

## Metabolic Drug Interactions with Newer Antipsychotics: A Comparative Review

Edoardo Spina<sup>1</sup> and Jose de Leon<sup>2</sup>

<sup>1</sup>Section of Pharmacology, Department of Clinical and Experimental Medicine and Pharmacology, University of Messina and IRCCS Neurological Center 'Bonino-Pulejo', Messina, Italy, and <sup>2</sup>University of Kentucky Mental Health Research Center at Eastern State Hospital, Lexington, KY, USA

(Received July 26, 2006; Accepted October 24, 2006)

**Abstract:** Newer antipsychotics introduced in clinical practice in recent years include clozapine, risperidone, olanzapine, quetiapine, sertindole, ziprasidone, aripiprazole and amisulpride. These agents are subject to drug–drug interactions with other psychotropic agents or with medications used in the treatment of concomitant physical illnesses. Most pharmacokinetic interactions with newer antipsychotics occur at the metabolic level and usually involve changes in the activity of the major drug-metabolizing enzymes involved in their biotransformation, i.e. the cytochrome P450 (CYP) monooxygenases and/or uridine diphosphate-glucuronosyltransferases (UGT). Clozapine is metabolized primarily by CYP1A2, with additional contribution by other CYP isoforms. Risperidone is metabolized primarily by CYP2D6 and, to a lesser extent, CYP3A4. Olanzapine undergoes both direct conjugation and CYP1A2-mediated oxidation. Quetiapine is metabolized by CYP3A4, while sertindole and aripiprazole are metabolized by CYP2D6 and CYP3A4. Ziprasidone pathways include aldehyde oxidase-mediated reduction and CYP3A4-mediated oxidation. Amisulpride is primarily excreted in the urine and undergoes relatively little metabolism. While novel antipsychotics are unlikely to interfere with the elimination of other drugs, co-administration of inhibitors or inducers of the major enzymes responsible for their metabolism may modify their plasma concentrations, leading to potentially significant effects. Most documented metabolic interactions involve antidepressant and anti-epileptic drugs. Of a particular clinical significance is the interaction between fluvoxamine, a potent CYP1A2 inhibitor, and clozapine. Differences in the interaction potential among the novel antipsychotics currently available may be predicted based on their metabolic pathways. The clinical relevance of these interactions should be interpreted in relation to the relative width of their therapeutic index. Avoidance of unnecessary polypharmacy, knowledge of the interaction profiles of individual agents, and careful individualization of dosage based on close evaluation of clinical response and, possibly, plasma drug concentrations are essential to prevent and minimize potentially adverse drug interactions in patients receiving newer antipsychotics.

Over the past decade, 'newer' or 'atypical' or 'second-generation' antipsychotics have become the treatment of choice for schizophrenia because of their more favourable tolerability profile as compared to traditional compounds. The second-generation antipsychotics currently available in most countries include clozapine, risperidone, olanzapine, quetiapine, sertindole, ziprasidone, aripiprazole and amisulpride. From a clinical perspective, these agents tend to be characterized by a low propensity to produce acute extrapyramidal symptoms and tardive dyskinesia, a weak potential to cause elevation of serum prolactin levels, and a broad spectrum of activity involving not only positive and negative symptoms, but also other symptom dimensions of schizophrenia (i.e. cognitive, aggressive and depressive symptoms) [1]. On the other hand, treatment with some of these medi-

cations has been associated with substantial risk of metabolic effects such as weight gain, hyperglycaemia and lipid dysregulation, and cerebrovascular adverse events, in particular stroke [2,3].

All newer antipsychotics are indicated for the treatment of schizophrenia and some are also approved for the treatment of bipolar disorder. In addition, they are increasingly used for the treatment of many other psychiatric conditions, either as monotherapy, or as an augmentation strategy [4]. As a consequence, second-generation antipsychotics are often prescribed in combination with other medications and this may result in clinically relevant drug interactions [5,6]. Combination pharmacotherapy is commonly used in clinical psychiatry to treat patients with comorbid psychiatric or physical illnesses, to control the side effects of a specific drug or to augment a medication effect. Therefore, the use of psychotropic agents with low potential for drug interactions is desirable, especially for elderly patients who are more likely to take many medications.

The aim of the present article is to provide an updated comparative review of metabolic drug interactions of second-generation antipsychotics. The information for this review

Author for correspondence: Edoardo Spina, Section of Pharmacology, Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, Policlinico Universitario, Via Consolare Valeria, 98125 Messina, Italy (fax +39 090 2213300, e-mail [espina@unime.it](mailto:espina@unime.it)).

was obtained from a MEDLINE search and hand-searching of a number of recent journals and recent reviews. Searches were performed for each of the newer antipsychotics. Obviously, more data (particularly from independent investigators) are available for those antipsychotics, such as clozapine, risperidone and olanzapine, released earlier for clinical use. Although several studies have been conducted, the design of many investigations has been inadequate to exclude significant drug interactions [7]. The next section describes the most important metabolic enzymes and our knowledge of how their physiology can be used to predict patterns of drug interactions even before they happen.

### Metabolic drug interactions

There are two basic types of drug interactions: pharmacokinetic and pharmacodynamic. Pharmacodynamic interactions take place at receptor sites and occur between drugs with similar or opposing therapeutic or adverse effects, resulting in additive, synergistic or antagonistic effects. Pharmacokinetic interactions consist of changes in the absorption, distribution, metabolism or excretion of a drug and/or its metabolites, or the quantity of active drug that reaches its site of action, after the addition of another chemical agent. This article focuses only on metabolic drug interactions that are the main type of pharmacokinetic interactions.

#### Major drug-metabolizing enzymes

Most pharmacokinetic interactions with newer antipsychotics occur at the metabolic level and usually involve changes in the activity of the major drug-metabolizing enzymes involved in their biotransformation, the cytochrome P450 (CYP) monooxygenases and/or uridine diphosphate-glucuronosyltransferases.

The cytochrome P450 system constitutes a superfamily of isoenzymes, located in the membranes of the smooth endoplasmic reticulum in the liver and in many extrahepatic tissues that mediate oxidative reactions of most drugs and xenobiotics, as well as many endogenous compounds [8]. The multiple CYP enzymes are subdivided into families, subfamilies and isoenzymes according to a nomenclature system based on amino acid sequence homology [9]. The major CYP enzymes involved in drug metabolism include CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Each CYP isoform is a specific gene product and possesses a characteristic but relatively broad spectrum of substrate specificity. There is a large variability in the expression and activity of these isoenzymes, which may lead to interindividual differences in drug exposure. Such variability results from genetic, pathophysiological and environmental factors, including concomitant administration of other drugs. A number of genes coded for CYP isoforms have variant alleles resulting from mutations, and these mutations can result in enzyme variants with higher, lower or no activity, or in the very absence of the enzyme. The existence of mutated alleles in at least 1% of

the population is referred to as genetic polymorphism [10]. The CYP polymorphisms that have the greatest clinical implications involve CYP2C9, CYP2C19 and CYP2D6. In recent years, the major CYP isoenzymes have been characterized at the molecular level and their different substrates, inhibitors and inducers have been identified [11].

Uridine diphosphate-glucuronosyltransferases (UGT) are enzymes which catalyse the glucuronidation of a large number of endobiotics and xenobiotics, located in the endoplasmic reticulum, mainly in the liver, but also in the kidney, intestine, skin, lung, prostate and brain [12]. UGT enzymes produce products that are more water-soluble, less toxic and more readily excreted than the parent compounds. While most substrates undergo glucuronide conjugation after phase I reactions, in some cases (i.e. olanzapine), direct conjugation occurs at the same time as other oxidative reactions. In recent years, at least 33 families within the UGT superfamily have been identified and classified by a nomenclature similar to that used for the CYP system [13]. The UGT1 and the UGT2 families seem to be the most important in drug metabolism. UGTs are less well understood than CYPs and this may be explained by several reasons, including (i) the overlapping activity of UGTs and the lack of selective probes; (ii) the complexity of the glucuronidation cycle; and (iii) the difficulty in developing analytic methods to measure glucuronides [14].

#### Enzyme inhibition and induction

Metabolic drug interactions generally result from one of two processes: enzyme inhibition or enzyme induction.

