation antiepileptic drugs

All new antiepileptic drugs (AEDs) are licensed, at least in the first instance, as adjunctive treatment with other AEDs and, consequently, their propensity to interact with other AEDs is very important. Substantial efforts are made to investigate possible interactions between potential new AEDs before licensing. These studies may either be formal, when a particular interaction is specifically investigated in volunteers or patients, or based on population data derived from the Phase II and III clinical trials of the drug. In addition, for AEDs that undergo hepatic metabolism, an effort is made to identify which isoenzymes are involved so as to allow anticipation of interactions, particularly for drugs that may be used for other nonepilepsy comorbidities.

Interactions can be divided into two groups: pharmacokinetic and pharmacodynamic. Pharmacokinetic interactions are interactions that can occur at essentially four sites (absorption – usually gastrointestinal; protein binding – usually serum albumin; metabolism – usually hepatic;

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excretion – usually renal) and are associated with a change in the serum concentration of the affected AED. For AEDs, there are many hundreds of pharmacokinetic interactions described in the literature and for many interactions their time course and magnitude has been characterized [1–5]. By contrast, pharmacodynamic interactions are those that occur at the site of action of a drug and are associated with a change in the clinical status of the patient – enhanced or attenuated efficacy or adverse effects. Pharmacodynamic interactions occur at the site of action of the drug and do not involve changes in serum concentrations. There are only a handful of such interactions described in the literature and the best characterized is that of valproate plus ethosuximide for absence seizures [6], and valproate plus lamotrigine for complex partial seizures [7,8]. By far the most important site of pharmacokinetic interactions is that of hepatic metabolism and the reason that the first-generation AEDs are particularly susceptible to pharmacokinetic interactions is because they all undergo metabolism via common isoenzymes (cytochrome P450 [CYP] and uridine glucuronyl transferases [UGTs]) that are highly inducible and readily inhibited. By contrast, many of the new AEDs do not undergo hepatic metabolism but are eliminated unchanged via the kidneys and, consequently, they are not susceptible to metabolic interactions and, therefore, their propensity to interact with other drugs is reduced substantially.

Population-based studies have shown that between 20 and 24% of patients with epilepsy use two or more AEDs and drug interactions are of particular concern in these patients [9,10]. Additionally, polytherapy with other drugs can occur throughout life and increases with age due to comorbidities, as illustrated by findings from elderly patients using AEDs in nursing homes, where the average number of other drugs was five to six [11]. For female patients, possible interactions with oral contraceptives (OCs) are of particular importance. A survey including 1855 women with epilepsy (aged 26–45 years old) showed that 22% of them used OCs, and more than 50% had not received any advice regarding possible interactions with their AEDs [12]. These results have recently been confirmed [13]. Because psychiatric and behavioral disturbances occur at a high rate in people with epilepsy, interactions between psychoactive drugs and AEDs is an important issue [14,15]. Another issue of importance regarding polytherapy is the increased use of AEDs in other disorders, such as in psychiatry and pain [16].

The purpose of the present review is to describe the clinically relevant interactions that can occur with the new second- and third-generation AEDs, both with regard to their interaction with other AEDs and also with other drugs used in the management of nonepilepsy comorbidities. The AEDs will be reviewed in alphabetical order and for each AED a summary of its pharmacokinetic characteristics that are relevant to its propensity to interact will be noted followed by a description of its pharmacokinetic interactions with other AEDs, pharmacokinetic interactions with nonepilepsy drugs and, finally, its pharmacodynamic interactions.

Search strategy & selection criteria

The present review is based on published articles and searches in PubMed and Google Scholar from July 2008 to October 2009. Peer-reviewed articles in international journals in English, from the earliest relevant data (1983) to 2009 are included. Primary sources were preferred but review articles of importance to the field were also used and references of interest from review articles were searched for individually. Case reports of clinical and general importance were considered and published abstracts were only included when a complete published article was not available. The search terms included the crosslinking of the terms from the following categories 1 and 2, followed by further detailed searches between Categories 1 and 3: Category 1: newer antiepileptic drugs: brivaracetam, carisbamate, eslicarbazepine, felbamate, gabapentin, ganaxolone, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, retigabine, rufinamide, stiripentol, talampanel, tiagabine, topiramate, vigabatrin and zonisamide; Category 2: interactions: pharmacology, pharmacokinetic, pharmacodynamic, enzyme induction, enzyme inhibition; Category 3: other drug classes: oral contraceptives, psychotropic drugs (antidepressants, antipsychotics) warfarin, antineoplastic drugs, immunosuppressants, antibiotics, and other drug classes (e.g., statins, calcium channel blockers, omeprazol, digoxin, triptanes).

Interactions involving the newer AEDs

Table 1 summarizes the serum concentration changes that can arise consequent to pharmacokinetic interactions occurring between AEDs and includes first-, second- and third-generation AEDs. Table 2 highlights interactions between the various AEDs and oral contraceptives, while Tables 3, 4 & 5 summarize the pharmacokinetic properties and susceptibility to interactions of the first-, second- and third-generation AEDs, respectively.

Eslicarbazepine acetate

Eslicarbazepine acetate was licensed for clinical use in Europe in 2009 as adjunctive therapy in adults with partial-onset seizures with or without secondary generalization. It is a derivative of carbamazepine and oxcarbazepine and acts as a prodrug to form the pharmacologically active eslicarbazepine (*S*-licarbazepine), which is one of the enantiomers of the monohydroxy derivative (MHD) of oxcarbazepine [17]. Eslicarbazepine acetate has not been used off-license for nonepilepsy disorders.

Pharmacokinetics

Eslicarbazepine acetate is rapidly absorbed after oral ingestion and subsequently undergoes rapid and almost complete conversion to its active metabolite eslicarbazepine. While eslicarbazepine acetate is not detectable in the circulation, other minor metabolites (*R*-licarbazepine and oxcarbazepine), which are also pharmacologically active, are detectable. The bioavailability of eslicarbazepine is 90% or more and is 30% protein bound in serum [18]. Glucuronic acid conjugation is the primary route of elimination of eslicarbazepine. This also occurs for *R*-licarbazepine and oxcarbazepine and all are excreted renally [19].

Interactions with AEDs

Phenytoin can increase the clearance of eslicarbazepine and decrease eslicarbazepine serum levels by 31–33%. A similar effect can occur with carbamazepine and indeed may occur with phenobarbital and

primidone. Eslicarbazepine can inhibit CYP2C19 and decrease the clearance of phenytoin and increase phenytoin serum levels by 31–35%. Furthermore, eslicarbazepine can increase the clearance of lamotrigine and topiramate and decrease lamotrigine and topiramate serum levels by 15 and 18%, respectively [18].

Interactions with other drugs

Eslicarbazepine (1200 mg daily) can decrease the AUC of levonorgestrel and ethinyloestradial by 37 and 42%, respectively, possibly due to induction of CYP3A4, and, therefore, reduce the effectiveness of these OCs [20].

Eslicarbazepine can enhance the metabolism of warfarin so that warfarin blood levels are decreased by 23% [20].

Pharmacodynamic interactions

Concomitant administration with carbamazepine is associated with a pharmacodynamic interaction whereby adverse effects, such as diplopia, abnormal coordination and dizziness, are more prevalent.

Felbamate

Felbamate was licensed in 1993. However, the clinical use of felbamate has diminished in recent years due to it being associated with serious idiosyncratic liver failure and bone marrow toxicity, and is now only rarely used in epilepsy [21]. Felbamate is recommended only in patients who responded inadequately to other AED treatments. Felbamate has not been used off-license for nonepilepsy disorders.

Pharmacokinetics

Felbamate is rapidly absorbed after oral ingestion, with a bioavailability of 90–95%. Felbamate is minimally protein bound (30%) and undergoes hepatic oxidative metabolism with the formation of parahydroxy- and 2-hydroxyl metabolites, which are subsequently excreted renally. Hydrolysis to monocarbamoyl felbamate also takes place in addition to the formation of the intermediate metabolite atropaldehyde, which is considered to be responsible for the idiosyncratic adverse effects of felbamate [22,23]. Felbamate is a substrate of CYP3A4 and CYP2E1.

