REVIEW ARTICLE

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Interactions between Antiepileptic and Antipsychotic Drugs

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Contents

Abstract

Antiepileptic and antipsychotic drugs are often prescribed together. Interactions between the drugs may affect both efficacy and toxicity. This is a review of human clinical data on the interactions between the antiepileptic drugs carbamazepine, valproic acid (sodium valproate), vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine, levetiracetam, pregabalin, felbamate, zonisamide, phenobarbital and phenytoin with the antipsychotic drugs risperidone, olanzapine, quetiapine, clozapine, amisulpride, sulpiride, ziprasidone, aripiprazole, haloperidol and chlorpromazine; the limited information on interactions between antiepileptic drugs and zuclopenthixol, periciazine, fluphenazine, flupenthixol and pimozide is also presented. Many of the interactions depend on the induction or inhibition of the cytochrome P450 isoenzymes, but other important mechanisms involve the uridine diphosphate glucuronosyltransferase isoenzymes and protein binding.

There is some evidence for the following effects. Carbamazepine decreases the plasma concentrations of both risperidone and its active metabolite. It also decreases concentrations of olanzapine, clozapine, ziprasidone, haloperidol, zuclopenthixol, flupenthixol and probably chlorpromazine and fluphenazine. Quetiapine increases the ratio of carbamazepine epoxide to carbamazepine and this may lead to toxicity. The data on valproic acid are conflicting; it may either increase or decrease clozapine concentrations, and it appears to decrease aripiprazole concentrations. Chlorpromazine possibly increases valproic acid concentrations. Lamotrigine possibly increases clozapine concentrations. Phenobarbital decreases clozapine, haloperidol and chlorpromazine concentrations. Phenytoin decreases quetiapine, clozapine, haloperidol and possibly chlorpromazine concentrations. There are major gaps in the data. In many cases there are no published clinical data on interactions that would be predicted on theoretical grounds.

Antiepileptic and antipsychotic drugs are being prescribed together to an increasing degree for a number of reasons. Firstly, there is a growing awareness of the high prevalence of psychiatric disorders in people with epilepsy and of the importance of providing appropriate treatment.[1-3] Secondly, an-

tiepileptic drugs (AEDs) are being used to treat a variety of psychiatric disorders, often in combination with other psychotropic drugs.[4] Thirdly, AEDs are being used for a number of other conditions that are not related to epilepsy, e.g. neuropathic pain,[5] which are common and may occur coincidentally in people who require antipsychotic medication. Furthermore, AEDs may sometimes precipitate psychiatric disorders[6] and antipsychotic medication can occasionally precipitate seizures.[7] Although the preferred management of such drug-induced adverse effects would be to change to another drug, this is not always a reasonable option. For example, if a patient with schizophrenia that is resistant to all other medication has seizures associated with clozapine, then adding antiepileptic medication might be justified. Interactions between AEDs and antipsychotic medication may lead to reduced efficacy or toxicity. If clinicians are aware of the possible interactions then steps can be taken either to avoid the adverse effects or at least to manage them promptly and effectively.

1. Scope and Strategy of the Review

Because of the large numbers of AEDs and antipsychotic drugs, not all the interactions have been examined. In general, the choice has been based on newer drugs, well established drugs that are commonly used, and a small selection of older drugs. The selection of AEDs has been confined to 14 drugs that are chosen for the following reasons. Carbamazepine and valproic acid (sodium valproate) are well established AEDs that are also widely used in psychiatry. The ten newer AEDs licensed for use in the US and UK have been included in the literature search, although there is remarkably little information available on the interactions between these drugs and antipsychotic medication. Although many doctors try to avoid prescribing them because of adverse effects, the two older AEDs, phenobarbital and phenytoin, are still commonly used on a worldwide basis. In particular, phenobarbital is the only drug available to many patients in developing countries. The antipsychotic drugs chosen are those that are commonly used, including a number of the newer atypical antipsychotic drugs (risperidone, olanzapine, quetiapine, clozapine, amisulpride, sulpiride, ziprasidone and aripiprazole) and two older drugs (haloperidol and chlorpromazine). On the first occasion that each antipsychotic drug appears (i.e. in the section on carbamazepine, the first AED discussed in this review) there is a brief comment on the metabolism. The very limited data on the interactions between AEDs and zuclopenthixol, periciazine, fluphenazine, flupenthixol and pimozide are reviewed separately in section 4.

The evidence for the interactions between the AEDs and each antipsychotic drug is presented. The term ‘antipsychotic’ is used for convenience, although it is acknowledged that these drugs are used for other conditions as well; e.g. several antipsychotic drugs are used for treating behavioural or mood disorders.

This is an evidence-based review of human data. Animal data have generally not been included because animal metabolism does not necessarily mimic human metabolism. Theoretical interactions that might occur can be deduced from table I. This table indicates which enzymes are inhibited or induced, but such interactions are not always clinically relevant, for the reasons stated in the next section. Table II indicates the interactions for which evidence could be found.

The information was obtained from a MEDLINE search (1966 to January 2005), hand-searching of a number of recent journals and recent reviews, and by requesting medical information from individual drug companies.

The MEDLINE search used the following keywords: ‘carbamazepine’, ‘tegretol’, ‘sodium valproate’, ‘epilim’, ‘valpoic acid’, ‘vigabatrin’, ‘sabril’, ‘lamotrigine’, ‘lamictal’, ‘gabapentin’, ‘neurontin’, ‘topiramate’, ‘topamax’, ‘tiagabine’, ‘gabitril’, ‘oxcarbazepine’, ‘trileptal’, ‘levetiracetam’, ‘keppra’, ‘pregabalin’, ‘lyrica’, ‘phenobarbitone’, ‘phenobarbital’, ‘phenytoin’, ‘epanutin’, ‘dilantin’ or ‘diphenylhydantoin’, and the name of the antipsychotic drug, and ‘interact’, ‘interacts’, ‘interaction’, ‘interactions’, ‘level’, ‘levels’, ‘concentra-

Table I. Cytochrome P450 (CYP) isoenzyme substrates, inducers and inhibitors[a]

Drug	Substrate for CYP								Induces CYP						Inhibits CYP		
	1A2	2C8	2C9	2C19	2D6	2E1	3A4	3A5	1A2	2B	2C8	2C9	2C19	3A4	2C9	2C19	2D6
Carbamazepine	+	+					+		+			+		+			
Valproic acid			+												+		
Vigabatrin																	
Lamotrigine																	
Gabapentin																	
Topiramate							+							+		+	
Tiagabine							+										
Oxcarbazepine																	
Levetiracetam																	
Pregabalin																	
Felbamate						+	+							+		+	
Zonisamide					+		+										
Phenobarbital			+	+		+			+	+	+	+	+	+			
Phenytoin			+	+			+					+		+			
Risperidone					+		+										
Olanzapine	+				+												
Quetiapine							+										
Clozapine	+	+	+	+	+		+	+									
Amisulpride																	+
Sulpiride																	
Ziprasidone							+										
Aripiprazole					+		+										
Haloperidol					+		+										+
Chlorpromazine					+												+

a Data from several sources (see text). Missing data from the table does not necessarily imply that there is no significant interaction. The published information is limited.

tion,' 'concentrations', 'disposition', 'inhibit', 'inhibits', 'inhibition', 'induce', 'induces', 'induction', '450', 'CYP' or 'isoenzyme'. Additional references were added during the preparation and review of the manuscript.

2. Theoretical Considerations

Accounts of the mechanisms underlying possible interactions between AEDs and antipsychotic medication have appeared in recent reviews.[8-10] A brief summary follows.

Interactions may be classified as pharmacokinetic or pharmacodynamic. A pharmacokinetic interaction causes a change in blood concentration of at least one of the drugs. Pharmacokinetic interactions occur during one or more of the phases of absorption, distribution, metabolism or excretion. Pharmacodynamic interactions do not produce changes in blood concentrations but are interactions that alter the effect of drugs at their site of action. These simple distinctions have been challenged but serve as a useful working model for classifying interactions. Most of the literature describes pharmacokinetic interactions but some pharmacodynamic interactions are also important, particularly those relating to carbamazepine.