Enzyme inhibition usually involves competition with another drug for the enzyme-binding site. A large number of compounds may inhibit the activity of drug-metabolizing enzymes. As a consequence, the rate of metabolism of a particular agent is decreased, resulting in increased plasma drug concentrations and potential enhancement of its pharmacological effects. Competitive inhibition is typically a rapid and dose-dependent process [15,16]. The initial effect usually occurs within 24 hr from the addition of the inhibitor, although the time to reach maximal inhibition will depend on the elimination half-lives of the affected drug and of the inhibiting agent. When the inhibitor is withdrawn, restoration of baseline (pre-interaction) conditions is also dependent on the rates of the elimination of the affected drug and of the inhibitor. Usually, potent inhibitors of a given enzyme are substrates of the same enzyme, but this is not always the case. For example, quinidine is a potent inhibitor of CYP2D6 [17], but it is metabolized by CYP3A4 [18]. Inhibition of non-oxidative phase I and conjugating phase II enzymes has also been documented. Most new antipsychotics undergo extensive biotransformation, and their metabolism is therefore vulnerable to inhibition by a large number of competitive substrates and enzyme inhibitors.

The activity of drug-metabolizing enzymes in the liver and/or extrahepatic tissues may be increased by chronic administration of several exogenous agents including medications, abused substances, industrial contaminants, dietary

substances, as well as by endogenous compounds [15,16]. Induction may influence several CYP isoenzymes, but does not affect CYP2D6. Other enzymes, particularly UGTs, may be induced. From a biological point of view, induction is an adaptive response that protects the cells from toxic xenobiotics by increasing the detoxification activity. Therefore, it is to be expected that induction will result in decreased concentration of an active compound. However, for those agents that are inactive (pro-drugs), but are biotransformed to active metabolites, enzyme induction may paradoxically increase pharmacological or toxicological activity. It should be acknowledged that also the elimination of active metabolites may be increased by enzyme inducers. Enzyme induction is a slow regulatory process, which is dose- and time-dependent. In other words, the extent of induction is generally proportional to the dose of the inducing agent and, since the process usually requires synthesis of the new enzyme, it occurs with some delay after the exposure to the inducing agent, generally from a few days to 1–2 weeks. Similarly, the time frame for de-induction is also gradual and depends on the rate of degradation of the enzyme and the time required to eliminate the inducing drug.

#### Clinical significance of a metabolic drug interaction

Information on the drug-metabolizing enzyme systems and their substrates, inhibitors and inducers may be of great value for clinicians in anticipating and possibly avoiding potential interactions. Co-administration of two substrates of the same enzyme, or co-administration of a substrate with an inhibitor or an inducer, entails the possibility of a drug interaction. As a consequence, plasma concentrations of the co-administered drugs may be increased or decreased, resulting in clinical toxicity or diminished therapeutic effect. Dosage adjustments may then be required to avoid adverse effects or therapeutic failure. A description for clinicians of the different drug interaction patterns with inhibitors and inducers has been provided [19].

Drug–drug interactions may initially be studied *in vitro* in order to predict the potential importance *in vivo*. However, it should be emphasized that not all theoretically possible drug interactions that are predicted from *in vitro* studies will

occur *in vivo*, and some may not be clinically significant anyway. As suggested by Sproule et al. [20], different aspects, including not only drug-related factors such as potency and concentration of the inhibitor/inducer, therapeutic index of the substrate, extent of metabolism of the substrate through the affected enzyme, presence of active or toxic metabolites, but also patient-related and epidemiological factors, must be taken into account when evaluating the potential occurrence, extent and clinical significance of a metabolic drug interaction.

#### Metabolism of newer antipsychotics and potential for metabolic interactions

In order to evaluate the potential for metabolic drug interactions of the newer antipsychotics, it is essential to know the effect of these agents on drug-metabolizing enzymes and the metabolic pathways of the various antipsychotics.

#### Effect of the newer antipsychotics on drug-metabolizing enzymes

With regard to the effect of the newer antipsychotics on the metabolism of other drugs, it is important to note that these agents appear to be neither inhibitors nor inducers of drug-metabolizing enzymes. In this respect, *in vitro* studies with human liver microsomes have documented that various second-generation antipsychotics do not significantly affect the activity of CYP isoenzymes [21,22]. As a consequence, it is unlikely that in typical circumstances they can interfere with the biotransformation of concomitantly administered medications. This represents an advantage as compared to some first-generation antipsychotics such as phenothiazines, which are potent inhibitors of some CYP enzymes, namely CYP2D6, and may therefore affect the pharmacokinetics of other agents [23].

#### Metabolism of newer antipsychotics

With the exception of amisulpride, currently available second-generation antipsychotics are extensively metabolized, primarily by oxidative processes, but also by direct glucuronidation [24–27]. The main pharmacokinetic properties of novel antipsychotics are reported in table 1.

Table 1.

Main pharmacokinetic parameters of newer antipsychotics (based on reference nos 24–27).

	Bioavailability (%)	Protein binding (%)	Half-life (hours)	Time to reach steady-state (days)	Enzymes responsible for biotransformation	Active metabolites
Clozapine	12–81	>90	6–33	4–8	<i>CYP1A2</i> , <sup>2</sup> <i>CYP2C19</i> , ( <i>CYP3A4</i> , <i>CYP2D6</i> )	Norclozapine
Risperidone	68	90	3–24	4–6	<i>CYP2D6</i> , <sup>2</sup> <i>CYP3A4</i> <sup>2</sup>	9-Hydroxy-risperidone
Olanzapine	60–80	93	20–70	5–7	<i>CYP1A2</i> , <sup>2</sup> <i>CYP2D6</i> , <i>UGT1A4</i> , <i>FMO</i> <sup>1</sup>	—
Quetiapine	Not available	83	5–8	2–3	<i>CYP3A4</i> <sup>2</sup>	—
Sertindole	75	99	85–99	15–20	<i>CYP2D6</i> , <sup>2</sup> <i>CYP3A4</i> <sup>2</sup>	—
Ziprasidone	60	>99	4–10	2–3	<i>CYP3A4</i> , aldehyde oxidase	—
Aripiprazole	Not available	>99	48–68	14	<i>CYP3A4</i> , <sup>2</sup> <i>CYP2D6</i> <sup>2</sup>	Dehydro-aripiprazole
Amisulpride	43–48	17	12	2–3	Not clinically relevant	—

<sup>1</sup>FMO, flavin-containing monooxygenase-3 system. <sup>2</sup>In italic and bold the most likely to have clinical relevance.

Clozapine has a complex hepatic metabolism in man with multiple CYP isoforms being involved in its biotransformation. The major metabolic pathways are the N-demethylation and the N-oxidation to form norclozapine, which has limited pharmacological activity, and clozapine N-oxide, respectively [24,26,27]. Currently available *in vitro* and *in vivo* evidence clearly indicate that CYP1A2 plays a major role in the metabolism of clozapine, although other CYP isoforms, including CYP2C19, CYP2D6, CYP3A4 and CYP2C9, also contribute to its biotransformation [28–32].

Risperidone is extensively metabolized in the liver, primarily by 9-hydroxylation, yielding an active metabolite 9-hydroxyrisperidone (9-OH-risperidone) [24–27]. According to *in vivo* and *in vitro* studies, CYP2D6 and, to a lesser extent, CYP3A4 are responsible for the 9-hydroxylation of risperidone [33–35]. The metabolite 9-OH-risperidone is approximately equipotent with the parent drug in terms of dopamine receptor affinity and the total risperidone active moiety (sum of plasma concentrations of parent drug and metabolite) should contribute to the overall antipsychotic effect and side effects.

The major metabolic pathways of olanzapine include direct N-glucuronidation, mediated by UGT1A4, and by N-demethylation, mediated by CYP1A2 [36,37]. Minor pathways of olanzapine biotransformation include N-oxidation, catalysed by flavin-containing monooxygenase-3 system, and 2-hydroxylation, metabolized by CYP2D6 [36,37].

Quetiapine, a dibenzothiazepine derivative, is extensively metabolized in the liver by sulfoxidation to form its major, but inactive, sulfoxide metabolite, and, as lesser metabolic pathways, by N- and O-dealkylation [24–27]. CYP3A4 appears to be the major isoenzyme involved in these metabolic reactions, whereas CYP2D6 may only play a minor role [38].

Sertindole undergoes extensive hepatic metabolism by CYP2D6 and CYP3A4 to two main metabolites: dehydro-sertindole (through oxidation) and norsertindole (through N-dealkylation) [39].