Interactions with AEDs

Felbamate is a potent inhibitor of hepatic enzymes and may increase serum concentrations of phenobarbital, phenytoin, valproic acid, carbamazepine-10,11-epoxide (the pharmacologically active metabolite of carbamazepine) and *N*-desmethyl-clobazam (the pharmacologically active metabolite of clobazam) [24–28]. The metabolism of felbamate is enhanced by enzyme-inducing AEDs (carbamazepine, phenobarbital, phenytoin and primidone) resulting in a decrease in half-life from up to 22 h to approximately 14 h and a decrease in serum concentrations [22,29]. These interactions are the consequence of induction of CYP3A4 (Table 1).

Gabapentin can reduce the elimination half-life of felbamate by 46% and reduce its clearance by 37%. These effects are considered to be the consequence of an interaction at the level of renal excretion [30].

Interactions with other drugs

Felbamate inhibits the metabolism of warfarin necessitating a dose reduction in warfarin so as to maintain anticoagulant control [31]. Felbamate can decrease the AUC of gestodone by 42%, but not ethinyl estradiol and, therefore, may reduce the effectiveness of oral contraception (Table 2) [32].

Pharmacodynamic interactions

To date, no clinically significant pharmacodynamic interactions involving felbamate have been reported.

Gabapentin

Gabapentin was licensed for clinical use in 1993. It is presently licensed for adjunctive treatment of partial seizures with or without secondary generalization in adults and children aged 6 years and older, and for monotherapy treatment of partial seizures with or without secondary generalization in adults and children aged 12 years and older. Gabapentin is also licensed for use in neuropathic pain and has been used off-license for the management of anxiety, bipolar disorder, trigeminal neuralgia and tremor [33].

Pharmacokinetics

Gabapentin is rapidly absorbed after oral ingestion, with a bioavailability of 50–70%. Gabapentin is not bound to serum proteins, does not undergo hepatic metabolism and is excreted unchanged renally [34]. The pharmacokinetic interaction potential for gabapentin is, therefore, very low.

Interactions with AEDs

To date, no clinically significant pharmacokinetic interactions between gabapentin and other AEDs have been reported (Table 1), except for the interaction with felbamate at the level of renal excretion, as described earlier [30].

Interactions with other drugs

Gabapentin is associated with variability in absorption from the GI tract, and its absorption may be reduced by up to 24% with some antacids, and cimetidine can decrease the oral clearance of gabapentin by 14% [34,35].

Pharmacodynamic interactions

To date, no clinically significant pharmacodynamic interactions involving gabapentin have been reported.

Lacosamide

Lacosamide was licensed for clinical use in 2008 and is presently licensed for adjunctive treatment of partial onset seizures with or without secondary generalization in patients with epilepsy aged 16 years or older. Lacosamide has been used off-license for the treatment of diabetic neuropathy [36].

Pharmacokinetics

Lacosamide is rapidly absorbed after oral ingestion, with a bioavailability of 100%. It is minimally bound to serum proteins (<15%) and undergoes moderate hepatic metabolism

Table 1. Interactions between the newer (second- and third-generation) AEDs and the older (first-generation) AEDs: expected changes in serum concentrations (levels) when an AED is added to a pre-existing AED regimen.

AED added	Pre-existing AED								
	CBZ	*CLB*	*ESL*	*FBM*	*GBP*	*LCM*	*LTG*	*LEV*	*OXC*
CBZ	AI	CLB↓↓ DMCLB↑↑	ESL↓	FBM↓↓	↔	↔	LTG↓↓	↔	H-OXC↓
CLB	?	–	?	?	NA	NA	?	↔	↔
ESL	?	?	–	?	NA	NA	LTG↓	NA	?
FBM	CBZ↓ CBZ-E↑	CLB↓↓ DMCLB↑↑	?	–	NA	NA	↔	NA	↔
GBP	↔	NA	NA	FBM↑	–	NA	NA	↔	NA
LCM	↔	NA	NA	NA	NA	–	↔	↔	↔
LTG	↔	↔	?	NA	NA	↔	–	↔	NA
LEV	↔	↔	NA	NA	↔	↔	↔	–	NA
OXC	CBZ↓	?	?	?	NA	↔	LTG↓	NA	–
PB	CBZ↓↓	CLB↓↓ DMCLB↑↑	?	FBM↓↓	↔	NA	LTG↓↓	↔	H-OXC↓
PHT	CBZ↓↓	CLB↓↓ DMCLB↑↑	ESL↓	FBM↓↓	↔	↔	LTG↓↓	↔	H-OXC↓
PGB	↔	NA	?	NA	?	NA	↔	↔	NA
PRM	CBZ↓↓	CLB↓↓ DMCLB↑↑	?	FBM↓↓	↔	NA	LTG↓↓	↔	?
RFN	CBZ↓	?	?	?	NA	NA	LTG↓	NA	?
STP	CBZ↑↑	CLB↑↑ DMCLB↑↑	?	?	NA	NA	?	NA	?
TGB	↔	NA	?	NA	NA	NA	NA	NA	↔
TPM	↔	?	?	?	NA	↔	↔	NA	?
VPA	CBZ-E↑↑	?	?	FBM↑	↔	↔	LTG↑↑	↔	↔
VGB	↔	NA	NA	↔	NA	NA	NA	NA	NA
ZNS	CBZ↓↑	?	?	?	NA	NA	↔	NA	?

*Free (pharmacologically-active) level may increase.
↔: No change.
↓ : A usually minor (or inconsistent) decrease in serum level.
↓↓: A usually clinically significant decrease in serum level.
↑: A usually minor (or inconsistent) increase in serum level.
↑↑: A usually clinically significant increase in serum level.
AED: Antiepileptic drug; AI: Autoinduction; CBZ: Carbamazepine; CLB: Clobazam; CBZ-E: Carbamazepine-10,11-epoxide (active metabolite of CBZ); DMCLB: *N*-desmethylclobazam (active metabolite of clobazam); ESL: Eslicarbazepine; FBM: Felbamate; GBP: Gabapentin; H-OXC: 10-hydroxy-oxcarbazepine (active metabolite of oxcarbazepine); LCM: Lacosamide; LEV: Levetiracetam; LTG: Lamotrigine; NA: None anticipated; NCCP: Not commonly coprescribed; OXC: Oxcarbazepine; PB: Phenobarbital; PHT: Phenytoin; PGB: Pregabalin; PRM: Primidone; RFN: Rufinamide; STP: Stiripentol; TGB: Tiagabine; TPM: Topiramate; VPA: Valproic acid; VGB: Vigabatrin; ZNS: Zonisamide.

(demethylation) to form *O*-desmethyl lacosamide (30%) and other unidentified metabolites (30%). Approximately 40% is excreted unchanged in urine [17]. Although CYP2C19 is considered to be primarily responsible for the formation of *O*-desmethyl lacosamide, inhibition of the isoenzyme has resulted in no significant affect on the pharmacokinetics of lacosamide and no differences have been observed in subjects who are poor- or extensive CYP2C19 metabolisers [17,37]. The pharmacokinetic interaction potential for lacosamide is, therefore, very low.

Interactions with AEDs

To date, no clinically significant pharmacokinetic interactions involving lacosamide and other AEDs have been reported (Table 1).

Interactions with other drugs

To date, no clinically significant pharmacokinetic interactions involving lacosamide and other non-AED drugs have been reported.

Table 1. Interactions between the newer (second- and third-generation) AEDs and the older (first-generation) AEDs: expected changes in serum concentrations (levels) when an AED is added to a pre-existing AED regimen (cont.).