Drug effects can be influenced by a large number of factors, including age, sex, ethnicity, individual genetic differences and concomitant disease (e.g. renal impairment). Some people metabolise particular drugs much more rapidly or much more slowly than average ('fast metabolisers' and 'slow metabolisers') and this can greatly affect the efficacy of a given dose. The growing interest in pharmacogenomics illustrates the recognition of the impor-

Table II. Reported changes to antipsychotic and antiepileptic drug concentrations resulting from interactions between the two[a]

Drug	Risperidone	Olanzapine	Quetiapine	Clozapine	Amisulpride	Sulpiride	Ziprasidone	Aripiprazole	Haloperidol	Chlorpromazine
Changes to antipsychotic drug concentrations resulting from the addition of an antiepileptic drug										
Carbamazepine	↓	↓	↓	↓			↓		↓	↓
Valproic acid	↔			↓[b]				NS	NS	NS
Vigabatrin										
Lamotrigine				↑[b]						
Gabapentin										
Topiramate									↑[b]	
Tiagabine										
Oxcarbazepine	↔	↔		↔						
Levetiracetam										
Pregabalin										
Felbamate										
Zonisamide										
Phenobarbital				↓					↓	↓
Phenytoin			↓	↓					↓	↓[b]
Changes to antiepileptic drug concentrations resulting from the addition of an antipsychotic drug										
Carbamazepine	↑		[c]						↑[b]	
Valproic acid	↑↓[b]								↔	↑
Vigabatrin										
Lamotrigine										↑[b]
Gabapentin										
Topiramate										
Tiagabine										
Oxcarbazepine										
Levetiracetam										
Pregabalin										
Felbamate										
Zonisamide										
Phenobarbital										
Phenytoin										↑[b]

a Data from several sources (see text). Missing data from the table does not necessarily imply that there is no significant interaction. The published information is limited. It should be noted that many expected interactions have not yet been published. For example, phenobarbital and phenytoin would be expected to decrease concentrations of several of the antipsychotic drugs. Many of the possible interactions can be predicted from table I, but predicted interactions may or may not be of clinical significance (refer to section 3).

b Change debated or doubtful from the evidence available.

c Quetiapine can increase carbamazepine-epoxide concentrations to toxic levels (see section 3.1.3).

NS = results not statistically significant to date; ↑ indicates increase; ↓ indicates decrease; ↑↓ indicates increase or decrease; ↔ indicates no change.

tance of differences between individuals.[11] Pharmacogenomics may yield useful predictive information on both pharmacokinetic and pharmacodynamic interactions. Lifestyle issues can also affect drug concentrations; smoking and food can affect the activity of some of the cytochrome P450 (CYP) isoenzymes.[12] For example, non-smoking women were found to have clozapine blood concentrations that were 40% higher than smokers in one study.[13] Although the primary focus of most reported pharmacokinetic interaction studies has been on hepatic metabolism, there is growing evidence that drug transport proteins, for example P-glycoprotein, are the rate-determining factor for the absorption and disposition of many drugs and they may have a role to play when considering the interactions between antipsychotics and AEDs. Carbamazepine, phenytoin, phenobarbital, lamotrigine and gabapentin are all actively transported by P-glycoprotein. Protein binding can also play an important role in drug interactions. Although the total concentration of the drug might not be altered by the addition of another medication, if the added medication is strongly protein bound, the free, unbound active fraction of the first drug may be increased by displacement from protein binding by the second. Drug concentration measurements may also be misleading if they only assay the parent drug and fail to determine the main active metabolites responsible for both therapeutic and toxic effects. Carbamazepine provides a good example: the metabolite carbamazepine epoxide is of similar potency to carbamazepine, having both therapeutic and toxic effects. In some cases, only the active metabolite is assayed because the parent drug is rapidly metabolised/eliminated. Oxcarbazepine is an example of this situation: the assay is carried out on the active metabolite because the parent drug is present in only very small concentrations in the blood.

The pathways of drug metabolism can be divided broadly into two major categories: phase I biotransformations, which include oxygenation, oxidation, reduction and hydrolysis (enzyme-mediated reactions in which a new functional group is introduced into the drug molecule or an existing functional group is modified); and phase II reactions (conjugations), which are also enzyme catalysed, and in which a functional group of a drug is masked by adding a new group (e.g. methyl, acetyl, sulphate or glucuronic acid). The enzymes that catalyse phase I reactions are the CYP mixed function oxidase isoenzymes, which are found in a wide variety of tissues and particularly in the liver, which is the most important organ for drug metabolism. Phase II reactions are catalysed by another important family of isoenzymes, the uridine diphosphate glucuronosyltransferase (UGT) system. There has been a tendency in the literature to concentrate on the role of CYP hepatic mixed oxidase isoenzymes in drug metabolism and interactions. The importance of the family of CYP enzymes is unequivocal, but there are many reactions responsible for drug metabolism and the UGT isoenzymes play a significant role.[14,15] For example, glucuronidation is the key metabolic pathway for the metabolism of lamotrigine that is inhibited by valproic acid and induced by a number hepatic enzyme-inducing drugs.[16] A more detailed discussion of the roles of these metabolic systems appears in recent reviews.[9,17,18] Table I provides a summary of the induction and inhibition of the various CYP isoenzymes. However, the fact that a drug inhibits or induces an enzyme responsible for the metabolism of another drug does not necessarily imply that this potential interaction is clinically relevant. Sproule et al.[19] have listed ten factors that need to be considered in this context. The key issues are whether the enzyme is responsible for the rate-limiting step of the metabolism and whether the degree of inhibition/induction is enough to make an important difference. The theoretical interactions that would be predicted from table II need to be substantiated by data collected from human studies. This review focuses on the currently available evidence for interactions.

3. Data on Interactions

3.1 Carbamazepine

Carbamazepine is extensively metabolised to the 10,11-epoxide via CYP3A4 and CYP2C8. The ep-

oxide is subsequently transformed into the 10,11-diol by epoxide hydrolase. A minor oxidative route of metabolism is via CYP1A2, which introduces a hydroxy group into the aromatic rings. In addition to these phase I transformations, conjugation occurs at the amide functional group and the various hydroxy groups.

Carbamazepine induces CYP1A2, CYP2C9 and CYP3A4. It is a substrate for CYP1A2, CYP2C8 and CYP3A4.[20] According to Patsalos et al.,[20] it might either induce or inhibit CYP2C19. As stated in section 2, the metabolite, carbamazepine epoxide, is pharmacologically active as it has both therapeutic and toxic effects. Carbamazepine may also induce UGT.[21] Protein binding of carbamazepine is 70–80%, and for the epoxide it is 50–60%.

3.1.1 Risperidone

Risperidone is primarily metabolised by CYP2D6, and probably to a lesser extent by CYP3A4, to an active metabolite, 9-hydroxyrisperidone.[22-24] Spina et al.[25] have commented that 7-hydroxylation and oxidative N-dealkylation also occur, but are quantitatively less important routes of biotransformation. Protein binding of risperidone is approximately 90% and of the 9-hydroxy metabolite is 77%.

In a single case report, de Leon and Bork[26] reported that the concentration of the metabolite of risperidone, 9-hydroxyrisperidone, was less than one-half the expected concentration of 10 μg/L in a 22-year-old non-smoking male with schizophrenia, who was taking risperidone 4 mg/day and was also taking carbamazepine (plasma concentration 7.9 μg/L). The concentration of the 9-hydroxyrisperidone was not stated. The risperidone dosage was doubled to 8 mg/day and the concentration of 9-hydroxyrisperidone increased to 19 μg/L. The carbamazepine was then tailed off and stopped. Ten days later the 9-hydroxyrisperidone concentration had more than doubled to 49 μg/L. They suggested that risperidone metabolism involves CYP3A4, which is induced by carbamazepine. In discussing this case report, Lane and Chang[27] questioned the role of CYP3A.