Ziprasidone has a complex metabolism and the major pathways include the oxidation of sulphur resulting in the formation of ziprasidone-sulfoxide and ziprasidone-sulphone and N-dealkylation [40]. The cytosolic aldehyde oxidase metabolizes approximately two-thirds of ziprasidone. CYP3A4 has a relatively minor metabolic role.

Aripiprazole is extensively metabolized by CYP3A4 and CYP2D6 [41]. The predominant active metabolite, dehydro-aripiprazole, represents 40% of the circulating dose of aripiprazole.

Amisulpride undergoes relatively little metabolism with about 50% of the dose excreted in the urine as unchanged drug. Its biotransformation in humans includes N-dealkylation and oxidation, but the isoenzymes involved in these reactions are yet unidentified [42]. Because of its marginal metabolic elimination, amisulpride is almost devoid of clinically relevant metabolic interactions.

Finally, recent evidence indicates that antipsychotics and their active metabolites are, to a various degree, substrates or inhibitors of the multidrug resistance transporter, P-

glycoprotein, which could limit their absorption or brain entry [43,44]. In this respect, the brain entry of 9-OH-risperidone may be limited by the presence in the blood-brain barrier of the P-glycoprotein that has greater affinity for 9-OH-risperidone than for risperidone [45].

#### *Potential for metabolic drug interactions*

Concomitant administration of drugs acting as inhibitors or inducers of the enzymes involved in the biotransformation of the newer antipsychotics may decrease or increase their elimination [5,6]. Plasma concentrations of the newer antipsychotics and/or their metabolites may therefore increase or decrease with subsequent clinical effects. For drugs such as olanzapine, whose major metabolic pathway is represented by glucuronidation, administration of CYP inhibitors will presumably result only in marginal changes. The addition of inducers can be problematic for all second-generation antipsychotics, but the decrease in plasma levels may be more dramatic for quetiapine, which is mainly dependent on CYP3A4. Moreover, for compounds forming active metabolites, such as risperidone and aripiprazole, it will be necessary to consider the changes in both parent drug and active metabolite in the evaluation of the consequences of inhibitors or inducers. As previously mentioned, the clinical relevance of changes in plasma concentrations should be considered in view of the therapeutic index of the compound whose elimination is affected. In this respect, the newer antipsychotics have a wider therapeutic index as compared to traditional agents, at least with regard to extrapyramidal side effects. An exception is represented by risperidone that shows a dose- and concentration-dependent risk for parkinsonian symptoms at dosages above 6 mg/day [46,47]. Moreover, compared to olanzapine, clozapine has a much narrower therapeutic index, and it is documented that central nervous system toxicity (e.g. generalized seizures, severe sedation, confusion and delirium) occurs more frequently at plasma concentrations above 1000 ng/ml [48].

### **Metabolic drug interactions of newer antipsychotics**

#### *Central nervous system drugs*

#### *Other antipsychotics*

Concomitant administration of two or more antipsychotics is not a rational therapeutic strategy, but it can be used in the treatment refractory cases. In addition to a pharmacodynamic potentiation with subsequent risk of adverse effects [49], pharmacokinetic interactions are theoretically possible. With regard to new antipsychotics, some cases have documented an increase in plasma concentrations of clozapine following co-administration with risperidone [50,51]. However, in an open 4-week trial involving 12 patients with chronic schizophrenia, the addition of risperidone was well tolerated and did not significantly affect serum clozapine concentrations [52]. A further study reported no significant modifications in serum clozapine concentrations in 18 patients after the addition of risperidone to clozapine treatment [53].

A pharmacokinetic investigation in 36 patients with various psychiatric disorders has investigated the pharmacokinetic parameters of quetiapine at steady-state (600 mg/day) during co-administration with haloperidol (15 mg/day), risperidone (6 mg/day) or thioridazine (400 mg/day) [54]. While haloperidol and risperidone did not alter significantly quetiapine pharmacokinetics, thioridazine caused a 40% decrease in the area under the concentration–time curve (AUC) of quetiapine and a 68% increase in its clearance. The mechanism of this interaction is unknown. Thioridazine, a potent inhibitor of CYP2D6, might induce an unknown metabolic pathway of quetiapine, modify its binding to plasma protein or reduce its absorption. It is likely, although not documented, that thioridazine as well as other phenothiazines, potent inhibitors of CYP2D6, may impair the elimination of newer antipsychotics mainly dependent on CYP2D6 such as risperidone and, to a lesser extent, sertindole and aripiprazole.

#### *Antidepressants*

Antidepressants, in particular those of more recent commercialization, may be used in combination with novel antipsychotics in patients with concomitant psychotic and depressive symptoms, as an adjunctive strategy for the treatment of negative symptoms of schizophrenia or in patients with refractory obsessive–compulsive disorder.

*Tricyclic antidepressants.* The possibility of metabolic interactions between tricyclic antidepressants and the newer antipsychotics has not been investigated formally. However, Smith and Risken [55] reported a doubling of the plasma concentrations of nortriptyline (a CYP2D6 substrate) after a patient was started on a clozapine therapy. This suspected pharmacokinetic interaction may have occurred through competitive inhibition of CYP2D6, although there is no *in vitro* evidence of inhibition of CYP2D6 by clozapine.

*Selective serotonin reuptake inhibitors.* Selective serotonin reuptake inhibitors (SSRIs) are the most widely used antidepressants because of their favourable tolerability and safety profile. On the other hand, SSRIs may cause a clinically relevant inhibition of CYP enzymes. The six marketed SSRIs differ considerably in their potency to inhibit individual CYP enzymes [56]. In particular, fluoxetine and paroxetine are potent inhibitors of CYP2D6, fluvoxamine is a potent inhibitor of CYP1A2 and CYP2C19, fluoxetine and fluvoxamine are moderate inhibitors of CYP2C9 and CYP3A4, sertraline is a moderate inhibitor of CYP2D6, whereas citalopram and escitalopram do not appear to significantly inhibit any CYP [57–61]. As the inhibitory effect on these enzymes is concentration-dependent, the potential for drug interactions is higher in the elderly, particularly for agents whose elimination is affected by age, such as citalopram and paroxetine, and for those which exhibit non-linear kinetics, such as fluoxetine and paroxetine.

(a) *Fluoxetine.* Different studies have reported an increase by approximately 40–70% in plasma concentrations of clozapine

in patients concomitantly treated with fluoxetine 20 mg/day [62–64]. This interaction was attributed to the potent inhibitory effect of fluoxetine on the activity of CYP2D6, an isoform that contributes, at least in part, to the biotransformation of clozapine. However, recent evidence suggests that fluoxetine may also inhibit CYP2C19 and CYP3A4, which also play a role in clozapine metabolism [65]. In addition, norfluoxetine, the major metabolite of norfluoxetine, is a moderate inhibitor of CYP3A4.

A clinically relevant pharmacokinetic interaction may occur between fluoxetine and risperidone [66,67]. Two patients with depression had dramatic increases in total risperidone moiety and major side effects [66]. In 10 schizophrenic patients stabilized on risperidone (4–6 mg/day), co-administration of fluoxetine (20 mg/day) caused a mean of 75% elevation of plasma concentration of the active fraction of risperidone [67]. One patient dropped out after 1 week of combination treatment because of occurrence of akathisia, whereas two patients developed parkinsonian symptoms, thus requiring anticholinergic medication. This interaction is presumably due to inhibition of CYP2D6, the major isoenzyme responsible for the 9-hydroxylation of risperidone, although it is possible that norfluoxetine may also inhibit CYP3A4, blocking both metabolic pathways for risperidone [66]. This interaction provides a rational explanation for previous clinical observations concerning patients who developed gynaecomastia [68], or urinary retention and extrapyramidal symptoms [69] when fluoxetine was added to risperidone treatment. Similar results were reported in another pharmacokinetic study where the increase in plasma risperidone concentrations was generally well tolerated [70]. A reduction in risperidone dosage is advisable in case of concomitant administration of fluoxetine.

The effect of fluoxetine on the pharmacokinetics of olanzapine was evaluated in healthy persons [36]. Fluoxetine caused statistically significant but ‘clinically insignificant’ modifications in plasma concentrations and rates of clearance of olanzapine. According to a published study from the pharmaceutical company of 15 non-smoking volunteers, after up to 8 days on fluoxetine, 60 mg/day, the increase in olanzapine concentration was only about 15% [71]. It cannot be ruled out that longer fluoxetine treatments may have greater effects because of the long time that fluoxetine needs to reach steady-state and stable inhibitory properties.