AED added	Pre-existing AED										
	PB	*PHT*	*PGB*	*PRM*	*RFN*	*STP*	*TGB*	*TPM*	*VPA*	*VGB*	*ZNS*
CBZ	↔	PHT↓↑	↔	PRM↓ PB↑	RFN↓	STP↓↓	TGB↓↓	TPM↓↓	VPA↓↓	↔	ZNS↓↓
CLB	?	PHT↑	NA	PRM↑	?	?	?	?	VPA↑	NA	?
ESL	?	PHT↑	NA	?	?	?	?	TPM↓	?	NA	?
FBM	PB↑↑	PHT↑↑	NA	?	?	?	?	?	VPA↑↑	↔	?
GBP	↔	↔	?	NA	NA	NA	NA	↔	↔	NA	NA
LCM	NA	↔	NA	NA	NA	NA	NA	↔	↔	NA	NA
LTG	↔	↔	↔	↔	↔	?	NA	↔	VPA↓	NA	↔
LEV	↔	↔	↔	↔	NA	NA	NA	NA	↔	NA	NA
OXC	PB↑	PHT↑	NA	?	?	?	?	TPM↓	↔	NA	?
PB	AI	PHT↓↑	↔	NCCP	RFN↓↓	STP↓↓	TGB↓↓	TPM↓↓	VPA↓↓		ZNS↓↓
PHT	PB↑	AI	↔	PRM↓ PB↑	RFN↓↓	STP↓↓	TGB↓↓	TPM↓↓	VPA↓↓	↔	ZNS↓↓
PGB	↔	↔	–	NA	NA	NA	↔	↔	↔	NA	NA
PRM	NCCP	PHT↓↑	NA	–	RFN↓↓	STP↓↓	TGB↓↓	TPM↓↓	VPA↓↓	↔	ZNS↓↓
RFN	PB↑	PHT↑	NA	?	–	?	?	↔	↔	NA	?
STP	PB↑↑	NA	NA	PRM↑↑	?	–	?	?	VPA↑↑	NA	?
TGB	↔	↔	↔	?	?	?	-	NA	↔	NA	NA
TPM	↔	PHT↑	↔	↔	?	?	?	–	VPA↓	NA	?
VPA	PB↑↑	PHT↓*	↔	PB↑↑	RFN↑	?	↔	TPM↓	–	↔	ZNS↓↓
VGB	↔	PHT↓	NA	↔	RFN↓	NA	NA	NA	↔	–	NA
ZNS	↔	PHT↑	NA	↔	?	?	NA	NA	↔	NA	–

*Free (pharmacologically-active) level may increase.
↔: No change.
↓ : A usually minor (or inconsistent) decrease in serum level.
↓↓: A usually clinically significant decrease in serum level.
↑: A usually minor (or inconsistent) increase in serum level.
↑↑: A usually clinically significant increase in serum level.
AED: Antiepileptic drug; AI: Autoinduction; CBZ: Carbamazepine; CLB: Clobazam; CBZ-E: Carbamazepine-10,11-epoxide (active metabolite of CBZ); DMCLB: *N*-desmethylclobazam (active metabolite of clobazam); ESL: Eslicarbazepine; FBM: Felbamate; GBP: Gabapentin; H-OXC: 10-hydroxy-oxcarbazepine (active metabolite of oxcarbazepine); LCM: Lacosamide; LEV: Levetiracetam; LTG: Lamotrigine; NA: None anticipated; NCCP: Not commonly coprescribed; OXC: Oxcarbazepine; PB: Phenobarbital; PHT: Phenytoin; PGB: Pregabalin; PRM: Primidone; RFN: Rufinamide; STP: Stiripentol; TGB: Tiagabine; TPM: Topiramate; VPA: Valproic acid; VGB: Vigabatrin; ZNS: Zonisamide.

Pharmacodynamic interactions

To date, no clinically significant pharmacodynamic interactions involving lacosamide have been reported.

Lamotrigine

Lamotrigine was licensed for clinical use in 1991. It is presently licensed for monotherapy in adults and children over 12 years of age for the treatment of partial seizures and primary and secondarily generalized tonic–clonic seizures; adjunctive therapy in adults and children over 2 years of age for the treatment of partial seizures and primary and secondarily generalized tonic–clonic seizures; and adjunctive therapy in adults and children over 2 years of age for seizures associated with Lennox–Gastaut syndrome. It is also licensed for use as maintenance treatment of bipolar I disorder and has been used off-license for a variety of conditions, including trigeminal neuralgia, peripheral neuropathy, migraine, neuropathic pain, psychosis and schizophrenia.

Table 2. Effects of antiepileptic drugs on oral hormone contraceptive metabolism.

Drug	Accelerates metabolism and therefore compromises contraception	Does not accelerate metabolism and therefore does not compromise contraception	Ref.
First-generation antiepileptic drugs			
Carbamazepine	Yes		
Phenobarbital	Yes		
Phenytoin	Yes		
Primidone	Yes		
Clobazam		Yes	
Clonazepam		Yes	
Ethosuximide		Yes	
Valproate		Yes	
Second-generation antiepileptic drugs			
Felbamate	Yes		[32]
Oxcarbazepine	Yes		[63,115]
Rufinamide	Yes		[65,67]
Topiramate (>200 mg/day)	Yes		[87,116]
Stiripentol*	Unknown		
Gabapentin		Yes	[117]
Lamotrigine‡		Yes	[45–49]
Levetiracetam		Yes	[118]
Pregabalin		Yes	[119]
Tiagabine		Yes	[120]
Vigabatrin		Yes	[121]
Zonisamide		Yes	[122]
Third-generation antiepileptic drugs			
Eslicarbazepine acetate	Yes		[18]
Lacosamide		Yes	[17]

*It is not known whether stiripentol affects hormonal contraception but theoretically it can increase serum levels of hormonal contraceptives and thus necessitate lower doses to be prescribed. In view of the indication for stiripentol, its administration during pregnancy and in women of childbearing potential would not be expected.
‡While lamotrigine has no effect on the oestrogen component of the contraceptive pill and in most patients will not compromise contraception, it enhances the metabolism of the progesterone component so that progesterone blood levels decrease by ~10%. This effect may be clinically significant in patients prescribed the progesterone-only contraceptive pill.

Pharmacokinetics

Lamotrigine is rapidly absorbed after oral ingestion, with a bioavailability of 95% or more. It is 55% protein bound in serum. Lamotrigine undergoes extensive metabolism in the liver by conjugation with glucuronic acid, to various pharmacologically inactive metabolites, 2-N-glucuronide and 5-N-glucuronide, a 2-N-methyl metabolite and other unidentified minor metabolites. Glucuronidation is via UGT and the isoform that is responsible for the N-glucuronidation of lamotrigine is UGT1A4.

Interactions with AEDs

Carbamazepine, oxcarbazepine, phenobarbital, phenytoin and primidone induce the metabolism of lamotrigine, increase lamotrigine clearance, and lower lamotrigine serum levels by 34–52%. Valproic acid inhibits the metabolism of lamotrigine so that lamotrigine clearance is decreased and lamotrigine serum levels increase by twofold. Half-life values typically increase from 30 to 60 h [38,39]. Conversely, lamotrigine can induce the metabolism of clonazepam and valproic acid, and decrease serum levels of clonazepam and valproic acid by 20–38 and 25%, respectively [40].

Interactions with other drugs

Sertraline and fluoxetine can increase lamotrigine serum levels by 100 and 50%, respectively, while acetaminophen, olanzapine, rifampicin and ritonavir can increase lamotrigine clearance and decrease lamotrigine serum levels by 20–44% [41–43].

The interaction between lamotrigine and OCs has been extensively studied and while lamotrigine does not affect the estrogen component of the OC pill (Table 2), it produces a small reduction (10–19%) in the progesterone level [44], which, although probably of no clinical significance in most patients, might result in contraceptive failure in some patients, particularly if they are prescribed the progesterone-only pill. Noteworthy is the observation that OCs enhance the metabolism of lamotrigine and decrease serum lamotrigine levels by more than 50% [44–47]. This effect is the consequence of metabolic induction by ethinyl estradiol (progesterone is without effect) [48]. This effect on lamotrigine may also be caused by endogenous estrogen during the luteal phase of the menstrual cycle in women without OCs [49].

Pharmacodynamic interactions

Concomitant administration with valproic acid is associated with a profound pharmacodynamic interaction whereby small doses of lamotrigine are associated with significant (synergistic) efficacy; however, adverse effects (e.g., disabling tremor) may also be exacerbated [7,8,50].

Concomitant administration with carbamazepine has been associated with an increased risk of adverse effects (nausea, dizziness, headache, blurred vision, diplopia and ataxia), and this can also occur with oxcarbazepine since both AEDs share the same mechanism of action, inhibiting voltage-gated sodium channels [5,51].

Levetiracetam

Levetiracetam was licensed for clinical use in 2000. It is presently licensed for monotherapy of partial seizures for those aged 16 years and older; adjunctive treatment of partial seizures with or without

secondary generalization in adults and children from 4 years of age; adjunctive treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy; and adjunctive treatment of primary generalized tonic–clonic seizures in adults and adolescents from 12 years of age with idiopathic generalized epilepsy. It has been used off-license for a variety of conditions, including neuropathic pain, chronic pain and mania.