Spina et al.[28] compared three groups of matched patients taking risperidone alone (n = 23), risperidone with carbamazepine (n = 11) and risperidone with valproic acid (n = 10). Compared with monotherapy, concentrations of both risperidone and the active metabolite 9-hydroxyrisperidone were lower in the carbamazepine co-medicated group but not in the valproic acid co-medicated group. The median sum of the concentration of risperidone plus the metabolite was 44 nmol/L in the carbamazepine group compared with 168 nmol/L in the valproic acid group and 150 nmol/L in the monotherapy group. They also compared risperidone and 9-hydroxyrisperidone concentrations in five patients with and without carbamazepine co-medication. Both risperidone and the metabolite were significantly lower when the patients were also taking carbamazepine. They concluded that the interaction was probably the result of induction of CYP3A4 and that it was clinically significant. Takahashi et al.[29] reported two patients who developed parkinsonian symptoms after discontinuing carbamazepine while taking risperidone. They attributed the effect to the cessation of the induction of CYP3A4 by carbamazepine when this drug was stopped. The symptoms resolved when the risperidone dose was decreased. Takahashi et al.,[29] Spina et al.[30] and Ono et al.[31] have suggested that CYP2D6 might also play a role in the interaction between carbamazepine and risperidone. Ono et al.[31] measured blood concentrations of risperidone and 9-hydroxyrisperidone in 11 patients taking risperidone 6 mg/day, before, during and after co-medication with carbamazepine 400 mg/day for 1 week. They also determined CYP2D6 genotypes using the polymerase chain reaction. The concentrations of both risperidone and the metabolite were significantly lower ($p > 0.01$) when the carbamazepine was added. The changes in risperidone concentrations correlated with the concentration ratios of risperidone/9-hydroxyrisperidone ($p < 0.01$), which were closely associated with CYP2D6 genotypes. They concluded that the decrease in risperidone concentration might be dependent on the CYP2D6 activity. This activity is largely genetically determined, as illustrated by their work. CYP2D6 is generally regarded as being non-inducible.[9]

Yatham et al.,[32] in a study of mood stabilisers plus risperidone in the treatment of mania, found that the median dose-normalised plasma concentrations of the active risperidone moiety (the sum of risperidone and 9-hydroxyrisperidone) were approximately 40% lower at the end of the 3-week double-blind phase in the carbamazepine-treated group of 14 patients.

There is little information on the effect of risperidone on carbamazepine plasma concentrations. Mula and Monaco[33] examined the influence of risperidone on carbamazepine concentrations in eight patients who had received carbamazepine monotherapy for at least 1 year. The mean steady state carbamazepine concentration increased from 6.67 mg/L to 7.37 mg/L ($p < 0.01$) at 24 hours and 7.95 mg/L ($p < 0.0001$) at 2 weeks after the addition of risperidone 1mg. They stated that the rise in carbamazepine concentration might be the result of inhibition of CYP3A4 or CYP2D6 by risperidone, which suggests that CYP2D6 might be involved in the metabolism of carbamazepine.

There is good evidence that carbamazepine decreases the blood concentrations of both risperidone and its hydroxy metabolite, probably through induction of CYP3A4 and possibly through CYP2D6, although the role of the latter isoenzyme has been questioned since it is debated whether CYP2D6 can be induced. A single small study of eight patients suggested that risperidone raised the concentration of carbamazepine; however, this needs to be confirmed.

3.1.2 Olanzapine

The two major pathways of olanzapine biotransformation are N-demethylation by CYP1A2 to form N-demethylolanzapine, and glucuronidation by UGT. Metabolism by CYP2D6 to form 2-hydroxymethylolanzapine is also reported as a minor pathway.[34] The glucuronidation of olanzapine was studied *in vitro* by Linnet[35] using cDNA-expressed human uridine diphosphate (UDP)-UGT enzymes and a pooled human liver microsomal preparation. They screened the following UGT-isoenzymes: 1A1, 1A3, 1A4, 1A6, 1A9, 2B7 and 2B15. Only UGT1A4 was able to glucuronidate olanzapine. The olanzapine glucuronidation reaction was inhibited by several drugs that are known substrates for UGT1A4. They concluded that competition for glucuronidation by UGT1A4 represents a possible mechanism for interaction but added that this still requires confirmation in clinical practice and its importance remained to be determined. Olanzapine is approximately 93% bound to plasma proteins.

Lucas et al.[36] assessed the effect of carbamazepine on olanzapine concentrations in 11 volunteers, who were given two single doses of olanzapine 10mg. The first was with no co-medication and the second was after they had been treated with carbamazepine 200mg twice daily for 2 weeks. Urinary 6β-hydroxycortisol/cortisol excretion was used to confirm induction of CYP3A4 by carbamazepine. The maximum concentration (C_{max}), area under the concentration-time curve (AUC) and half-life of olanzapine were all significantly lower with the carbamazepine pretreatment, and the clearance and volume of distribution were significantly increased. Although they acknowledged that carbamazepine decreased the olanzapine concentrations, they suggested that this was not of clinical significance because of the wide therapeutic index for this drug. This is a surprising statement in view of the degree to which olanzapine concentrations decrease with carbamazepine, as demonstrated by the following reports.

Skogh et al.[37] compared olanzapine blood concentrations in ten patients taking carbamazepine, some of whom were receiving polytherapy, with those taking olanzapine monotherapy ($n = 44$). The median olanzapine concentration in those taking carbamazepine was 59% lower ($p < 0.001$) than the olanzapine monotherapy group, although the dosages of olanzapine were twice as high in the carbamazepine-treated group (median 20 mg/day, range 10–25 mg/day) compared with the monotherapy group (median 10 mg/day, range 2.5–40 mg/day). The patients receiving carbamazepine had a 50% lower median olanzapine : N-demethylolanzapine ratio than the olanzapine monotherapy group ($p < 0.001$). When corrected for dose, the median concentration/dose ratio for olanzapine in

the carbamazepine co-medication group was 71% lower than in the monotherapy group ($p < 0.001$). The carbamazepine co-medication group also had lower olanzapine concentrations than the whole group of patients taking olanzapine (n = 194). These results suggest that carbamazepine greatly decreases olanzapine concentrations by inducing CYP1A2 and also possibly by inducing UGT.

3.1.3 Quetiapine

Quetiapine is extensively metabolised in the liver by sulfoxidation, carboxylic acid formation on the ethoxyethanol side chain and 7-hydroxylation. At least 20 metabolites have been detected, but only 7-hydroxyquetiapine has significant pharmacological activity.

DeVane and Nemeroff[38] have examined the clinical pharmacokinetics of quetiapine. It is predominantly metabolised by CYP3A4. This implies that carbamazepine, phenobarbital, phenytoin and to a lesser extent felbamate and oxcarbazepine, which induce CYP3A4, should consequently increase the rate of metabolism of quetiapine. Quetiapine does not induce CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 at clinically relevant concentrations. It is approximately 83% bound to plasma proteins. Although two active metabolites have been identified, they are probably not of clinical importance.

Fitzgerald and Okos[39] described a marked elevation of the active metabolite carbamazepine epoxide and the carbamazepine epoxide/carbamazepine ratio in two patients who were taking carbamazepine when quetiapine was added; the ratio rose 3- to 4-fold. Carbamazepine epoxide can cause toxicity. The carbamazepine epoxide concentrations returned to baseline when the quetiapine was stopped. One of the patients had ataxia and agitation while receiving the quetiapine, which resolved when the carbamazepine was replaced by oxcarbazepine. Unlike carbamazepine, oxcarbazepine is not metabolised to carbamazepine epoxide. It was suggested that quetiapine might inhibit epoxide hydrolase and/or glucuronidation of carbamazepine-10,11-trans-diol, although the latter reaction is unlikely to be of clinical relevance since this metabolite does not appear to be active. The authors recommended the monitoring of carbamazepine epoxide concentrations when quetiapine is added to carbamazepine.

3.1.4 Clozapine

Clozapine undergoes moderate first-pass metabolism. It is metabolised by N-demethylation, N-oxidation, oxidation of the chlorine-containing aromatic ring and thiomethyl conjugation. Only the desmethyl metabolite shows pharmacological activity, but this is far less than the parent drug. Protein binding is about 95%.