In a study of 13 patients with various psychiatric disorders stabilized on quetiapine, 300 mg twice daily, the addition of fluoxetine, 60 mg/day for only 8 days, did not substantially alter the quetiapine area under the plasma concentration time curve during a 12-hr interval nor the minimum plasma concentration at the end of the dosing interval [72].

(b) *Paroxetine.* Data concerning the possibility of a metabolic interaction between paroxetine and clozapine are contradictory. Some studies have documented a moderate elevation of plasma clozapine concentrations (by approximately 20–40%), presumably not associated with clinically relevant effects, following administration of therapeutic doses of paroxetine, 20 mg/day [63,73]. This effect has been attributed

to the inhibition of CYP2D6, an isoform that is partially responsible for clozapine biotransformation. Conversely, another investigation has documented only minor, insignificant changes in serum concentrations of clozapine and its metabolites during concomitant treatment with paroxetine [74].

In a pharmacokinetic study involving 10 schizophrenic patients stabilized on risperidone therapy (4–8 mg/day), co-administration of paroxetine (20 mg/day) resulted in a mean 45% increase in plasma concentrations of the active fraction of risperidone [75]. The drug combination was well tolerated with the exception of one patient who developed extrapyramidal symptoms in the second week of adjunctive therapy. In a patient with side effects on risperidone and paroxetine, it was possible to observe that the patient had an inverted ratio (risperidone > 9-OH-risperidone) and a very long half-life of risperidone both compatible with high inhibition of CYP2D6 in spite of the fact that he was not a CYP2D6 poor metabolizer, but had only one active copy of the gene [76]. Therefore, the interaction is presumably mediated through inhibition of CYP2D6. A subsequent investigation in schizophrenic patients has indicated that paroxetine increases plasma concentrations of risperidone in a dose-dependent manner [77].

There is no documentation of pharmacokinetic interactions between paroxetine and other new antipsychotics.

(c) *Fluvoxamine*. The pharmacokinetic interaction between fluvoxamine and clozapine is one of the most extensively investigated in clinical psychopharmacology. Formal kinetic studies and case reports have demonstrated that concomitant administration of fluvoxamine may cause a 5 to 10 times increase in plasma concentrations of clozapine [74,78–84]. In some patients the fluvoxamine-induced elevation of plasma clozapine levels was associated with the occurrence of extrapyramidal symptoms [85]. This interaction has been attributed not only to inhibition of CYP1A2, the major enzyme responsible for clozapine metabolism, but also to additional inhibitory effects of fluvoxamine on CYP2C19 and CYP3A4 that also contribute to its biotransformation [86,87]. Clinicians should be aware of a potential interaction between clozapine and fluvoxamine. If clozapine and fluvoxamine are given concurrently, it is advisable to monitor patients for increased serum clozapine concentrations, worsening of psychosis and development of adverse symptoms. Downward dosage adjustments of clozapine may be necessary. However, because of the magnitude of this interaction, a pharmacokinetic augmentation strategy has been proposed for the co-administration of fluvoxamine with low doses of clozapine [83,88,89]. Clinicians using that strategy should use careful plasma level monitoring and have a high level of pharmacokinetic expertise.

Several studies have documented that fluvoxamine may also elevate plasma levels of olanzapine by approximately two times, presumably through inhibition of CYP1A2, with possible occurrence of unwanted effects [90–92]. In particular, in eight patients stabilized on olanzapine therapy (10–20 mg/day), the addition of fluvoxamine (100 mg/day) for 8

weeks increased plasma olanzapine levels by about 80% [92]. The magnitude of the effect of fluvoxamine on plasma levels of olanzapine is lower than observed with clozapine, as olanzapine is metabolized by multiple enzyme systems, namely UGT, whose activity is not affected by fluvoxamine. Combined olanzapine and fluvoxamine should be used cautiously and controlled clinically and by therapeutic drug monitoring to avoid olanzapine-induced adverse effects (sedation, orthostatic hypotension, tachycardia, transaminase elevations or seizures).

A recent investigation in schizophrenic patients on a chronic treatment with risperidone has evaluated the possibility of a metabolic interaction between fluvoxamine and risperidone [93]. Whereas in the six patients receiving adjunctive treatment with fluvoxamine at the dose of 100 mg/day no significant modifications in plasma levels of risperidone and its active metabolite were observed, concentrations increased slightly but significantly (by a mean of 26% over pretreatment;  $P < 0.05$ ) in the subgroup of five patients treated with a final fluvoxamine dose of 200 mg/day. A dose-dependent inhibitory effect of fluvoxamine on CYP2D6- and/or CYP3A4-mediated 9-hydroxylation of risperidone provides a rational explanation for this interaction. It is unclear if this pharmacokinetic mechanism may account for the development of a severe neurotoxic syndrome occurring in a patient soon after the addition of fluvoxamine to a stable treatment with risperidone [94].

(d) *Sertraline*. Formal kinetic studies have indicated that sertraline does not significantly affect plasma concentrations of clozapine and its major metabolite norclozapine [63,73]. On the other hand, two case reports have documented a moderate increase in plasma concentrations of clozapine after co-administration with sertraline at doses of 50 and 300 mg/day, respectively [95,96]. Sertraline does not interfere with the elimination of olanzapine, as demonstrated by measurement of this antipsychotic in 21 patients treated with this combination [90]. A recent study in 11 patients with schizophrenia or schizoaffective disorder stabilized on risperidone therapy (4–6 mg/day) has demonstrated that an 8-week co-medication with sertraline, 50–100 mg/day, did not change significantly steady-state plasma concentrations of risperidone active fraction [97]. However, in the two patients receiving the highest dose of sertraline, 150 mg/day, at week 8 total plasma risperidone concentrations were increased by 36% and 52%, respectively, as compared to baseline values, presumably because of a dose-dependent inhibition of CYP2D6-mediated 9-hydroxylation of risperidone.

(e) *Citalopram/escitalopram*. Concomitant administration of citalopram (20–40 mg/day) was found not to modify steady-state plasma concentrations of clozapine and norclozapine, as reported in two studies in patients with schizophrenia [98,99]. However, a case report has documented an increase in plasma levels of clozapine after co-medication of citalopram, attributed to a presumed inhibitory effect of citalopram on CYP1A2 or CYP3A4 [100]. No changes in steady-state plasma

concentrations of risperidone and 9-OH-risperidone were observed in seven patients after administration of citalopram, 40 mg/day [99].

The effect of SSRIs on plasma concentrations on novel antipsychotics is summarized in table 2.

*Other new antidepressants.* Unlike SSRIs, other new antidepressants, with the exception of nefazodone, do not interfere significantly with CYP enzymes [56].

Venlafaxine, a serotonin and noradrenaline reuptake inhibitor, is a weak inhibitor of CYP2D6. In a study of 30 healthy volunteers, treatment with venlafaxine, 150 mg/day, caused no significant changes in the pharmacokinetics of a single 1 mg oral dose of risperidone [101].

Nefazodone, a serotonin 5-HT<sub>2</sub> receptor antagonist that also inhibits both serotonin and noradrenaline reuptake, is a potent inhibitor of CYP3A4 [102]. Consistent with this, an increase in plasma levels of clozapine and norclozapine, associated with development of anxiety, dizziness and mild hypotension, was described after administration of nefazodone [103]. However, a previous investigation has documented that nefazodone has only minimal effects on clozapine and norclozapine concentrations [104]. A case of high total risperidone levels and side effects on nefazodone has been described [66].

Reboxetine is a selective noradrenaline reuptake inhibitor, with a weak inhibitory effect on the activity of CYP enzymes. The possibility of a pharmacokinetic interaction between reboxetine and the newer antipsychotics clozapine and risperidone was investigated in 14 patients with schizophrenia or schizoaffective disorder on chronic treatment with clozapine (250–500 mg/day) or risperidone (4–6 mg/day) [105]. Co-administration of reboxetine, 8 mg/day, for 4 weeks did not affect plasma concentrations of clozapine (seven patients), risperidone (seven patients) and their active metabolites.