Pharmacokinetics

Levetiracetam is rapidly absorbed after oral ingestion, with a bioavailability of 95% or more. It is not bound to serum proteins. Levetiracetam undergoes minimal metabolism with approximately 30% of the dose metabolized by hydrolysis to a deaminated metabolite. This metabolism is independent of the hepatic cytochrome P450 system and is via a type-B esterase enzyme located in whole blood [52,53]. The pharmacokinetic interaction potential for levetiracetam is, therefore, very low.

Interactions with AEDs

To date, no clinically significant pharmacokinetic interactions between levetiracetam and other AEDs have been reported (Table 1).

Interactions with other drugs

To date, no clinically significant pharmacokinetic interactions between levetiracetam and other non-AED drugs have been reported.

Pharmacodynamic interactions

An encephalopathic state induced by the addition of levetiracetam to valproate has been described, and disabling symptoms compatible with carbamazepine toxicity were reported in patients in whom levetiracetam was added to carbamazepine [54].

Topiramate-related adverse effects were exacerbated in children coprescribed levetiracetam [55].

Oxcarbazepine

Oxcarbazepine was licensed for clinical use in 1990. It is presently licensed for monotherapy or adjunctive treatment of partial seizures with or without secondary generalization in patients of 6 years or more of age. Oxcarbazepine has been used off-license for a variety of conditions including trigeminal neuralgia and bipolar disorder.

Pharmacokinetics

Oxcarbazepine is rapidly absorbed after oral ingestion, with a bioavailability of 100%. It is 60% bound to serum proteins whereby its pharmacologically active metabolite 10-hydroxycarbazepine is 40% bound. Oxcarbazepine is rapidly metabolized to its pharmacologically active metabolite, 10-hydroxycarbazepine, by stereoselective biotransformation mediated by cytosolic arylketone reductase. 10-hydroxycarbazepine is subsequently metabolized by conjugation with glucuronic acid [56].

Interactions with AEDs

Oxcarbazepine induces the metabolism of carbamazepine, lamotrigine and topiramate and decreases their serum levels by 13–34% [57,58]. In addition, oxcarbazepine can inhibit CYP2C19 and affect the metabolism of phenobarbital and phenytoin and increase their serum levels by 15–40% [59].

The metabolism of oxcarbazepine is induced by all enzyme-inducing AEDs (e.g., carbamazepine, phenytoin and phenobarbital) so that serum 10-hydroxycarbazepine levels are decreased by 15–29% (Table 1) [57,60,61].

Valproic acid can displace 10-hydroxycarbazepine from its serum protein-binding sites but the clinical significance of this interaction is uncertain.

Interactions with other drugs

Oxcarbazepine induces the metabolism of felodipine and can decrease serum felodipine levels by 34%. Viloxazine can increase 10-hydroxycarbazepine serum levels by 15% whilst verapamil can decrease 10-hydroxycarbazepine serum levels by 20% [58,62].

Oxcarbazepine (1200 mg/day) induces the metabolism of the OCs, ethinyl estradiol and levonorgestrel, as their AUCs were reduced by 47%, accompanied by a 45% decrease in their half-life values [63], possibly due to induction of UGT1A4 by estrogen (Table 2).

Pharmacodynamic interactions

Concomitant administration of oxcarbazepine with lamotrigine has been associated with an increased risk of adverse effects (nausea, somnolence, dizziness and headache), as described earlier [5,51].

Pregabalin

Pregabalin was licensed for clinical use 2004. It is presently licensed for adjunctive treatment of partial seizures with or without secondary generalization. It is also licensed for use in peripheral and central neuropathic pain and generalized anxiety disorders. Pregabalin has been used off-license for a variety of conditions including panic disorder, social anxiety disorder and fibromyalgia.

Pharmacokinetics

Pregabalin is rapidly absorbed after oral ingestion, with a bioavailability of 90% or more. Pregabalin is not bound to serum proteins, does not undergo hepatic metabolism and is excreted unchanged renally. The pharmacokinetic interaction potential for pregabalin is, therefore, very low.

Interactions with AEDs

To date, no clinically significant pharmacokinetic interactions between pregabalin and other AEDs have been reported (Table 1).

Interactions with other drugs

To date, no clinically significant pharmacokinetic interactions between pregabalin and other non-AEDs have been reported (Table 2).

Pharmacodynamic interactions

Pregabalin exerts additive effects on the cognitive and motor function impairment caused by oxycodone, and potentiates the CNS effects of ethanol and lorazepam [64]. CNS adverse effects, particularly somnolence can increase in patients coprescribed antispasticity agents.

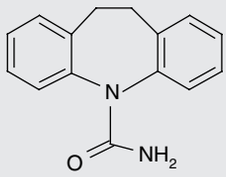
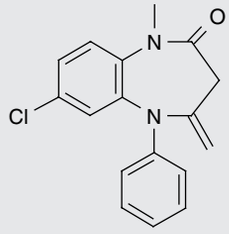
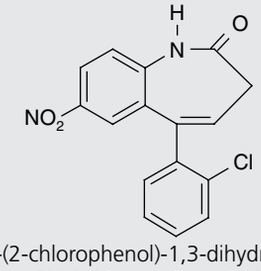
Rufinamide

Rufinamide was licensed in 2007 via the EMEA Orphan Drug Programme. It is presently licensed for adjunctive treatment of seizures in Lennox–Gastaut syndrome in patients 4 years and older. Rufinamide has not been used off-license for nonepilepsy disorders.

Pharmacokinetics

The absorption of rufinamide after oral ingestion is delayed and its bioavailability has yet to be determined. Its protein binding is 34%. Rufinamide is metabolized in the liver, primarily by hydrolysis, which is not CYP-dependent, to the metabolite CGP

Table 3. Characteristics of the first-generation antiepileptic drugs and their propensity to interact with other drugs.

Parameter	Antiepileptic drugs		
	Carbamazepine	*Clobazam*	*Clonazepam*
Structure and chemical name	 5H-dibenz[b,f]azepine-5-carboxamide	 7-chloro-1-methyl-5-phenyl-1,5-benzodiazepine-2,4-dione	 5-(2-chlorophenol)-1,3-dihydro-7-nitro-2H-1,4 benzodiazepin-2-one
Protein binding	Substantial (75%)	Substantial (85%)	Substantial (86%)
Displacement interactions are clinically significant?	No	No	No
Elimination by hepatic metabolism	Substantial (98%)	Substantial (100%)	Substantial (99%)
Elimination by renal excretion	Minimal (2%)	None (0%)	Minimal (1%)
Enzymes involved in metabolism	CYP1A2, CYP2C8, CYP3A4	CYP3A4	CYP3A4
Drugs that inhibit metabolism	AEDs: stiripentol and valproic acid Non-AEDs: cimetidine, clarithromycin, danazol, delavirdine, diltiazem, erythromycin, fluoxetine, fluconazole, fluvoxamine, gemfibrozil, haloperidol, indinavir, isoniazid, josamycin, ketoconazole, metronidazole, nefazodone, propoxyphene, ritonavir, ticlopidine, trazodone, troleandomycin, verapamil and viloxazine	AEDs: felbamate and stiripentol Non-AEDs: none identified to date	AEDs: none identified to date Non-AEDs: amiodarone and ritonavir
Drugs that induce metabolism	AEDs: felbamate, oxcarbazepine, phenobarbital, primidone, phenytoin and rufinamide Non-AEDs: efavirenz, nevirapine, rifampicin and St John's wort	AEDs: carbamazepine, felbamate, phenobarbital, phenytoin and primidone Non-AEDs: none identified to date	AEDs: carbamazepine, lamotrigine, phenobarbital, phenytoin and primidone Non-AEDs: none identified to date
Does AED induce the metabolism of other drugs?	Yes	No	No
Does AED inhibit the metabolism of other drugs?	Yes	No	No
Overall propensity to interact	Substantial	Moderate	Moderate

AED: Antiepileptic drug.

47292. This pharmacologically inactive metabolite is subsequently excreted in urine [65].

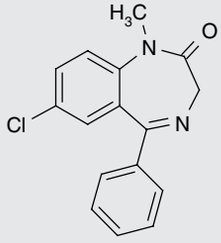
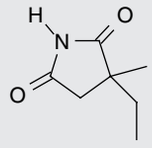
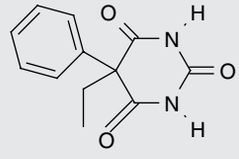
Interactions with AEDs

Carbamazepine, phenobarbital, phenytoin, primidone and vigabatrin can increase rufinamide clearance and decrease rufinamide serum levels by 25% [65]. By contrast, valproic acid may decrease the clearance of rufinamide by 17% and thus increase rufinamide serum levels [66]. In addition rufinamide can decrease serum levels of carbamazepine and lamotrigine and increase serum levels of phenobarbital and phenytoin (Table 1) [65].