Taylor[40] has reviewed interactions with clozapine and has commented that the metabolism of this drug appears largely to be controlled by CYPIA2 but that drugs which inhibit CYP2D6 have also been reported to elevate clozapine plasma concentrations. Fang et al.[41] discussed the individual CYP enzymes involved in the metabolism of clozapine. They concluded that CYP1A2, CYP3A4, CYP2D6, CYP2C8 and CYP2C9 and to a lesser extent CYP2C9-cys, CYP2C9-arg and CYP3A5, were apparently involved in N-demethylation. CYP1A2, CYP 3A4 and to a lesser extent CYP2D6, CYP2C19 and CYP3A5 catalysed the formation of clozapine N-oxide.

Raitasuo et al.[42] reported two patients whose clozapine concentrations rose after stopping carbamazepine. The increases within 2 weeks of stopping the carbamazepine were from 1.4 to 2.4 μmol/L and from 1.5 to 3.0 μmol/L, respectively. These concentrations are above the upper limit of the reference range for clozapine (1.1 μmol/L). The same research group subsequently published data on six patients with difficult-to-treat psychosis who were switched from carbamazepine to oxcarbazepine.[43] The plasma concentrations of the antipsychotics, which were haloperidol, chlorpromazine or clozapine, increased by 50% to 200%. Two of these patients were receiving clozapine, but it would appear from the data that these were probably the same two male patients already reported.[42]

Jerling et al.[44] calculated the concentration/dose ratios of four matched groups of patients receiving clozapine: patients treated with benzodiazepines; patients taking drugs that inhibit CYP2D6; patients

taking carbamazepine; and patients not taking any of these drugs. The mean concentration/dose ratio in the group taking carbamazepine was 50% lower than that of the monotherapy group ($p < 0.001$) and appeared to be inversely related to the daily dose of carbamazepine. They also examined concentration changes in eight individual patients and confirmed that there was a substantial decrease of the clozapine concentration with carbamazepine.

Tiihonen et al.[45] compared the effect of carbamazepine and oxcarbazepine on clozapine concentrations in 12 patients. They found that the clozapine concentration was 47% lower with carbamazepine than with oxcarbazepine ($p < 0.005$).

It has been pointed out that the combination of carbamazepine and clozapine should probably be avoided, because both drugs can cause haematological problems.[46,47] In addition, it appears that carbamazepine may decrease clozapine concentrations markedly.

3.1.5 Amisulpride

Amisulpride is primarily excreted in the urine. It is said to undergo relatively little metabolism,[48] which includes N-dealkylation and N-oxidation.[25] Protein binding is 16%. It is unlikely to be affected in a clinically significant way by drug interactions. Gillet et al.[49] examined the *in vitro* effect of amisulpride on CYP isoenzymes in microsomes from six pooled human liver biopsies. The only isoenzyme that was inhibited more than 10% was CYP2D6, which was inhibited by 26% with the highest dose of amisulpride. It was concluded that amisulpride has a low potential for interactions through the CYP isoenzymes. No additional relevant references were found.

3.1.6 Sulpiride

Sulpiride is mainly cleared unchanged in urine, which implies that hepatic metabolism should not be relevant.[50] It is not strongly protein bound; the protein binding is <40%.

No relevant references regarding interactions with AEDs were found.

3.1.7 Ziprasidone

Spina et al.[25] have commented that ziprasidone has complex metabolism and that the major pathways include oxidation to ziprasidone sulfoxide and ziprasidone sulfone and N-dealkylation.[51] CYP3A4 is the primary isoenzyme involved in the metabolism of ziprasidone.[52] This implies that drugs that are inducers or inhibitors of CYP3A4 might be expected to affect ziprasidone blood concentrations. Ziprasidone does not appear to induce CYP2D6.[53]

Miceli et al.[54] reported a 27% mean decrease in the ziprasidone C_{max} and a 36% decrease in the AUC in healthy volunteers when carbamazepine was added. This was probably the result of CYP3A4 induction by carbamazepine. No other relevant references were found.

3.1.8 Aripiprazole

Aripiprazole is extensively metabolised. The main pharmacologically active metabolite is dehydro-aripiprazole; both this metabolite and the parent drug are extensively bound to plasma protein (99%).

Winans[55] has pointed out that aripiprazole is a substrate for CYP3A4 and CYP2D6, implying a potential for drug interactions. Since carbamazepine induces CYP3A4 it might decrease the concentration of aripiprazole, but no clinically relevant references were found.

3.1.9 Haloperidol

Haloperidol is metabolised by oxidative N-dealkylation and also by reduction of the ketone group to a secondary alcohol (reduced haloperidol). Metabolites that have been identified in urine are 4-fluorobenzoylpropionic acid together with its glycine conjugate. Protein binding is 92%.

Kudo and Ishizaki[56] have reviewed the pharmacokinetics of haloperidol. The enzymes involved in the biotransformation of haloperidol include members of the CYP family, carbonyl reductase and UGT. CYP3A4 appears to be the predominant isoenzyme responsible for the metabolism of haloperidol. CYP2D6 is also important in the metabolism of haloperidol but there is a great variation between genetically determined very slow and

very rapid metabolisers with regard to this isoenzyme.[57] Haloperidol is an inhibitor of CYP2D6. The metabolite, reduced haloperidol, is also metabolised by CYP3A4 and inhibits CYP2D6.

There are many reports of decreased haloperidol concentrations with carbamazepine, the first of which were published approximately 20 years ago.[58-60] In one of the earlier reports, Jann et al.[59] found that the haloperidol concentrations in three patients with schizophrenia were decreased by 59–61% with concomitant carbamazepine. The effects occurred in 2 or 3 weeks. Arana et al.[60] found that haloperidol concentrations decreased by a mean of 60% when carbamazepine was added to the treatment of seven patients with psychosis. In two of the patients the haloperidol concentrations were undetectable and their symptoms became worse. Martin Munoz et al.[61] examined ten patients treated with haloperidol and carbamazepine and ten who were treated with haloperidol alone, at the same dose. They all had a diagnosis of paranoid schizophrenia and a similar clinical improvement was noted between the groups, but the patients treated with carbamazepine had less neurological adverse effects. These authors did not report the haloperidol blood concentrations, but it seems likely that the reduction in neurological adverse effects was a result of a decrease in the haloperidol concentrations. Kahn et al.[62] compared haloperidol serum concentrations in patients initially receiving haloperidol alone and subsequently in combination with carbamazepine. Both the haloperidol concentrations and the concentration/dose ratio dropped about 50% in those taking carbamazepine. One patient had worsening symptoms associated with the fall in serum haloperidol concentrations. Iwahashi et al.[63] confirmed that haloperidol serum concentrations were decreased by carbamazepine but also found that the carbamazepine serum concentrations were significantly less (approximately 40%) in patients who were not treated with haloperidol. Hesslinger et al.[64] treated 27 patients with schizophrenia or schizoaffective disorder with haloperidol monotherapy, haloperidol and carbamazepine, or haloperidol and valproic acid; there were nine patients in each group. They found that the haloperidol plasma concentrations were much lower in the nine patients who were treated with carbamazepine co-medication than in the other groups. After 28 days of carbamazepine treatment the mean (± SD) haloperidol concentration was 4.6 ± 0.8 ng/mL, which was much lower than in the haloperidol monotherapy group 7.3 ± 0.3 ng/mL ($p = 0.004$) and in the valproic acid group 11.9 ± 1.9 ng/mL. The psychiatric outcome was also worse in the carbamazepine co-medication group.

Hirokane et al.[65] looked at the serum concentration data from 231 inpatients with schizophrenia and examined differences in the haloperidol plasma concentrations. The group that received carbamazepine co-medication had a haloperidol concentration : dose ratio 37% lower than those who were not treated with carbamazepine. Yukawa et al.[66] reviewed 270 serum concentration measurements from 191 patients and confirmed that concomitant antiepileptic medication with phenobarbital, phenytoin or carbamazepine increased the haloperidol clearance by 32%; data on the effects of the individual AEDs were not provided. Fukuda[67] examined haloperidol serum concentrations from 102 inpatients, including a small subgroup of five patients who had intermittent co-medication with carbamazepine and/or barbiturates. They also confirmed a significant decrease in the haloperidol concentration with these AEDs. Yasui-Furukori et al.[68] performed a study in 11 inpatients with schizophrenia and found that the decrease in haloperidol serum concentrations depended on the dose of carbamazepine. The mean haloperidol concentrations with 100mg, 300mg and 600mg of carbamazepine daily were 75%, 39% and 15% of the pre-carbamazepine concentrations, respectively. The mean carbamazepine dosage that produced a 50% decrease of haloperidol concentration was 250 mg/day and the carbamazepine serum concentration was 3.5 mg/L. This study showed a clear effect of carbamazepine dosage on the extent of the haloperidol concentration decrease.