Mirtazapine is a noradrenergic and specific serotonergic antidepressant. The effect of mirtazapine on steady-state plasma concentrations of the atypical antipsychotics clozapine, risperidone and olanzapine was evaluated in 24 patients with chronic schizophrenia [106]. In order to treat residual negative symptoms, mirtazapine, 30 mg/day, was added for 6 weeks to patients stabilized on clozapine (n = 9; 200–650 mg/day), risperidone (n = 8; 3–8 mg/day) or olanzapine (n = 7; 10–20 mg/day). There were only minimal and statistically insignificant changes in the mean plasma concentrations of clozapine, risperidone, olanzapine and their major metabolites during the study period, indicating lack of pharmacokinetic interaction between mirtazapine and these antipsychotics.

### *Benzodiazepines*

Atypical antipsychotics are often used in combination with benzodiazepines. Apart from a specific potentiation of sedative effects, this combination is usually well tolerated. An exception may be clozapine. Within 24 or 48 hr after the first clozapine dose some patients taking benzodiazepines

develop lethargy, ataxia, loss of consciousness and, rarely, respiratory arrest [107]. The respiratory arrest associated with the co-administration of benzodiazepines and clozapine appears to be an idiosyncratic reaction because many individuals can tolerate this combination, even in the first days of clozapine treatment, without any obvious side effects. However, it is safer to avoid benzodiazepines the week before starting clozapine and during the first week of dose titration.

There is no evidence of pharmacokinetic interactions between benzodiazepines and newer antipsychotics.

### *Antiepileptics and/or mood stabilizers*

Antiepileptic drugs, particularly those with mood-stabilizing properties, are often used in combination with antipsychotics and may affect their biotransformation [108].

*Carbamazepine.* Carbamazepine is a first-generation anti-convulsant widely used for the treatment of bipolar disorder. This agent is a potent inducer of several drug-metabolizing enzymes including CYPs, namely CYP3A4, CYP2C9, CYP2C19 and, possibly CYP1A2, as well as UGTs [108,109]. In this respect, carbamazepine has been reported to decrease plasma concentrations of various novel antipsychotics. As a consequence, increased doses of the newer antipsychotics may be required to achieve or maintain a desired antipsychotic effect in patients receiving carbamazepine, whereas a dosage reduction should be considered in case of carbamazepine discontinuation.

The combined use of carbamazepine and clozapine should probably be avoided because of concerns about potential additive adverse haematological effects [110]. In addition, two studies have documented that carbamazepine may cause a decrease of approximately 50% in plasma clozapine concentrations, presumably explained by the induction of CYP1A2 and CYP3A4 [79,111].

A clinically significant metabolic interaction may also occur between carbamazepine and risperidone. The first documentation of this interaction came from a case report describing a patient who had risperidone levels that were less than expected during carbamazepine therapy, along with decreased risperidone efficacy [112]. The risperidone level dramatically increased when carbamazepine was discontinued. A subsequent study in psychiatric patients indicated that steady-state plasma concentrations of risperidone and its pharmacologically active metabolite were approximately 70% lower in patients co-medicated with carbamazepine (n = 11) than in patients treated with risperidone alone (n = 23) or receiving valproate (n = 10) [113]. Moreover, in five patients assessed on and off carbamazepine co-medication, dose-normalized plasma risperidone and 9-OH-risperidone concentrations were significantly lower during combination therapy than on risperidone alone. Further evidence came from a pharmacokinetic investigation of 11 schizophrenic inpatients indicating that plasma concentrations of risperidone and 9-OH-risperidone were decreased by about 50% when carbamazepine was given concomitantly [114]. The clinical

Table 2.

Effect of various selective serotonin reuptake inhibitors (SSRI) on plasma concentrations of novel antipsychotics (only controlled studies are described).

SSRIs	Antipsychotic	Effect on plasma concentrations	Proposed mechanism	References	Number of participants, design
Fluoxetine	Clozapine	Increase (40–70%)	Inhibition of various CYP isoforms (CYP2D6, CYP2C19 and CYP3A4)	Centorrino et al., 1994 [62] Centorrino et al., 1996 [63] Spina et al., 1998 [64]	6, parallel 14, parallel 10, sequential
	Risperidone	Increase (75%)	Inhibition of CYP2D6 and, to a lesser extent, CYP3A4	Spina et al., 2002 [67]	9, sequential
	Olanzapine Quetiapine	No change or minimal increase No change	Inhibition of CYP2D6	Gossen et al., 2002 [71] Potkin et al., 2002 [72]	15, sequential 13, sequential
Paroxetine	Clozapine	Increase (20–40%)	Inhibition of CYP2D6	Centorrino et al., 1996 [63] Wetzel et al., 1998 [73]	16, parallel 14, sequential
	Risperidone	Increase (40–50%)	Inhibition of CYP2D6	Spina et al., 2000 [74] Spina et al., 2001 [75] Saito et al., 2005 [77]	9, sequential 10, sequential 12, sequential
Fluvoxamine	Clozapine	Increase (up to 5–10 times)	Inhibition of CYP1A2 and, to a lesser extent, CYP2C19 and CYP3A4	Hiemke et al., 1994 [78] Jerling et al., 1994 [79] Wetzel et al., 1998 [73] Szegedi et al., [83]	3, case report 4, case report 16, sequential 16, sequential
	Risperidone	Minimal increase (10–20%)	Inhibition of CYP2D6 and CYP3A4	Fabrazzo et al., 2000 [84] D'Arrigo et al., 2005 [93]	16, sequential 11, sequential
	Olanzapine	Increase (up to 100%)	Inhibition of CYP1A2	Weigmann et al., 2001 [90] Hiemke et al., 2002 [92]	10, parallel 8, sequential
Sertraline	Clozapine	No change		Centorrino et al., 1996 [63] Spina et al., 2000 [74]	10, parallel 8, sequential
	Risperidone	Minimal increase	Inhibition of CYP2D6	Spina et al., 2004 [97]	11, sequential
	Olanzapine	No change		Weigmann et al., 2001 [90]	21, parallel
Citalopram/ escitalopram	Clozapine	No change		Taylor et al., 1998 [98] Avenoso et al., 1998 [99]	5, sequential 8, sequential
	Risperidone	No change		Avenoso et al., 1998 [99]	7, sequential



relevance of this interaction was documented in a case study, concerning a patient with chronic schizophrenia in whom addition of carbamazepine to pre-existing risperidone therapy resulted in a marked decrease in the plasma concentrations of both risperidone and its 9-hydroxy-metabolite and in an acute exacerbation of psychotic symptoms [115]. This interaction may be attributed to the inducing effect of carbamazepine on CYP3A4-mediated metabolism of risperidone. An increase in risperidone dose may need to be considered if carbamazepine is co-administered. If carbamazepine is discontinued, the dosage of risperidone should be re-evaluated and, if necessary, decreased.

Evidence from case reports, pharmacokinetic studies in healthy volunteers and therapeutic drug monitoring data from patients clearly indicates that carbamazepine, most likely through induction of CYP1A2 and UGT, may stimulate the biotransformation of olanzapine, thus decreasing its plasma concentrations [116–120]. In a study of 11 healthy volunteers, concurrent administration of olanzapine and carbamazepine resulted in a 46% increase in olanzapine clearance and in a 34% decrease in its AUC [116]. In patients co-medicated with carbamazepine, the median dose-normalized concentrations of olanzapine were 36–71% lower than in patients treated with olanzapine monotherapy [117,119,120]. Doses of olanzapine may need to be adjusted when given concomitantly with carbamazepine.

Carbamazepine may also accelerate the metabolism of quetiapine and ziprasidone, probably as a result of CYP3A4 induction. In a pharmacokinetic study in psychiatric patients, carbamazepine, 200 mg three times daily, decreased quetiapine plasma  $C_{max}$  by 80%, AUC by 87% and increased its apparent oral clearance 7.5 times [121]. A case of toxicity in the combination of carbamazepine and quetiapine has been described; it was interpreted as due to interference in carbamazepine metabolism at the CYP3A pathway [122]. Miceli et al. [123] reported a 27% mean decrease in the  $C_{max}$  of ziprasidone and a 36% decrease in its AUC in healthy volunteers when carbamazepine was added. It is possible that this study was not long enough to establish full induction by carbamazepine.