Interactions with other drugs

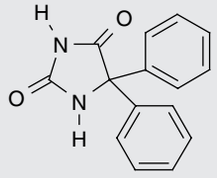
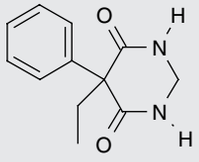
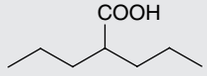
Rufinamide can induce metabolism of triazolam, possibly via an effect on CYP3A4, increasing its clearance by 55% and decreasing serum triazolam levels [65]. It can increase the clearance of OCs via induction of CYP3A4, and decrease serum concentrations of ethinyl estradiol and norethindrone by 22% and 14%, respectively [65,67].

Table 3. Characteristics of the first-generation antiepileptic drugs and their propensity to interact with other drugs.

Parameter	Antiepileptic drugs		
	Diazepam	*Ethosuximide*	*Phenobarbital*
Structure and chemical name	 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4 benzodiazepin-2-one	 3-ethyl-3-methyl-pyrrolidine-2,5-dione	 5-ethyl-5-phenylpyrrimidine-2,4,6 (1H,3H,5H)-trione
Protein binding	Substantial (98%)	Not protein bound (0%)	Moderate (50%)
Displacement interactions are clinically significant?	Yes	No	No
Elimination by hepatic metabolism	Substantial (95%)	Substantial (80%)	Substantial (80%)
Elimination by renal excretion	Minimal (5%)	Minimal (20%)	Minimal (20%)
Enzymes involved in metabolism	CYP2B, CYP2E1, CYP3A4	CYP2B, CYP2E1, CYP3A4	CYP2E1, CYP2C19
Drugs that inhibit metabolism	AED: valproic acid Non-AEDs: cimetidine, disulfiram and omeprazole	AED: valproic acid Non-AEDs: isoniazid and ritonavir	AEDs: felbamate, oxcarbazepine, phenytoin, rufinamide, stiripentol and valproic acid Non-AEDs: chloramphenicol, dicoumarol and propoxyphene
Drugs that induce metabolism	AEDs: phenytoin and primidone Non-AEDs: none identified to date	AEDs: caramazepine, phenobarbital, phenytoin and primidone Non-AEDs: rifampicin	AEDs: none identified to date Non-AEDs: none identified to date
Does AED induce the metabolism of other drugs?	No	No	Yes
Does AED inhibit the metabolism of other drugs?	No	No	No
Overall propensity to interact	Minimal	Moderate	Substantial

AED: Antiepileptic drug.

Table 3. Characteristics of the first-generation antiepileptic drugs and their propensity to interact with other drugs.

Parameter	Antiepileptic drugs		
	Phenytoin	*Primidone*	*Valproic acid*
Structure and chemical name	 5,5-diphenylimidazolidine-2,4-dione	 5-ethyl-5-phenyl-hexahydropyrimidine-4,6-dione	 2-propylpentanoic acid
Protein binding	Substantial (90%)	Minimal (10%)	Substantial (90%)
Displacement interactions are clinically significant?	Yes	No	Yes
Elimination by hepatic metabolism	Substantial (95%)	Minimal (35%)	Substantial (97%)
Elimination by renal excretion	Minimal (5%)	Moderate (65%)	Minimal (3%)
Enzymes involved in metabolism	CYP2C9, CYP2C19	CYP2E1, CYP2C9?, CYP2C19?	CYP2A6, CYP2C9, CYP2C19, CYP2B6, UGT1A3, UGT2B7
Drugs that inhibit metabolism	AEDs: clobazam, eslicarbazepine, felbamate, oxcarbazepine, rufinamide, stiripentol and valproic acid Non-AEDs: allopurinol, amiodarone, azapropazone, bleomycin, chlorphenamine, clarithromycin, chloramphenicol, cimetidine, clinafloxacin, cotrimoxazole, disulfiram, dextropropoxyphene (propoxyphene), dicoumarol, diltiazem, doxifluridine, erythromycin, esomeprazole, fenyramidol, fluconazole, 5-fluorouracil, fluoxetine, fluvoxamine, imipramine, indinavir, isoniazid, itraconazole, methylphenidate, metronidazole, miconazole, nelfinavir, nifedipine, omeprazole, risperidone, ritonavir, saquinavir, sertraline, sulfinpyrazone, tamoxifen, tegafur, ticlopidine, trazodone, verapamil, viloxazine and voriconazole	AEDs: clobazam, stiripentol and valproic acid Non-AEDs: isoniazid; see phenobarbital section	AEDs: clobazam and felbamate Non-AEDs: chlorpromazine, fluoxetine, isoniazid and sertraline
Drugs that induce metabolism	AEDs: carbamazepine and phenobarbital Non-AEDs: acyclovir, carboplatin, carmustine, cisplatin, dexamethasone, diazoxide, etoposide, loxapine, methotrexate, rifampicin, St John's wort, sucralfate, theophylline and vinblastine	AEDs: carbamazepine and phenytoin Non-AEDs: see phenobarbital section	AEDs: carbamazepine, lamotrigine, phenobarbital, primidone, phenytoin, stiripentol and topiramate Non-AEDs: amikacin, diflunisal, meropenem, naproxen, paripenem, rifampicin and ritonavir
Does AED induce the metabolism of other drugs?	Yes	Yes	No

AED: Antiepileptic drug.

Table 3. Characteristics of the first-generation antiepileptic drugs and their propensity to interact with other drugs.

Parameter	Antiepileptic drugs		
	Phenytoin	*Primidone*	*Valproic acid*
Does AED inhibit the metabolism of other drugs?	No	No	Yes
Overall propensity to interact	Substantial	Substantial	Substantial

AED: Antiepileptic drug.

Pharmacodynamic interactions

To date, no clinically significant pharmacodynamic interactions involving rufinamide have been reported.

Stiripentol

Stiripentol was licensed in 2008 via the European Medicines Agency Orphan Drug Programme. It is presently licensed for adjunctive treatment of seizures in children with severe myoclonic epilepsy in infancy (Dravet syndrome). Stiripentol has not been used off-license for nonepilepsy disorders.

Pharmacokinetics

Stiripentol is rapidly absorbed after oral ingestion but its bioavailability has not been determined. It is 99% bound to serum proteins [68,69]. Stiripentol is extensively metabolized by four main pathways (oxidation, hydroxylation, *O*-methylation and glucoronidation) to 13 different metabolites, and only a trace amount is excreted unchanged in the urine [68].

Interactions with AEDs

Stiripentol is a potent inhibitor of CYP3A4, CYP1A2, CYP2D6 and CYP2C19 and can increase serum levels of phenytoin, carbamazepine, phenobarbital, valproic acid, clobazam and its pharmacologically active metabolite, N-desmethyl-clobazam [68,70]. Enzyme-inducing AEDs (carbamazepine, phenobarbital, phenytoin and primidone) induce the metabolism of stiripentol so that stiripentol clearance is increased and lower stiripentol serum levels occur (Table 1) [71].

Interactions with other drugs

To date, no significant pharmacokinetic interactions between stiripentol and other non-AED drugs have been reported. However, because stiripentol is a potent inhibitor of CYP2C19, CYP1A2, CYP3A4 and CYP2D6, caution needs to be exercised if clinical circumstances require combining stiripentol with drugs that are metabolized by these isoenzymes (e.g., citalopram, omeprazole [CYP2C19], astemizole, chlorpheniramine, calcium channel blockers, statins, codeine [CYP3A4], propranalol, fluoxetine, sertraline, haloperidol and tramadol [CYP2D6]) [72].

It is not known whether stiripentol can have a clinically important effect on hormonal contraception but it could theoretically increase serum levels of hormonal contraceptives, implying that lower doses might need to be prescribed.

Pharmacodynamic interactions

In combination with valproate, stiripentol is associated with enhanced anorexia and loss of appetite [72,73].