Most of the papers dealing with the interaction between carbamazepine and haloperidol have ex-

amined the pharmacokinetic interaction. One or two papers have suggested that there may also be a pharmacodynamic interaction. Brayley and Yellowlees[69] described a 37-year-old woman with cerebral palsy and bipolar affective disorder who developed drowsiness and slurred speech on two occasions with the combination of haloperidol and carbamazepine but not with carbamazepine alone. Iwahashi[70] examined 21 patients treated with haloperidol and carbamazepine. Eleven showed a corrected QT (QTc) interval of >440 msec with a mean change of 29%. Two patients developed congestive cardiac failure. The authors suggested that carbamazepine co-medication with a higher haloperidol concentration and QTc interval prolongation may herald heart failure. However, these open-label case reports with small numbers of patients must be interpreted with caution.

Although there are many publications confirming that carbamazepine reduces haloperidol concentrations, there seems to be a lack of carefully conducted prospective studies using large numbers of patients. The available evidence for a rise in carbamazepine serum concentrations with haloperidol is sparse. The evidence for a pharmacodynamic interaction between carbamazepine and haloperidol remains inadequate.

3.1.10 Chlorpromazine

Chlorpromazine is extensively metabolised, primarily by CYP2D6. The metabolic routes include sulfoxidation, N-demethylation, hydroxylation, N-oxidation and glucuronic acid conjugation. A large number of metabolites have been identified and some are pharmacologically active, particularly 7-hydroxychlorpromazine. Protein binding of chlorpromazine is about 95%. Chlorpromazine is a potent inhibitor of CYP2D6.[71]

Raitasuo et al.[43] reported changes in antipsychotic plasma concentrations in seven patients with psychosis, four of whom were taking chlorpromazine, when carbamazepine was changed to oxcarbazepine. The chlorpromazine plasma concentrations increased in the four patients as follows: from 270 nmol/L to 345 nmol/L, from 59 nmol/L to 87 nmol/L, from 74 nmol/L to 130 nmol/L, and from 172 nmol/L to 317 nmol/L, respectively, when the patients were switched from carbamazepine to oxcarbazepine. Although these results are, strictly speaking, indirect evidence, they imply that carbamazepine has a major effect on chlorpromazine plasma concentrations.

3.2 Valproic Acid (Sodium Valproate)

Valproic acid is extensively metabolised, mainly by oxidation, to a number of metabolites including 3-oxovalproic acid, 2-propylglutaric acid, 3-hydroxyvalproic acid, 4-hydroxyvalproic acid, 5-hydroxyvalproic acid and valpro-1,4-lactone.[72] Approximately 20% of a dose is excreted in urine as the glucuronide of valproic acid and most of the remainder as glucuronides of metabolites. Protein binding is about 90%, but is concentration dependent. Valproic acid is said to be both a substrate and an inhibitor of CYP2C9.

No relevant references were found for interactions between valproic acid and the following antipsychotics: quetiapine, amisulpride, sulpiride and ziprasidone.

3.2.1 Risperidone

Spina et al.[28] found no changes in the concentrations of risperidone or its hydroxy metabolite in three patients with and without valproic acid, in contrast to the effect of carbamazepine on risperidone concentrations in the same study.

A single case report of a 10-year-old boy by van Wattum[73] suggested that risperidone might increase the valproic acid concentration. In contrast, Vitiello[74] observed that risperidone possibly decreased valproic acid serum concentrations by 30%. Bertoldo,[75] in a single case report of a 15-year-old girl, found that the valproic acid concentration fell from 80 μg/mL to 57 μg/mL when risperidone was added.

Valproic acid concentrations tend to fluctuate widely and depend greatly on the timing of the blood sample, which implies that it would be unwise to draw firm conclusions from small numbers of patients. Sund et al.[76] found no change in the valproic acid concentration/dose ratios with risperidone nor did they find any change in the valproic acid concen-

trations with and without risperidone in two patients.

3.2.2 Olanzapine

Both valproic acid and olanzapine are metabolised partly by glucuronidation. This suggests that competition for glucuronidation might lead to an increase in blood concentration of one or both drugs when they are prescribed together. No published data on this possible interaction were available and no relevant references were found on pharmacokinetic or pharmacodynamic interactions between olanzapine and valproic acid with regard to the CNS effects of these two drugs. However, Gonzalez-Heydrich et al.,[77] in a study of 52 children aged 3–18 years, pointed out that the combination of valproate semisodium (divalproex) and olanzapine (n = 12) led to higher hepatic enzyme levels than either valproate semisodium (n = 23) or olanzapine (n = 17) alone. Two patients receiving the combined treatment had to discontinue therapy because of medical complications, namely pancreatitis and steatohepatitis. No firm conclusions can be drawn from such small numbers, but careful monitoring of patients taking this combination of drugs appears to be warranted.

Freeman and Stoll[78] have drawn attention to the possibility of additive adverse effects of weight gain and drowsiness with the combination of valproic acid and olanzapine or clozapine.

3.2.3 Clozapine

Centorrino et al.[79] examined serum concentrations of clozapine, norclozapine and clozapine-N-oxide in patients with psychosis treated with clozapine alone (n = 17) or clozapine with valproic acid (n = 11). The concentrations were corrected for the daily dose of clozapine (mg/kg of bodyweight). The (mean ± SD) corrected clozapine concentrations for the two groups were 80 ± 46.3 ng/mL per mg/kg and 111 ± 43 ng/mL per mg/kg, respectively. The results for norclozapine were 70.9 ± 35.6 ng/mL per mg/kg and 49.1 ± 17.6 ng/mL per mg/kg, and those for clozapine-N-oxide were 18 ± 9.8 ng/mL per mg/kg and 19.6 ± 7.5 ng/mL per mg/kg, respectively. The same researchers also published results on a larger group of patients and concluded that in the subgroup taking valproic acid there was a 6% increase in clozapine plus its metabolites; details of this subgroup were not reported.[13]

In contrast, Finley and Warner[80] found that clozapine concentrations decreased by 41% when valproic acid was commenced in four male patients. Serial assays were performed before and during treatment with valproic acid. They suggested that displacement from protein binding might have been responsible, which led to increased metabolism of the unbound fraction and a decrease in the total (protein bound + unbound) concentration. They considered that induction of clozapine metabolism by valproic acid was unlikely because the latter more often causes inhibition of metabolism. They pointed out that, although the total clozapine concentration decreased, this did not necessarily mean that the unbound active clozapine concentration altered and that adjustment to the previous total concentration might even lead to toxicity. Longo and Salzman[81] found that valproic acid decreased clozapine concentrations by a mean of 15% in seven patients with schizophrenia who had been taking high-dose clozapine for >6 months when valproic acid was added for seizure prophylaxis. The (mean ± SD) concentrations before and after the addition of valproic acid were 353 ± 179 ng/mL and 298 ± 79 ng/mL, respectively ($p = 0.05$). The norclozapine concentrations were even more markedly decreased by 65% in the four patients in whom these were measured; the norclozapine concentrations before and after the addition of valproic acid were 394 ± 221 ng/mL and 138 ± 43 ng/mL ($p = 0.04$).

Costello and Suppes[82] published a case report of a 37-year-old man who became sedated, confused and disorientated when clozapine was added to valproic acid and lithium. These symptoms resolved when the valproic acid was stopped but reappeared 4 days after this drug was reintroduced. There were insufficient data in this case report to determine whether this was a pharmacokinetic or a pharmacodynamic interaction.