*Valproic acid.* Like carbamazepine, valproic acid is a traditional anticonvulsant largely used for the treatment of bipolar disorder. Valproic acid is not an inducer, but it may inhibit various UGTs and CYPs, particularly CYP2C9, which plays no major role in the metabolism of the newer antipsychotics [108,109]. As a consequence, valproic acid appears to be free of clinically relevant interactions with atypical antipsychotics.

There are conflicting findings concerning the effect of valproic acid on clozapine metabolism. In fact, plasma concentrations of clozapine and its metabolites have been reported to be either decreased or increased slightly after the addition of valproic acid [62,124–127]. These changes are unlikely to be clinically significant.

Differently from carbamazepine, valproic acid does not affect the elimination of risperidone. In a study of patients

stabilized on risperidone treatment, steady-state plasma concentrations of risperidone and 9-OH risperidone did not differ between patients treated with risperidone alone and patients co-medicated with valproic acid at doses up to 1200–1500 mg/day [113]. Moreover, no major changes in the levels of risperidone and its metabolite were observed in three patients assessed with and without valproate.

Both valproate and olanzapine are metabolized, at least partly, by glucuronidation. However, by the use of therapeutic drug monitoring data, Gex-Fabry et al. [128] found that co-medication of valproic acid did not affect plasma concentrations of olanzapine.

In a recent study in psychiatric patients stabilized on quetiapine, dose-normalized plasma concentrations of quetiapine were 77% higher in patients on valproate co-medication than in those receiving quetiapine alone [129]. This suggests the possibility that valproate may inhibit quetiapine metabolism.

In an open investigation involving 10 patients with schizophrenia, addition of valproate caused a decrease of 26% in the  $C_{max}$  and of 24% in the AUC of aripiprazole [130].

*Phenobarbital and Phenytoin.* Phenobarbital and phenytoin are recognized as the prototypical inducers of several drug-metabolizing enzymes including CYPs, namely CYP1A2, CYP2C and CYP3A4, as well as UGTs, and may therefore stimulate the biotransformation of the newer antipsychotics [108,109].

Facciola et al. [131] have reported that plasma concentrations of clozapine were 35% lower in patients co-medicated with phenobarbital, compared with patients receiving clozapine monotherapy. This effect was attributed to induction of CYP1A2 and CYP3A4. Conversely, discontinuation of phenobarbital treatment was associated with a marked elevation of plasma clozapine concentrations [132]. In two patients described by Miller [133], concomitant administration of phenytoin caused a decrease by 65–85% of plasma clozapine concentrations associated with worsening of psychiatric conditions. Co-administration of quetiapine 250 mg three times daily and phenytoin 100 mg three times daily increased the mean oral clearance of quetiapine by five times [134]. Quetiapine is metabolized by CYP3A4, which is induced by the administration of phenytoin.

*Other newer antiepileptics.* Differently from traditional anticonvulsants, the newer antiepileptics, namely lamotrigine, gabapentin, topiramate and oxcarbazepine, have a low potential for metabolic interactions. Although these agents are commonly used as mood stabilizers, limited information is available concerning their potential pharmacokinetic interactions with atypical antipsychotics [108].

Two studies have investigated the effect of antipsychotics on serum lamotrigine concentrations. In the first study, which was based on a systematic evaluation of lamotrigine concentrations in a routine clinical setting, concomitant administration of clozapine, risperidone or olanzapine were found not to significantly affect dose-normalized serum

lamotrigine levels [135]. In contrast, in a recent formal pharmacokinetic investigation in healthy volunteers, co-treatment with olanzapine (15 mg/day) was associated with a mean 24% reduction in the area under the concentration–time curve of lamotrigine [136]. With regard to the effect of lamotrigine on the elimination of novel antipsychotics, the possibility of a metabolic interaction between lamotrigine and clozapine or risperidone has been suggested by two case reports describing an approximately three and five times elevation in plasma concentrations of clozapine and risperidone, respectively, along with toxic effects, when lamotrigine was added to a stable regimen with these medications [137,138], whereas another report has shown no evidence of a drug interaction between risperidone and lamotrigine [139]. However, a randomized controlled trial in patients with treatment-resistant schizophrenia has documented no changes in plasma clozapine levels during lamotrigine treatment [140]. Moreover, adjunctive lamotrigine, at dosages up to 200 mg/day, did not affect the plasma levels of clozapine, risperidone and their active metabolites, whereas it caused a modest elevation in plasma olanzapine concentration, possibly as a result of inhibition of UGT1A4-mediated olanzapine glucuronidation, unlikely to be of clinical significance [141]. In this respect, other investigations have reported no modifications in the pharmacokinetics of olanzapine during co-administration of lamotrigine in healthy volunteers [136,142].

Differently from its congener carbamazepine, the new anticonvulsant oxcarbazepine seems to have only a modest inducing effect on CYPs. Consistent with this, in a study involving 25 outpatients with bipolar or schizoaffective disorder on a chronic treatment with risperidone (2–6 mg/day) or olanzapine (5–20 mg/day), a 5-week treatment with therapeutic doses of oxcarbazepine, 900–1200 mg/day, caused only minimal and no significant changes in the mean plasma levels of risperidone, 9-OH-risperidone and olanzapine [143].

Topiramate is a new antiepileptic with a favourable drug interaction profile. A randomized, double-blind, placebo-controlled trial in patients with treatment-resistant schizophrenia has shown that the addition of topiramate, 300 mg/day, to an ongoing treatment with newer antipsychotics did not significantly alter plasma concentrations of clozapine and olanzapine in 12 and 5 patients, respectively [144]. A recent study in 38 patients with psychotic disorders has documented that topiramate, at the dosages up to 200 mg/day, does not affect steady-state plasma levels of the new antipsychotics clozapine, olanzapine, risperidone and quetiapine [145].

The effect of antiepileptics on plasma concentrations on novel antipsychotics is summarized in table 3.

#### *Cholinesterase inhibitors*

Antipsychotic medications are often used to treat behavioural and psychological symptoms in patients with dementia and may therefore be co-administered with cholinesterase inhibitors, such as tacrine, donepezil, rivastigmine or galantamine. In this respect, isolated case reports have documented the occurrence or the worsening of extrapyramidal

adverse effects in patients receiving a combination of donepezil and risperidone [146,147]. This interaction probably has a pharmacodynamic basis and may be attributable to a relative imbalance of cholinergic and dopaminergic activity in the striatum, which may occur following concomitant administration of a dopaminolytic and a cholinesterase inhibitor. Consistent with this, recent studies have documented the lack of a pharmacokinetic interaction between risperidone and donepezil [148,149], rivastigmine [150] or galantamine [151] in patients with dementia or healthy volunteers, elderly or not.

#### *Drugs of abuse*

Two studies have investigated the possibility of a pharmacometabolic interaction between second-generation antipsychotics and cocaine and methadone. In an experimental pharmacokinetic investigation involving eight cocaine addicts, clozapine, administered at increasing doses (12.5, 25 and 50 mg), was found to cause a dose-dependent elevation in cocaine levels associated with a syncopal episode in one patient [152]. In a study aimed at evaluating the efficacy of olanzapine in methadone patients abusing cocaine, olanzapine, 5–10 mg/day, did not affect plasma methadone levels [153].

#### **Other drugs**

##### *Fluoroquinolones*

Ciprofloxacin, a broad-spectrum fluoroquinolone antimicrobial, is a potent inhibitor of CYP1A2 and might therefore interfere with the elimination of those antipsychotics predominantly metabolized by this enzyme [154]. Consistent with this, in a pharmacokinetic study of seven schizophrenic inpatients, concomitant administration of ciprofloxacin, 250 mg twice daily for 7 days, increased mean serum concentrations of clozapine and norclozapine by 29% and 31%, respectively [155].

The possibility of a pharmacokinetic interaction between ciprofloxacin and olanzapine has been suggested by two case reports. The first report describes the case of a patient on stable treatment with olanzapine whose plasma antipsychotic concentration was almost doubled after the initiation of ciprofloxacin, 250 mg twice daily, suggesting the possibility of a metabolic interaction between these two drugs [156]. In the second case, an elderly patient receiving a long-term treatment with olanzapine developed a marked QT interval prolongation after intravenous administration of ciprofloxacin [157].

##### *Macrolides*

Macrolide antibiotics, in particular erythromycin and troleandomycin, are potent inhibitors of CYP3A4 and can interact adversely with substrates for this enzyme [158]. Controversial findings have been reported concerning the interaction between erythromycin and clozapine. Two case reports have indicated that concomitant treatment with erythromycin resulted in an elevation of plasma clozapine levels, along with toxic effects such as somnolence, disorientation,

Table 3.