Tiagabine

Tiagabine was licensed for clinical use in 1997. It is presently licensed for adjunctive treatment of partial seizures with or without secondary generalization in adults and children aged 12 years and older. Tiagabine has been used off-licence in anxiety disorders, other psychiatric disorders and essential tremor [74,75].

Pharmacokinetics

Tiagabine is rapidly absorbed after oral ingestion, with a bioavailability of 90% or more. It is 96% bound to serum proteins. Tiagabine is metabolized in the liver, primarily by CYP3A4, to two 5-oxo-tiagabine isomers (E5 and Z-5), which represents approximately 60% of its metabolism. The remaining 40% of metabolites have yet to be identified.

Interactions with AEDs

Tiagabine may lower valproic acid serum levels via an unknown mechanism. Comedication with enzyme-inducing AEDs (carbamazepine, phenobarbital, phenytoin and primidone) can increase tiagabine clearance by 50–65% and shorten its half-life to 2–5 h (from ~7 h) and lower tiagabine serum levels [76]. Valproic acid displaces tiagabine from its albumin protein binding sites and increases free pharmacologically active tiagabine levels [77].

Interactions with other drugs

Highly protein-bound drugs, such as salicylates and naproxen, can displace tiagabine from its albumin protein-binding sites and increase free pharmacologically active tiagabine levels [77]; however, the clinical relevance of these interactions has not been ascertained (Table 2).

Pharmacodynamic interactions

To date, no clinically significant pharmacodynamic interactions involving tiagabine have been reported.

Topiramate

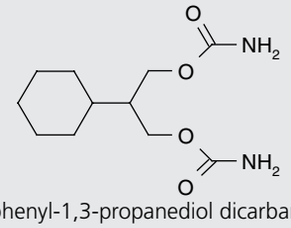
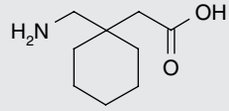
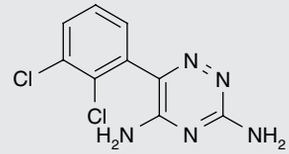
Topiramate was licensed for clinical use in 1995. It is presently licensed for adjunctive therapy for adults and children over

2 years of age who are inadequately controlled on conventional first-line AEDs for partial seizures with or without secondarily generalized seizures; seizures associated with Lennox–Gastaut syndrome; and for primary generalized tonic–clonic seizures. Topiramate is also licensed for migraine prophylaxis and has been used off-license for a variety of conditions, including psychotropic drug-induced weight gain and binge-eating disorder.

Pharmacokinetics

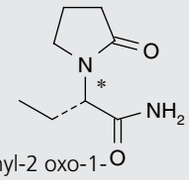
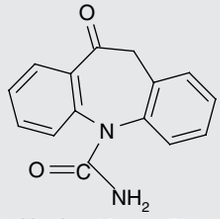
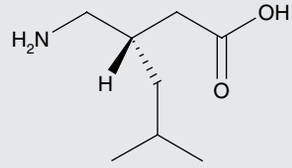
Topiramate is rapidly absorbed after oral ingestion with a bioavailability of 80% or more. It is 15% bound to serum proteins. Topiramate is not extensively metabolized, as 70–80% of a dose is excreted unchanged in the urine [78,79]. Six metabolites formed by hydroxylation, hydrolysis and glucuronidation have been identified, but none account for over 5% of a total dose [78,79]. Although the specific CYP isoenzymes for the

Table 4. Characteristics of the second-generation antiepileptic drugs and their propensity to interact with other drugs.

Parameter	Antiepileptic drugs		
	Felbamate	*Gabapentin*	*Lamotrigine*
Structure and chemical name	 2-phenyl-1,3-propanediol dicarbamate	 1-(aminomethyl)-cyclohexaneacetic acid	 3,5-diamino-6[2,3-dichlorophenyl]-1,2,4-triazine
Protein binding	Minimal (25%)	Not protein bound (0%)	Moderate (55%)
Displacement interactions are clinically significant?	No	No	No
Elimination by hepatic metabolism	Moderate (50%)	Not metabolized	Substantial (90%)
Elimination by renal excretion	Moderate (50%)	Substantial (100%)	Minimal (10%)
Enzymes involved in metabolism	CYP3A4 and CYP2E1	Not applicable	UGT1A4
Drugs that inhibit metabolism	AED: valproic acid Non-AEDs: none identified to date	Not applicable	AEDs: valproic acid Non-AEDs: sertraline
Drugs that induce metabolism	AEDs: carbamazepine, phenobarbital, phenytoin and primidone Non-AEDs: none identified to date	Not applicable	AEDs: carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone and rufinamide Non-AEDs: acetaminophen, olanzapine, rifampicin and ritonavir
Does AED induce the metabolism of other drugs?	No	No	Yes
Does AED inhibit the metabolism of other drugs?	Yes	No	No
Overall propensity to interact	Moderate	Noninteracting	Substantial

AED: Antiepileptic drug.

Table 4. Characteristics of the second-generation antiepileptic drugs and their propensity to interact with other drugs.

Parameter	Antiepileptic drugs		
	Levetiracetam	*Oxcarbazepine*	*Pregabalin*
Structure and chemical name	 (S)-α-ethyl-2 oxo-1-pyrrolidine acetamide	 10,11-dihydro-10-oxo-5H-dibenz(b,f)azepine-4-carboxamide	 S-3-(aminomethyl)-5-methylhexanoic acid
Protein binding	Not protein bound (0%)	Minimal: 10-hydroxycarbazepine – 40% Moderate: oxcarbazepine – 60%	Not protein bound (0%)
Displacement interactions are clinically significant?	No	No	No
Elimination by hepatic metabolism	Minimal (30%) Nonhepatic; occurs in whole blood	Substantial (95%)	Minimal (2%)
Elimination by renal excretion	Moderate (66%)	Minimal (5%)	Substantial (98%)
Enzymes involved in metabolism	Type-B esterase	Arylketone reductase Glucuronidation	Not applicable
Drugs that inhibit metabolism	AEDs: none identified to date Non-AEDs: none identified to date	AEDs: None identified to date Non-AEDs: Viloxazine	Not applicable
Drugs that induce metabolism	AEDs: none identified to date Non-AEDs: none identified to date	AEDs: carbamazepine, phenobarbital, phenytoin and primidone Non-AEDs: verapamil	Not applicable
Does AED induce the metabolism of other drugs?	No	Yes	No
Does AED inhibit the metabolism of other drugs?	No	Yes	No
Overall propensity to interact	Noninteracting	Moderate	Noninteracting

AED: Antiepileptic drug.

metabolism of topiramate have not been identified, it is evident that isoenzymes induced by carbamazepine and phenytoin play a major role.

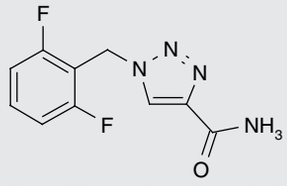
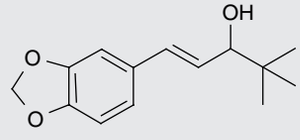
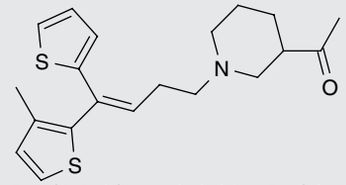
Interactions with AEDs

Carbamazepine, oxcarbazepine, phenobarbital, phenytoin and primidone may increase the clearance of topiramate and lower topiramate serum levels by 30–68%, whereas valproic acid increases its clearance and lowers topiramate serum levels by up to 17% [80–84]. Furthermore, topiramate may decrease the clearance of phenytoin and increase phenytoin serum levels, and also increase the clearance of valproic acid and decrease valproic acid serum levels [81,83].

Interactions with other drugs

Topiramate can increase the clearance and decrease the serum levels of digoxin, glibenclamide, pioglitazone, risperidone and sumatriptan. By contrast, topiramate can decrease the clearance

Table 4. Characteristics of the second-generation antiepileptic drugs and their propensity to interact with other drugs.