Facciola et al.[83] carried out two separate studies to assess the effect of valproic acid on plasma concentrations of clozapine and its major metabolites

norclozapine and clozapine N-oxide in patients with psychosis. The first study was a between-group comparison of concentrations of clozapine and metabolites. One group took clozapine and valproic acid (n = 15) and the other took clozapine alone (n = 22). The patients were matched for sex, age, bodyweight and antipsychotic dose. The patients taking valproic acid tended to have higher clozapine concentrations and lower norclozapine concentrations, but the differences did not reach statistical significance. In the second study the plasma concentrations of clozapine and its metabolites were compared in six patients with schizophrenia before and after treatment with valproic acid for 4 weeks. The mean plasma concentrations of clozapine and its metabolites did not change significantly throughout this study but there was a trend for clozapine concentrations to be higher and for norclozapine concentrations to be lower after valproic acid. They concluded that valproic acid may inhibit the conversion of clozapine to norclozapine via CYP1A2 or CYP3A4 but that the interaction is unlikely to be clinically significant. It should be noted that there do not appear to be other reports indicating that valproic acid inhibits CYP1A2 or CYP3A4.

Conca et al.[84] presented a single case report of a 33-year-old female patient who was a heavy smoker and had a schizoaffective disorder. When she had a seizure, valproic acid was commenced and the serum concentrations of clozapine decreased. They suggested that this was evidence of induction of the clozapine metabolism by valproic acid. However, this single case may be confounded by other factors. For example, smoking can alter clozapine concentrations by 40%, according to Centorrino et al.[13]

Spina and Perucca[9] have drawn attention to the inconsistency in the literature of the effect of valproic acid on clozapine, with some reports suggesting an increase and others a decrease in clozapine concentrations when valproic acid is added.

With regard to possible pharmacodynamic interactions between valproic acid and clozapine, Kando et al.[85] carried out a chart review of 55 patients taking this combination; they concluded that it was effective and found that the main reason for withdrawal from the combination was sedation. As already stated, Freeman and Stoll[78] have drawn attention to the possibility of additive adverse effects of weight gain and drowsiness with the combination of valproic acid and olanzapine or clozapine.

3.2.4 Aripiprazole

In an open-label study of ten chronically institutionalised patients with schizophrenia or schizoaffective disorder, Citrome et al.[86] added valproate semisodium to aripiprazole. The AUC of the aripiprazole was decreased by 24% and the C_{max} by 26%. There were minimal effects on the active metabolite of aripiprazole. They concluded that valproate semisodium had no clinically significant effects on the pharmacokinetics of aripiprazole. No other relevant references were found.

3.2.5 Haloperidol

Hesslinger et al.[64] (see section 3.1.9) compared haloperidol plasma concentrations in nine patients treated with this drug alone and nine patients with valproic acid co-medication. After 28 days the (mean ± SD) haloperidol concentration in the valproic acid group was 11.9 ± 1.9 ng/mL, which was not statistically different from that in the haloperidol monotherapy group (7.3 ± 0.3 ng/mL). They concluded that valproic acid had no significant effect on the haloperidol concentrations or on the psychiatric outcome.

Ishizaki et al.[87] examined valproic acid trough concentrations in six patients with and without haloperidol and found no significant effect of the haloperidol.

3.2.6 Chlorpromazine

Chlorpromazine is said to inhibit the metabolism of valproic acid[18] but clinical data to support this statement could not be readily located, apart from the paper by Ishizaki et al.[87] who examined valproic acid trough concentrations in six patients with and without chlorpromazine. The mean values were 33.2 mg/L and 27.1 mg/L, respectively, with each based on 25 samples. The difference was significant ($p < 0.01$).

3.3 Vigabatrin

Vigabatrin is notable for a lack of interactions with other drugs.[88] It is not metabolised, being excreted entirely unchanged in urine. Against this background it is perhaps not surprising that no relevant references for interactions with any of the antipsychotic drugs were found.

3.4 Lamotrigine

Lamotrigine is about 55% protein bound[89] and is metabolised in the liver, mainly to an N-2 glucuronide (80%) and an N-5 glucuronide (10%). Formation of these glucuronides requires UDP-UGT and a number of isoforms exist that are identified by a similar nomenclature to that used for the CYP450 isoenzymes. The isoenzyme responsible for lamotrigine glucuronidation is UGT1A4. Other drugs that are metabolised by glucuronidation may be involved in interactions, notably valproic acid, which increases lamotrigine plasma concentrations markedly.[90]

No relevant references were found for interactions between lamotrigine and the following antipsychotics: risperidone, quetiapine, amisulpride, sulpiride, ziprasidone, aripiprazole and haloperidol.

3.4.1 Olanzapine

Both lamotrigine and olanzapine are metabolised to some extent by glucuronidation. As stated earlier, Linnet[35] studied the glucuronidation reaction of olanzapine *in vitro* using cDNA-expressed human UDP-UGT enzymes and a pooled human liver microsomal preparation, and found that only UGT1A4 was able to glucuronidate olanzapine. The olanzapine glucuronidation reaction was inhibited by several drugs that are known substrates for UGT1A4, including lamotrigine. This suggests that lamotrigine might raise olanzapine blood concentrations. However, no clinical references on the interaction between lamotrigine and olanzapine were found.

3.4.2 Clozapine

Kossen et al.[91] reported that a 35-year-old male patient had an increase in clozapine plasma concentration from 350 μg/L to 1020 μg/L when lamotrigine 100 mg/day was added to 400mg of clozapine. He reported feelings of dizziness and sedation. The lamotrigine was tailed off over 2 weeks, when the clozapine concentration returned to 450 μg/L. The authors could not explain this apparent interaction, pointing out that neither inhibition of CYP isoenzymes nor protein binding issues should be relevant.

3.4.3 Chlorpromazine

Magdalou et al.[92] found that chlorpromazine inhibited the glucuronidation of lamotrigine in human liver microsomes *in vitro*. This would suggest that chlorpromazine might raise lamotrigine plasma concentrations in patients, but no clinical data on this could be found.

3.5 Gabapentin

Gabapentin is not protein bound, does not induce hepatic enzymes and is not metabolised but is renally excreted.[93] This implies that many of the common drug interactions would not be expected to occur with gabapentin. The search revealed no evidence of interactions with any of the antipsychotic drugs.

3.6 Topiramate

Topiramate is largely excreted unchanged, but significant metabolism occurs in patients taking enzyme-inducing drugs. The main pathways include hydroxylation, hydrolysis and glucuronidation, with six metabolites identified.

Topiramate is minimally protein bound (13–17%) and is said to not inhibit CYP1A2, CYP2A6, CYP2C9, CYP2D6, CYP2E1 or CYP3A4, but it is an inhibitor of CYP2C19.[94,95] It is a weak inducer of CYP3A4.[96] Enzyme-inducing drugs such as carbamazepine decrease topiramate blood concentrations, which suggests that it may be a substrate for CYP3A4.

There is considerable interest in combining topiramate with antipsychotic medication both for therapeutic effects[97] and to reduce the weight gain that is such a common adverse effect of antipsychotic drugs.[98,99] In the light of this, it is surprising that

very little data were found on the interaction between topiramate and the antipsychotic drugs. Doose et al.[100] and Bialer et al.[101] reported that there were no clinically important effects of topiramate on haloperidol concentrations. The mean AUC was increased by 15% and the greatest increase was 28%.[100] These increases were considered unlikely to be of clinical significance.

3.7 Tiagabine

Tiagabine is rapidly and extensively metabolised via CYP3A4. Two metabolic pathways have been identified: thiophene ring oxidation leading to 5-oxo-tiagabine and glucuronidation. Protein binding is 96%.[102]

There is one report suggesting that tiagabine might be used in the treatment of dyskinesias in humans, based on haloperidol-treated rats that showed a reduction in dyskinesias when treated with tiagabine.[103] However, the search revealed no evidence for this effect in humans and no data on interactions with antipsychotic drugs.

3.8 Oxcarbazepine

Oxcarbazepine is rapidly metabolised in the liver to 10-hydroxycarbamazepine, which possesses antiepileptic activity. 10-Hydroxycarbamazepine is further metabolised by hydroxylation and conjugation with glucuronic acid. Protein binding is 40%.[104]

No relevant references were found for interactions between oxcarbazepine and the following antipsychotics: amisulpride, sulpiride, ziprasidone, aripiprazole, haloperidol and chlorpromazine.