Effect of various anti-epileptics on plasma concentrations of novel antipsychotics (only controlled studies are described).

Antiepileptic	Antipsychotic	Effect on plasma concentrations	Proposed mechanism	References	Number of participants, design	
Carbamazepine	Clozapine	Decrease (50%)	Induction of CYP1A2, CYP3A4 and UGT	Jerling et al., 1994 [79]	17, parallel, and 8, sequential	
	Risperidone	Decrease (50–70%)	Induction of CYP3A4	Tiihonen et al., 1995 [111]	12, sequential	
	Olanzapine	Decrease (30–70%)	Induction of CYP1A2 and UGT	Spina et al., 2000 [113]	11, parallel, and 5, sequential	
	Quetiapine	Decrease (80%)	Induction of CYP3A4	Ono et al., 2002 [114]	11, sequential	
	Ziprasidone	Decrease (20–40%)	Induction of CYP3A4	Olesen & Linnet 1999 [117]	5, parallel	
Valproic acid	Clozapine	No change or minimal increase	Enzyme inhibition?	Linnet & Olesen 2002 [119]	16, parallel	
				Skogh et al., 2002 [120]	10, parallel	
				Grimm et al., 2005 [121]	18, sequential	
				Miceli et al., 2000 [123]	9, sequential	
				Centorrino et al., 1994 [62]	11, parallel	
Phenobarbital	Clozapine	Decrease (30–40%)	Induction of CYP1A2, CYP3A4 and UGT	Finley & Warner 1994 [124]	4, sequential	
				Longo & Salzman 1995 [126]	7, sequential	
				Facciola et al., 1999 [127]	15, parallel, and 6, sequential	
				Spina et al., 2000 [113]	10, parallel	
				Gex-Fabry et al., 2003 [128]	32, parallel	
Phenytoin	Quetiapine	Decrease (80%)	Induction of CYP3A4	Aichorn et al., 2006 [129]	9, parallel	
				Citrome et al., 2005 [130]	10, sequential	
Lamotrigine	Clozapine	No change	Enzyme inhibition?	Wong et al., 2001 [134]	7, parallel	
				Competitive inhibition of UGT1A4	Spina et al., 2006 [141]	11, sequential
					Spina et al., 2006 [141]	14, sequential
Oxcarbazepine	Risperidone	No change		Sidhu et al., 2006 [136]	16, sequential	
	Olanzapine	No change		Jann et al., 2006 [142]	14, sequential	
Topiramate	Clozapine	No change	Competitive inhibition of UGT1A4	Spina et al., 2006 [141]	14, sequential	
				Muscatello et al., 2005 [143]	12, sequential	
				Muscatello et al., 2005 [143]	13, sequential	
				Tiihonen et al., 2005 [144]	12, sequential	
				Migliardi et al., (in press) [145]	10, sequential	
Topiramate	Olanzapine	No change	Competitive inhibition of UGT1A4	Tiihonen et al., 2005 [144]	5, sequential	
				Migliardi et al., (in press) [145]	12, sequential	
				Migliardi et al., (in press) [145]	9, sequential	
				Migliardi et al., (in press) [145]	7, sequential	
Topiramate	Risperidone	No change				
	Quetiapine	No change				

dizziness, nausea and seizures [159,160]. Conversely, in a study in 12 healthy volunteers, the pharmacokinetics of clozapine, administered as a single dose of 12.5 mg, were not significantly modified during co-administration with erythromycin, 1500 mg/day, suggesting a limited involvement of CYP3A4 in the metabolism of clozapine in humans [161]. However, erythromycin steady-state was not reached in this study, and the doses of clozapine used were lower than those typically used in clinical practice. In 19 patients receiving quetiapine (200 mg, twice daily), co-administration with erythromycin (1500 mg/day) increased the half-life of quetiapine by 92% and decreased its clearance by 55% [162]. In a study in 10 healthy volunteers who received a single 4-mg dose of sertindole, a novel antipsychotic partly metabolized by CYP3A4, concomitant administration of erythromycin, 250 mg taken orally four times daily, caused a small (15%), but significant increase in the  $C_{max}$  of sertindole [163].

#### *Antimycobacterial agents*

The antimycobacterial agent rifampicin is a potent inducer of CYP1A2, CYP3A4 and possibly UGTs [164]. In a case report by Joos et al. [165], a schizophrenic patient stabilized on clozapine therapy experienced a significant decrease in his clozapine plasma concentration when rifampicin was added to therapy, resulting in an exacerbation of psychotic symptoms. Quetiapine, a CYP3A4 substrate, is likely to be susceptible to induction by rifampicin.

#### *Azole antimycotics*

The azole antimycotics itraconazole, ketoconazole and, to a lesser extent, fluconazole are potent inhibitors of CYP3A4, an isoform playing a major role in the biotransformation of quetiapine, ziprasidone and aripiprazole and contributing to that of clozapine and risperidone [166].

A formal kinetic study in schizophrenic patients has documented no significant changes in pharmacokinetic parameters of clozapine during co-administration with itraconazole, clearly indicating that CYP3A4 does not significantly contribute to clozapine metabolism [167].

Jung et al. [168] investigated the effect of a treatment with itraconazole, 200 mg/day for a week, on plasma concentrations of risperidone and its active metabolite in 19 schizophrenic patients stabilized on risperidone therapy (2–8 mg/day), in relation to CYP2D6 genotype. Itraconazole increased the mean steady-state plasma concentrations of risperidone active fraction by 71% and 73% in CYP2D6 extensive and poor metabolizers, respectively. As the ratio of risperidone/9-OH-risperidone, an index of CYP2D6 activity, was not affected by itraconazole administration, this interaction was attributed to inhibition of CYP3A4, an isoform playing a secondary role in the 9-hydroxylation of risperidone.

In 27 patients treated with quetiapine, concomitant administration of ketoconazole, 400 mg/day, resulted in a four times increase in mean quetiapine peak plasma concentration [38]. In 12 healthy volunteers receiving 25 mg quetiapine before and after 4 days of treatment with ketoconazole 200 mg

daily, concomitant use of ketoconazole increased the mean  $C_{max}$  and AUC of quetiapine by 235% and 522%, respectively, and decreased its clearance by 84% [121]. A placebo-controlled crossover study in healthy volunteers has documented an increase of 21% in the  $C_{max}$  and of 33% in the AUC of ziprasidone, administered as a single dose of 40 mg, after co-administration of ketoconazole, 400 mg/day for 2 weeks [169]. Co-administration of itraconazole, 100 mg/day for 7 days, to healthy volunteers increased the  $C_{max}$ , the AUC and the half-life of aripiprazole and its main metabolite by 19.4%, 48.0% and 18.6% and by 18.6%, 38.8% and 53.4%, respectively [170].

#### *Antivirals*

Psychotic symptoms are relatively common in patients with human immunodeficiency virus (or AIDS), so that antipsychotics and antiretroviral agents may be prescribed in combination. Some protease inhibitors, namely ritonavir and indinavir, are inhibitors of CYP3A4 and inducers of CYP1A2 and UGT [171]. Two case reports have documented the occurrence of reversible coma and extrapyramidal symptoms in patients receiving risperidone associated with ritonavir and/or indinavir, presumably as a result of inhibition of risperidone metabolism [172,173]. A pharmacokinetic study in healthy volunteers has demonstrated that a 2-week treatment with ritonavir, at a final dose of 1000 mg/day, caused a two times increase in the clearance of olanzapine and an approximate 50% decrease in its AUC, consistent with induction of olanzapine presumably through CYP1A2 and/or UGT by ritonavir [174].

#### *Warfarin*

A substantial increase in the international normalized ratio was described in a patient after the addition of quetiapine to warfarin therapy [175]. After switching to olanzapine, the international normalized ratio returned to baseline. The mechanism of this interaction was attributed to competitive inhibition of warfarin metabolism by quetiapine and/or its metabolites. However, the interpretation of this case is complicated by concomitant treatment with phenytoin that is a substrate and an inhibitor of CYP2C9 (the main warfarin metabolic pathway) and an inducer of various CYPs.