Parameter	Antiepileptic drugs		
	Rufinamide	*Stiripentol*	*Tiagabine*
Structure and chemical name	 1-[(2,6-difluorophenyl) methyl]-1-hydro-1,23-triazole-4-carboxamide	 (4,4-dimethyl-1[3,4(methylenedioxy)-phenyl]-1-pentan-3-ol	 R-n-(4,4-di(3-methyl-thien-2-yl)-but-3-enyl)-nipecotic acid hydrochloride
Protein binding	Minimal (35%)	Substantial (99%)	Substantial (96%)
Displacement interactions are clinically significant?	No	Not investigated but potentially Yes	Yes
Elimination by hepatic metabolism	Substantial (96%)	Substantial (73%)	Substantial (98%)
Elimination by renal excretion	Minimal (4%)	Minimal (27%)	Minimal (< 2%)
Enzymes involved in metabolism	Unknown (but nonCYP dependent)	CYP1A2, CYP2C19, CYP3A4	CYP3A4
Drugs that inhibit metabolism	AEDs: valproic acid Non-AEDs: none identified to date	AEDs: none identified to date Non-AEDs: none identified to date	AEDs: none identified to date Non-AEDs: none identified to date
Drugs that induce metabolism	AEDs: carbamazepine, phenobarbital, phenytoin, primidone and vigabatrin Non-AEDs: none identified to date	AEDs: carbamazepine, phenobarbital, phenytoin and primidone Non-AEDs: none identified to date	AEDs: carbamazepine, phenobarbital, phenytoin and primidone Non-AEDs: none identified to date
Does AED induce the metabolism of other drugs?	Yes	No	No
Does AED inhibit the metabolism of other drugs?	Yes	Yes	No
Overall propensity to interact	Moderate	Substantial	Minimal

AED: Antiepileptic drug.

and increase the serum levels of amitriptyline, haloperidol, hydrochlorothiazide, lithium and metformin [79,85,86]. Amitriptyline, lithium, metformin, propranolol and sumatriptan can decrease the clearance of topiramate and increase topiramate serum levels [86].

Serum levels of OCs are significantly decreased by topiramate at doses over 200 mg/day (clearance increased by 18–33%) (Table 2) [87].

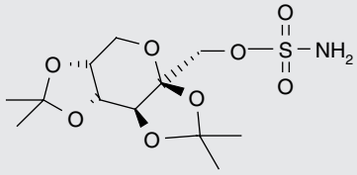
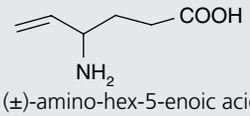
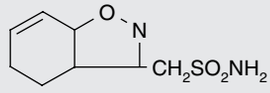
Pharmacodynamic interactions

Topiramate may enhance the risk of valproate-associated side effects, including elevated ammonium, hyperammonemic encephalopathy, elevated transaminases, apathy and hypothermia. Furthermore, symptoms of decreased appetite, weight loss and nervousness by topiramate can be exacerbated by levetiracetam, particularly in children [55].

Vigabatrin

Vigabatrin was licensed for clinical use in 1989. However, the clinical use of vigabatrin has diminished in recent years because of the high rate of visual fields defects [88]. It is presently licensed for adjunctive treatment of partial seizures with and without secondary generalization, not satisfactorily controlled with other AEDs;

Table 4. Characteristics of the second-generation antiepileptic drugs and their propensity to interact with other drugs.

Parameter	Antiepileptic drugs		
	Topiramate	*Vigabatrin*	*Zonisamide*
Structure and chemical name	 2,3:4,5-bis-*O*-(1-methylethylidene)-b-D-fructopyranose sulfamate	 (±)-amino-hex-5-enoic acid	 1,2-benzisoxazole-3-methanesulfonamide
Protein binding	Minimal (15%)	Not protein bound (0%)	Moderate (40%)
Displacement interactions are clinically significant?	No	No	No
Elimination by hepatic metabolism	Moderate (50%)	Not metabolized	Moderate (65%)
Elimination by renal excretion	Moderate (50%)	Substantial (100%)	Minimal (35%)
Enzymes involved in metabolism	Not identified but involve CYP isoenzymes	Not applicable	CYP3A4
Drugs that inhibit metabolism	AEDs: none identified to date Non-AEDs: amitriptyline, lithium, metformin, propranolol and sumatriptan	Not applicable	AEDs: none identified to date Non-AEDs: none identified to date
Drugs that induce metabolism	AEDs: carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin, primidone and valproic acid Non-AEDs: none identified to date	Not applicable	AEDs: carbamazepine, phenobarbital, phenytoin, primidone and valproic acid Non-AEDs: risperidone
Does AED induce the metabolism of other drugs?	Yes	No	No
Does AED inhibit the metabolism of other drugs?	Yes	No	No
Overall propensity to interact	Substantial	Noninteracting	Minimal

AED: Antiepileptic drug.

and as monotherapy for the management of infantile spasms (West syndrome). Vigabatrin has not been used off-license for nonepilepsy disorders.

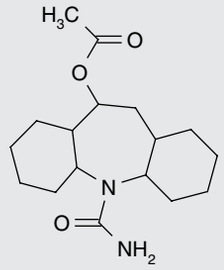
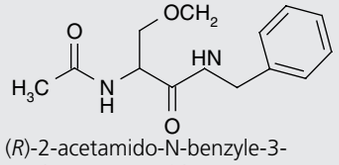
Pharmacokinetics

Vigabatrin is rapidly absorbed after oral ingestion, with a bioavailability of 60–80%. It is not bound to serum proteins and is excreted unchanged through the kidneys [89]. The pharmacokinetic interaction potential for vigabatrin is, therefore, very low.

Interactions with AEDs

Theoretically, vigabatrin should not be susceptible to pharmacokinetic interactions. Nevertheless, a decrease of up to 30% in phenytoin serum levels has been reported to occur when co-prescribed with phenytoin through an as yet unknown mechanism

Table 5. Characteristics of the third-generation antiepileptic drugs and their propensity to interact with other drugs.

Parameter	Antiepileptic drugs	
	Eslicarbazepine acetate	*Lacosamide*
Structure and chemical name	 (*S*)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide	 (*R*)-2-acetamido-N-benzyle-3-methoxypropramide
Protein binding	Moderate (<40%)	Minimal (<15%)
Displacement interactions are clinically significant?	No	No
Elimination by hepatic metabolism	Substantial (>99%)	Moderate (60%)
Elimination by renal excretion	Minimal (<1%)	Minimal (40%)
Enzymes involved in metabolism	Not identified but involve UGTs	Demethylation
Drugs that inhibit metabolism	AEDs: none identified to date Non-AEDs: none identified to date	AEDs: none identified to date Non-AEDs: none identified to date
Drugs that induce metabolism	AEDs: carbamazepine and phenytoin Non-AEDs: none identified to date	AEDs: none identified to date Non-AEDs: none identified to date
Does AED induce the metabolism of other drugs?	Yes	No
Does AED inhibit the metabolism of other drugs?	Yes	No
Overall propensity to interact	Minimal	Noninteracting

AED: Antiepileptic drug.

(metabolism, protein binding and absorption have been excluded as possible mechanisms) (Table 1) [90].

Interactions with other drugs

To date, no clinically significant pharmacokinetic interactions between vigabatrin and other non-AED drugs have been reported (Table 2).

Pharmacodynamic interactions

To date, no clinically significant pharmacodynamic interactions involving vigabatrin have been reported.

Zonisamide

Zonisamide was licensed for clinical use in 2000 (Europe and the USA) but was first approved in Japan in 1989. It is presently licensed for adjunctive therapy in adult patients with partial seizures with or without secondary generalization. Zonisamide has been used off-license for a variety of conditions including bipolar disorder, chronic neuropathic pain, migraine, Parkinson's disease, psychotropic drug-induced weight gain, and binge-eating disorder.

Pharmacokinetics

Zonisamide is rapidly absorbed after oral ingestion, with an oral bioavailability of 90% or more. It is 40% bound to serum proteins and binding decreases with increasing zonisamide concentrations. Zonisamide is metabolized by acetylation and by CYP3A4-mediated reduction to form 2-sulfamoylacetylphenol and subsequent glucuronidation, while 15–30% is eliminated unchanged [91].

Interactions with AEDs

Carbamazepine, phenobarbital, phenytoin, primidone and valproic acid may increase the clearance of zonisamide and lower zonisamide serum levels (Table 1) [92,93].

Interactions with other drugs

Risperidone can decrease serum zonisamide levels by 50%, as shown in a case report [94].

Pharmacodynamic interactions

To date, no clinically significant pharmacodynamic interactions involving zonisamide have been reported.