3.8.1 Risperidone

Muscatello et al.[105] measured the concentrations of risperidone and its active metabolite, 9-hydroxyrisperidone, in 12 patients with bipolar or schizoaffective disorder before and after oxcarbazepine was added. The (mean ± SD) risperidone concentrations were 5.6 ± 3.6 ng/mL and 4.8 ± 2.6 ng/mL, respectively and the 9-hydroxyrisperidone concentrations were 23.6 ± 7.5 ng/mL and 24.7 ± 7.45 ng/mL, respectively. The changes were considered to be minimal and not significant.

3.8.2 Olanzapine

Muscatello et al.[105] also measured the concentrations of olanzapine in 13 patients with bipolar or schizoaffective disorder before and after oxcarbazepine was added. The (mean ± SD) olanzapine concentrations were 26.5 ± 5.7 ng/mL and 27.8 ± 5.1 ng/mL, respectively. Again, the changes were considered to be minimal and not significant.

3.8.3 Quetiapine

Fitzgerald and Okos[39] (see section 3.1.3) reported that quetiapine may elevate the concentration of the carbamazepine metabolite carbamazepine epoxide; they found that switching to oxcarbazepine resolved the problem because this drug does not have an epoxide metabolite.

3.8.4 Clozapine

Tiihonen et al.[45] compared the effect of oxcarbazepine and carbamazepine on clozapine concentrations (see section 3.1.4). The large decrease in clozapine concentrations with carbamazepine, which induces CYP1A2 and 2C9, was not seen with oxcarbazepine.

Raitasuo et al.[43] (see section 3.1.4) noted that large increases in chlorpromazine and clozapine blood concentrations may occur when the patient is switched from carbamazepine to oxcarbazepine.

3.9 Levetiracetam

This drug does not inhibit CYP or UGT isoenzymes and does not appear to be a CYP inducer.[106] It probably does not affect the metabolism of other drugs. No clinically relevant references were found.

3.10 Pregabalin

Pregabalin is not subject to hepatic metabolism as it is entirely cleared unchanged by the kidney,[107,108] which implies that pharmacokinetic interactions with other drugs are unlikely to occur. For this reason and because it has only recently received

a product license, it is not surprising that no relevant references were found.

3.11 Felbamate

Felbamate is metabolised by conjugation, hydroxylation (2-hydroxy and p-hydroxy metabolites) and also by removal of a carbamate group. It is a substrate for CYP2E1 and CYP3A4. It induces CYP3A4 and inhibits CYP2C19.[109] Protein binding is about 30%.

Although this drug has a considerable effect on valproic acid concentrations and also on carbamazepine and epoxide concentrations, no relevant references to interactions with antipsychotic drugs were found.

3.12 Zonisamide

Zonisamide is metabolised by acetylation to N-acetylzonisamide and reduction mediated by CYP3A4 to 2-sulphamoylacetyl-phenol; further glucuronidation also occurs.[110] The metabolites are inactive. Zonisamide is 40–60% protein bound. Both CYP3A4 and CYP2D6 are involved in the metabolism of zonisamide.[111] This implies that drugs that affect these isoenzymes might alter zonisamide blood concentrations, but no clinically relevant references on such interactions were found.

3.13 Phenobarbital

This drug is metabolised to 4-hydroxyphenobarbital together with its glucuronide conjugate and N-glucopyranosylphenobarbital. Two dihydrodiol compounds and a hydroxymethyl metabolite are also reported. Protein binding is about 50%.

Phenobarbital induces CYP1A2, CYP2B, CYP2C8, CYP2C9, CYP2C19 and CYP3A4.[112,113] It is a substrate for CYP2C9 and, to a lesser extent, CYP2C19 and CYP2E1.[114] Although this drug is generally avoided now because of sedation in adults and behavioural disturbance in children, it is considered here because for many patients in developing countries it may be the only option. It is very cheap compared with most other AEDs.

No relevant references were found for interactions between phenobarbital and the following antipsychotics: risperidone, olanzapine, quetiapine, amisulpride, sulpiride, ziprasidone and aripiprazole.

3.13.1 Clozapine

Lane et al.[115] published a single case report of a patient who was taking clozapine and phenobarbital and in whom the clozapine plasma concentration increased markedly when the phenobarbital was discontinued. The patient was taking a stable dosage of clozapine 400 mg/day and phenobarbital 60 mg/day. The plasma concentration of clozapine was 346 ng/mL. Two and 4 weeks after the phenobarbital was discontinued, the clozapine concentrations were 608 ng/mL and 602 ng/mL, respectively. The plasma concentrations of two of the clozapine metabolites also rose. Facciola et al.[116] examined the steady state plasma concentrations of clozapine and its two major metabolites, norclozapine and clozapine N-oxide, in seven patients treated with phenobarbital compared with 15 patients treated with clozapine alone. The (mean ± SD) clozapine concentrations were significantly lower in the phenobarbital-treated patients than in the monotherapy patients (232 ± 104 ng/mL vs 356 ±138 ng/mL, $p < 0.05$). The plasma norclozapine concentrations did not differ significantly between these two groups of patients (195 ± 91 ng/mL vs 172 ± 61 ng/mL). The clozapine N-oxide concentrations were significantly higher in the phenobarbital group (115 ± 49 ng/mL vs 53 ± 31 ng/mL, $p < 0.01$). The norclozapine **:** clozapine and clozapine N-oxide **:** clozapine ratios were also significantly higher ($p < 0.001$) in the patients who took phenobarbital. The authors concluded that phenobarbital probably stimulates the metabolism of clozapine by inducing both N-oxidation and demethylation pathways.

3.13.2 Haloperidol

Linnoila et al.[117] reported that phenobarbital and phenytoin decreased plasma concentrations of haloperidol. The data in their paper do not separate the results for phenobarbital and phenytoin but the nine patients taking these AEDs (two taking phenobarbital, three taking phenytoin and four taking a combination of the two) had significantly lower

concentrations on day 42 of treatment with haloperidol (19.4 ± 5.7 ng/mL), than those who were not taking these AEDs (36.6 ± 16.5 ng/mL). Kudo and Ishizaki[56] have reviewed the pharmacokinetics of haloperidol. Basing their comments on previous studies, they noted that phenobarbital was liable to decrease the haloperidol concentration to an extent that could be important clinically. Hirokane et al.[65] found that the mean haloperidol concentration/dose ratio in 61 patients treated with phenobarbital was 21.7% lower than those who were not treated with phenobarbital (59.0 ± 28.7 ng/mL per mg/kg vs 75.4 ± 32.6 ng/mL per mg/kg, $p < 0.001$). Fukuda[67] examined serum haloperidol concentration measurements in a retrospective, case-record study. However, only three patients were taking phenobarbital without additional concomitant medication. The concentration dose ratios for the three patients taking phenobarbital and haloperidol without additional medication, compared with those taking haloperidol alone, were 50.9 ± 10.5 ng/mL per mg/kg and 82.4 ± 28.8 ng/mL per mg/kg, respectively ($p < 0.05$). In a study of population pharmacokinetics, Yukawa et al.[118] examined haloperidol concentrations in 218 Japanese patients. Sixty patients were taking phenobarbital, phenytoin or carbamazepine. These AEDs resulted in a 32% increase in haloperidol clearance but details of the effects of the individual AEDs were not provided.

3.13.3 Chlorpromazine

Loga et al.[119] found that phenobarbital 50mg taken 8 hourly for 3 weeks decreased chlorpromazine blood concentrations in 12 patients. The data presented were not sufficiently detailed to allow a calculation of the extent of the decrease.

Haidukewych and Rodin[120] studied the effect of phenothiazines on AED concentrations. They found that the (mean ± SD) phenobarbital concentration/dose ratio was decreased from 14.27 ± 3.75 μg/mL per mg/kg/day to 10.81 ± 1.63 μg/mL per mg/kg/day in five patients. The phenothiazines were thioridazine, chlorpromazine and mesoridazine. No data were provided on the effects of the individual phenothiazines and it is consequently not possible to determine the specific effect of chlorpromazine from their paper.

3.14 Phenytoin

Phenytoin is extensively metabolised to form p-hydroxyphenyl phenylhydantoin and, to a lesser extent, the dihydrodiol. The isoenzymes responsible for catalysing these oxidative biotransformations are CYP2C9 and CYP2C19. These two hydroxylated derivatives are then further metabolised into o-glucuronide conjugates, which are the major metabolites of phenytoin excreted in the urine. Minor metabolic pathways involving CYP2C9, CYP2C19 and CYP3A4 have also been described.[121] Protein binding of phenytoin is approximately 90%.

Phenytoin is a potent inducer of CYP3A4 and CYP2C9. Because of this, clinically important interactions with antipsychotic drugs might be expected to occur. Furthermore, phenytoin is strongly protein bound, implying that it might displace other drugs and increase the concentration of the free, active form. Some references on possible interactions between antipsychotic drugs and phenytoin were published decades ago,[122,123] but provide little data. For example, Kutt and McDowell[122] stated that in rare instances in their laboratory a number of drugs, including chlorpromazine, were noted to impair phenytoin metabolism, but they gave no details or references.

There is surprisingly little clinical information on interactions between phenytoin and antipsychotic drugs in the published literature. No relevant references were found for interactions between phenytoin and the following antipsychotics: olanzapine, amisulpiride, sulpiride, ziprasidone and aripiprazole.

3.14.1 Risperidone

Sanderson[124] reported that a 31-year-old man with schizophrenia, who was treated with risperidone 6 mg/day, developed acute extrapyramidal symptoms when 200mg of phenytoin was accidentally administered. She suggested that the risperidone concentration might have been increased by competitive inhibition. Risperidone is approximately 90% protein bound and an alternative explanation

would be that phenytoin, which is also a strongly protein-bound drug, might have displaced risperidone from protein binding sites and resulted in a higher proportion of the free, pharmacologically active drug. It is also possible that this might have been a pharmacodynamic interaction. However, this single case report must be interpreted with caution. No additional relevant references were found.

3.14.2 Quetiapine

DeVane and Nemeroff[38] commented that phenytoin increases the clearance of quetiapine. Wong et al.[125] studied the effect of adding phenytoin 100mg three times daily to quetiapine 250mg three times daily in ten male patients. The geometric mean AUC, C_{max} and C_{min} were decreased by 19%, 27% and 12%, respectively. The addition of phenytoin resulted in a 5-fold increase in the clearance of quetiapine.

3.14.3 Clozapine

It is interesting to note that Lieberman et al.[126] originally recommended that the clozapine dose should be halved and that phenytoin should be commenced in patients who have clozapine-induced seizures. Because phenytoin is a powerful inducer of CYP3A4 and CYP2C9, a decrease in the clozapine concentration might be expected with this AED. Miller[127] reported a decrease in clozapine concentrations in two patients treated with phenytoin. A man and a woman with schizophrenia both had a seizure after clozapine was commenced and were treated with phenytoin. In the first patient, the clozapine concentrations after 1 and 2 weeks of treatment with 400 mg/day, before phenytoin was added, were 282.2 ng/mL and 295.9 ng/mL, respectively; after phenytoin 300 mg/day was added, clozapine concentrations were 56.2 ng/mL and 48.7 ng/mL, respectively. In the second patient, the clozapine concentration at a dosage of 250 mg/day was 940.4 ng/mL before phenytoin was added; after phenytoin 300 mg/day was added it was 334.7 ng/mL. In both patients there was a worsening of the psychosis and the clozapine dose had to be increased. In the light of these results, it might be better to choose an AED that is not a potent enzyme inducer when treating clozapine-related seizures. More recently, gabapentin has been suggested as a suitable drug.[128]

3.14.4 Haloperidol

Reference has already been made (see section 3.13.2) to the early paper by Linnoila et al.[117] who pointed out that phenobarbital and phenytoin could lower haloperidol concentrations significantly, but this paper did not present the data on these two AEDs separately.

Reference has also been made to the paper by Yukawa et al.[118] (see section 3.13.2), which states that that AED treatment with phenobarbital, phenytoin or carbamazepine increased the haloperidol clearance by 32% but, again, this paper did not provide data on the individual AEDs.

Kudo and Ishikazi[56] commented that phenytoin decreases haloperidol concentrations. However, surprisingly little detailed information was found in the literature.

3.14.5 Chlorpromazine

Haidukewych and Rodin[120] found that phenothiazines decreased phenytoin concentration/dose ratios from 3.65 ± 1.26 μg/mL per mg/kg/day to 2.36 ± 1.19 μg/mL per mg/kg/day, $p < 0.005$. However, as stated previously, no data were provided on the effects of the individual phenothiazines and it is consequently not possible to determine the specific effect of chlorpromazine from their paper.

Houghton and Richens[123] commented that case reports suggest that chlorpromazine may inhibit phenytoin metabolism to a significant degree, but neither their paper nor the reference they quoted[122] provided details.

4. Interactions of Antiepileptic Drugs with the Antipsychotic Drugs Zuclopenthixol, Periciazine, Fluphenazine, Flupenthixol and Pimozide

Very little information on interactions between these drugs and AEDs was found in either the published literature or in data from pharmaceutical companies. Zuclopenthixol is metabolised by CYP2D4 and flupenthixol is thought to be metabolised by the

same route. The manufacturer of these two antipsychotics, Lundbeck, has stated that pharmacokinetic interactions between zuclopenthixol or flupenthixol and AEDs resulting from inhibition or induction of CYP isoenzymes are unlikely. However, Gex-Fabry et al.[129] noted a 2-fold median decrease in zuclopenthixol concentrations with carbamazepine. The median ratio with/without carbamazepine was 0.47 ($p < 0.05$). The corresponding median ratio for flupenthixol was 0.58 (significance not stated). Other enzyme-inducing AEDs such as phenobarbital and phenytoin might be expected to have a similar effect, but no clinical information was found.

No data were found on interactions between AEDs and periciazine or pimozide. In a single case report, Jann et al.[130] reported a rise in fluphenazine concentration from 0.6 to 1.17 ng/mL in a patient taking fluphenazine decanoate 37.5 mg/week when carbamazepine 800 mg/day was stopped, which suggested that carbamazepine can decrease fluphenazine concentrations.

5. Conclusions

Good patient management requires some knowledge of how to achieve effective concentrations of therapeutic agents without causing toxicity. An understanding of interactions that might influence therapeutic efficacy or result in toxicity is essential in this context. There are several well established interactions between AEDs and antipsychotic drugs that are of considerable clinical importance, although not all clinicians may be aware of them.

There is some evidence for the following effects. Carbamazepine decreases the plasma concentrations of both risperidone and its active metabolite. It also decreases concentrations of olanzapine, clozapine, ziprasidone, haloperidol and probably chlorpromazine. Quetiapine increases the ratio of carbamazepine epoxide to carbamazepine and this may lead to toxicity. The data on valproic acid is conflicting; it may either increase or decrease clozapine concentrations, and it appears to decrease aripiprazole concentrations. Chlorpromazine possibly increases valproic acid concentrations. Lamotrigine possibly increases clozapine concentrations. Phenobarbital decreases clozapine, haloperidol and chlorpromazine concentrations. Phenytoin decreases quetiapine, clozapine, haloperidol and possibly chlorpromazine concentrations.

There are many more interactions that might be expected to occur but for which published clinical data are not yet available. There is clearly a need for more prospective studies on the potential interactions between AEDs and antipsychotic drugs. These should target both the newer drugs for which interaction data are currently not available and also drug combinations for which the data are controversial. The studies should be undertaken on sufficiently large groups of patients to confer adequate statistical power and should follow a systematic design, preferably with collection of sufficient samples to allow determination of the plasma elimination half-life of the antipsychotic drug before and after the introduction of the AED, or determination of the plasma elimination half-life of the AED before and after the introduction of the antipsychotic drug.

Evidence for pharmacodynamic interactions is very limited. It has been suggested that carbamazepine and clozapine should not be combined because both can have adverse haematological effects and that the combination of valproic acid with antipsychotic drugs that also cause weight gain, such as risperidone, olanzapine and clozapine, should be avoided.

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