Expert commentary

Since many patients with epilepsy require long-term treatment with AEDs and because a high proportion of these patients will require other non-AED drugs to treat comorbidities, AEDs that do not interact with non-AED drugs would be a major advantage. Regrettably, the AEDs are associated with more drug–drug interactions than any other therapeutic class of drugs and this can be attributed primarily to the first-generation AEDs, carbamazepine, phenytoin, phenobarbital and valproate. These AEDs not only undergo elimination by metabolism in the liver via common isoenzymes, which are susceptible to interference (inhibition and/or induction) but in addition these AEDs both induce (carbamazepine, phenytoin, phenobarbital, valproate) and inhibit (phenytoin, valproate) the metabolism of other drugs. Phenytoin is associated with more drug–drug interactions than any other AED and this is attributable to the fact that it has nonlinear saturable pharmacokinetic properties.

By contrast, the new second- and third-generation AEDs have more desirable pharmacokinetic characteristics in that many are excreted renally (gabapentin, levetiracetam, pregabalin, vigabatrin), which is not readily susceptible to interference, or undergo minimal/moderate metabolism with non-CYP- and non-UGT-dependent isoenzyme systems (levetiracetam, lacosamide), which similarly are not susceptible to interference. Of the new AEDs, lamotrigine and topiramate are most interacting and their interaction profiles can be considered to be substantial. Indeed, the interactions associated with lamotrigine are of such clinical significance that complicated dosing regimens have had to be formulated so as to counter their consequences. Significantly, the development of stiripentol was curtailed due to its substantial pharmacokinetic interaction potential and is now only licensed for use in the difficult-to-treat Dravet syndrome. Overall, however, the new AEDs have a significantly reduced propensity to interact pharmacokinetically with other drugs and it would appear from the preliminary data available thus far from the various other new AEDs in development that this trend of licensing AEDs with a reduced capacity of drug–drug interactions is set to continue. This is a desirable development both in terms of ease of prescribing by the physician and in terms of less complicated therapeutic outcomes for patients.

Five-year view

Presently there are numerous new AEDs undergoing Phase II and III clinical evaluation, and several are expected to be licensed for clinical use in the next 5 years [95]. A key emphasis for new AED development is that of enhanced efficacy and reduced adverse effect profiles. However, an integral component of these studies is to ascertain the interaction potential of the candidate AED. Some limited data in this regard have been published and more can be expected.

Brivaracetam, a derivative of levetiracetam, was designed to improve the selectivity for the target protein of levetiracetam. It is rapidly absorbed with a bioavailability of approximately 100%, and is approximately 20% bound to serum proteins [96,97]. In contrast to levetiracetam, brivaracetam undergoes extensive metabolism by hydrolysis and CYP2C8-mediated hydroxylation to pharmacologically inactive metabolites [98]. It appears to have a minimal potential for pharmacokinetic interactions in that carbamazepine AUC values can decrease by 13% and small decreases in phenytoin serum levels have also been reported [96,99]. Serum carbamazepine-epoxide levels may increase 2.5-fold [71].

Carisbamate is a derivative of felbamate but without the adverse effects of felbamate. It is rapidly absorbed after oral ingestion with a bioavailability of 95%, and is approximately 44% bound to serum proteins [100,101]. Carisbamate is extensively metabolized by *O*-glucuronidation and hydrolysis [100]. It decreases serum valproic acid and lamotrigine levels by 20% [102,103], while carbamazepine induces the metabolism of carisbamate, as seen by a 30% reduction in AUC values [104], and the serum carisbamate levels are reduced by 20–30% by OCs [105].

Fluorofelbamate is an analogue of felbamate that has been designed to have the clinical efficacy of felbamate but without the adverse effects of felbamate. Its bioavailability is 82–100%, and urinary excretion is the primary route of elimination [106]. At present its drug-interaction profile is unknown.

Ganaxolone, a neurosteroid, is rapidly absorbed after oral ingestion and is highly bound to serum proteins (>99%) [107]. It undergoes metabolism in the liver by CYP3A4 to 16-hydroxy ganaxolone [71]. To date, ganaxolone has not been associated with any significant drug interactions with concomitant AEDs [108].

JZP-4 is a structural analogue of lamotrigine. In healthy volunteers, the apparent oral clearance of a single dose of JZP-4 was associated with a twofold increase in clearance during co-administration with carbamazepine but was unaffected by valproic acid co-administration [17].

Retigabine, a drug with a broad spectrum of activity, is rapidly absorbed after oral ingestion, with a bioavailability of 60% [109]. It is 80% protein bound and undergoes metabolism in the liver by *N*-glucuronidation and *N*-acetylation. Retigabine does not affect serum levels of carbamazepine, valproic acid, phenytoin, phenobarbital or topiramate. However, retigabine can increase lamotrigine clearance by 22% and decrease AUC values by 18% [110,111]. Additionally, lamotrigine can decrease AUC values by 15% [110]. The enzyme-inducing AEDs carbamazepine and phenytoin can increase its clearance by 30%, while phenobarbital enhances the clearance of retigabine by only 10% [71,109,110]. Topiramate and valproic acid do not affect the pharmacokinetics of retigabine [107].

Talampanel, an AMPA receptor antagonist similar to topiramate. It is rapidly and well absorbed after oral ingestion and its serum protein binding is 67–88% [112]. Talampanel is metabolized via *N*-acetylation and *O*- and *N*-glucuronidation. The drug is an irreversible inhibitor of CYP3A4 and increases carbamazepine and valproic acid serum levels. The clearance of talampanel is enhanced by enzyme-inducing AEDs, such as carbamazepine and phenytoin [112].

Valrocemide is a valproyl derivative of glycine. It is rapidly absorbed after oral ingestion, with a bioavailability of approximately 88% [113]. Approximately 10–20% of the drug is excreted unchanged in urine and 40% is metabolized to valproyl glycine and 4–6% to valproic acid. Valrocemide metabolism is enhanced by enzyme-inducing AEDs, such as carbamazepine and phenytoin [71].

Overall, these limited data would suggest that the general trend of developing AEDs that are associated with a reduced propensity for pharmacokinetic interactions continues. This is important because, for many patients with epilepsy, treatment with AEDs is for life and, therefore, the complications associated with pharmacokinetic interactions can be problematic both with regard to seizure control and with regard to adverse effects.

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Key issues

- In total, 14 new anti-epileptic drugs (AEDs), referred to as second- and third-generation AEDs, have been marketed since 1989, the latest being eslicarbazepine acetate, which was licensed in September 2009.
- Felbamate and vigabatrin have limited clinical use consequent to their associated adverse effects, while rufinamide and stiripentol are licensed as orphan drugs and, therefore, also have limited clinical use.
- New AEDs are generally less susceptible to pharmacokinetic interactions than the first-generation AEDs due to their more favourable pharmacokinetic profiles.
- Gabapentin, lacosamide, levetiracetam, pregabalin and vigabatrin are essentially not associated with clinically significant pharmacokinetic interactions.
- Of the new AEDs, lamotrigine and topiramate are most interacting and their interaction profile can be considered to be substantial within this grouping.
- All the major first-generation AEDs (carbamazepine, phenobarbital, phenytoin and valproic acid) have an interaction profile that can be considered to be substantial and their interaction profile is orders of magnitude greater that any of the new AEDs – by far the most interacting of all the AEDs is phenytoin.
- The metabolism of felbamate, tiagabine, topiramate and zonisamide may be induced by AEDs with enzyme-inducing properties but are less vulnerable to inhibition by inhibitors such as valproic acid.
- The metabolism of lamotrigine is susceptible to both enzyme inhibition and enzyme induction by enzyme-inducing drugs and significantly by oral contraceptives (OCs).
- Only five of the new AEDs (eslicarbazepine acetate, felbamate, oxcarbazepine, rufinamide and topiramate) interact with OCs and compromise contraception control.
- For patients that are to be prescribed an AED or a non-AED that is known to interact with their usual AED medication, it may be of considerable benefit to undertake therapeutic drug monitoring so as to quantify the serum concentration changes and thus allow a rational and gradual dose adjustment to compensate for the interaction – this is particularly important in patients where pharmacokinetic changes are more substantial (e.g., children) or in patients that are sensitive to pharmacokinetic changes (e.g., pregnant women and the elderly) [114].
- Presently there are numerous putative AEDs in development and the limited data available to date would suggest that the general trend of developing AEDs that are associated with a reduced propensity for pharmacokinetic interactions is set to continue.

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