#### *Statins*

Anecdotal case reports have suggested the possibility of a pharmacokinetic interaction between the new antipsychotics and statins. The first case described a patient with schizophrenia also treated for dyslipidaemia who developed a prolonged QTc interval while taking quetiapine and lovastatin [176]. QTc returned to baseline when the lovastatin dose was reduced. Two other cases have documented the occurrence of rhabdomyolysis following co-administration of risperidone with cerivastatin or simvastatin [177,178].

#### *H<sub>2</sub>-Antagonists*

Cimetidine is a wide spectrum inhibitor of several CYP isoenzymes and may therefore decrease the elimination of

various drugs including atypical antipsychotics. An elevation in the serum level of clozapine and subsequent side effects developed after the administration of cimetidine, 1200 mg/day, in a patient receiving clozapine 900 mg/day [179]. A slight but not significant elevation of plasma concentrations of quetiapine not associated with adverse effects has been documented in seven patients after co-administration with cimetidine, 1200 mg/day [180]. Similarly, in a study of healthy volunteers, pharmacokinetic parameters of ziprasidone were almost unchanged during concomitant treatment with cimetidine [181]. Other H<sub>2</sub>-antagonists, such as ranitidine and famotidine, do not interfere with the activity of the major drug-metabolizing enzymes and may therefore be co-administered safely with second-generation antipsychotics.

#### *Proton pump inhibitors*

Omeprazole is a proton pump inhibitor with an inducing effect on CYP1A2. Consistent with this, in two patients with schizoaffective disorder treated with clozapine at a daily dose of 325 mg, co-medication with omeprazole was associated with a more than 40% reduction in the plasma levels of clozapine [182]. A subsequent retrospective study has documented that the inducing effect of omeprazole on clozapine metabolism was evident only in non-smoking patients [183].

#### *Oral contraceptives*

The possibility of a drug interaction between clozapine and oral contraceptives has been recently suggested based on the case of a 47-year-old woman on a long-term oral contraceptive treatment with norethindrone (0.5 mg)/ethinyl-oestradiol (0.035 mg) also treated with clozapine 550 mg/day [184]. After discontinuation of oral contraceptives, a decrease by about 50% in plasma concentrations of clozapine was observed and attributed to the inhibition of CYP1A2, CYP2C19 and CYP3A4 by oral contraceptives.

#### *Smoking*

Tobacco smoking is associated with induction of drug-metabolizing enzymes, namely CYP1A2 and, possibly, UGTs, due to its by-products, in particular the polycyclic aromatic hydrocarbons [185]. As a consequence, smoking may influence the elimination of those antipsychotics, such as clozapine and olanzapine, whose metabolism is mainly dependent on CYP1A2 and UGTs. In this respect, different studies have shown that plasma concentrations of clozapine (and its metabolite norclozapine) and olanzapine are lower, at the same dose, in smokers as compared to non-smokers [36,120,186–189]. Concerning clozapine, the inducing effect of smoking was more evident in men than in women [187]. Smoking cessation, if not accompanied by a dosage decrease, may be associated with increased plasma concentrations of these antipsychotics, possibly resulting in dose-related toxic effects. With regard to this, McCarty [190] described the case of a patient on a stable clozapine dose who developed a myoclonic seizure and a generalized crisis a few weeks

following sudden smoking cessation. Meyer [191] has documented a mean increase of 72% in clozapine concentration in 11 patients following smoking withdrawal, with occurrence of unwanted effects in the patient showing the highest increase.

#### *Caffeine*

Caffeine may significantly inhibit clozapine metabolism, when taken in amounts between 400 and 1000 mg/day [192]. Caffeine is metabolized by the same isoform, CYP1A2, primarily responsible for clozapine biotransformation [189]. It is therefore likely that caffeine and clozapine compete for the same enzyme. As caffeine exhibits dose-dependent kinetics, clozapine elimination is generally decreased when caffeine is taken in moderate to elevated amounts [192]. This interaction was first documented by Vainer and Chouinard [193], who described a patient with side effects on clozapine after the addition of caffeine. A controlled study in patients with schizophrenia has documented an approximate 50% reduction of plasma clozapine concentrations after the removal of caffeine from the diet [194]. In a recent investigation in 10 psychiatric patients, interestingly, instant coffee drinking elevated the mean serum clozapine concentrations by about 20% to 26%, compared to the decaffeinated phase [195]. This increase was most probably a result of the inhibition of CYP1A2 by caffeine.

#### *Grapefruit juice*

Grapefruit juice can inhibit the activity of CYP3A4 in the intestine and in the liver and may elevate plasma concentrations of substrates for this isoform. With regard to this, plasma concentrations of clozapine and norclozapine were not affected by repeated ingestion of grapefruit juice [196,197]. This confirms that enzymes other than CYP3A4, namely CYP1A2, play a major role in clozapine disposition. An increase in plasma levels of quetiapine, a CYP3A4 substrate, is likely to occur following grapefruit juice ingestion, but it has not been documented.

### Conclusions

The newer antipsychotics are involved in metabolic drug–drug interactions with other psychotropic agents or with compounds used in the treatment of concomitant somatic illnesses. Some of these interactions are well documented and may be clinically important, whereas others have been reported only anecdotally or reflect pharmacokinetic observations of doubtful practical relevance. In general, currently available novel antipsychotics do not affect the activity of major drug-metabolizing enzymes and consequently have minimal effects on the elimination of concomitantly given medications. On the other hand, drugs that inhibit or induce the CYP or UGT isoenzymes involved in metabolism of the various antipsychotic compounds may alter their plasma concentrations with subsequent risk of adverse effects or decreased efficacy. The therapeutic index of each atypical antipsychotic probably has major influence on the clinical significance of the interactions.

There are differences in the interaction potential of the marketed newer antipsychotics that may be anticipated, based on the knowledge of CYP or UGT isoenzymes involved in their metabolism. Clozapine, which is predominantly metabolized by CYP1A2, is subject to clinically relevant interactions with potent CYP1A2 inhibitors, such as fluvoxamine, whereas risperidone, a substrate of CYP2D6, is susceptible to the effect of strong CYP2D6 inhibitors, such as fluoxetine and paroxetine. The effect of CYP inhibitors appears to be relatively modest for olanzapine, which is principally metabolized by direct N-glucuronidation. As CYP3A4 plays a major role in the biotransformation of quetiapine, this antipsychotic is susceptible to the effect of potent inhibitors of this isoform, such as ketoconazole. The risk of clinically relevant metabolic drug interactions with CYP inhibitors appears to be lower for sertindole, ziprasidone and aripiprazole, which are also the compounds less extensively investigated. The addition of inducers of drug metabolism (i.e. carbamazepine or phenytoin) can affect the elimination of all second-generation antipsychotics, but the decrease in plasma levels appears to be more relevant for quetiapine, which is mainly dependent on CYP3A4. Because of its negligible metabolic elimination, amisulpride is almost devoid of clinically relevant metabolic interactions. In certain situations, knowledge of the interaction profiles of individual antipsychotics might be useful in selecting an appropriately effective agent that is less likely to interfere with medication(s) concomitantly administered. Finally, it should be emphasized that potentially adverse drug interactions in patients treated with the newer antipsychotics may be prevented and minimized by careful dosage adjustments based on close evaluation of clinical response and, possibly, plasma antipsychotic concentration monitoring.

#### Acknowledgements

This work is supported by grants from the University of Messina (PRA 2003).

#### References

- 1 Stahl S. *Essential Psychopharmacology of Antipsychotics and Mood Stabilizers*. Cambridge University Press, Cambridge, UK, 2002.
- 2 Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. *CNS Drugs* 2005;**19** (Suppl 1):1–93.
- 3 Herrmann N, Lanctot KL. Do atypical antipsychotics cause stroke? *CNS Drugs* 2005;**19**:91–103.
- 4 Jeste DV, Dolder CR. Treatment of non-schizophrenic disorders: focus on atypical antipsychotics. *J Psychiatr Res* 2004;**38**:73–103.
- 5 Spina E, Scordo MG. Newer antipsychotics: comparative review of drug interactions. *Expert Rev Neurother* 2001;**1**:171–82.
- 6 Prior TI, Baker GR. Interactions between the cytochrome P450 system and the second-generation antipsychotics. *J Psychiatry Neurosci* 2003;**28**:99–112.
- 7 de Leon J, Armstrong SC, Cozza KL. The dosing of atypical antipsychotics. *Psychosomatics* 2005;**46**:262–73.
- 8 Guengerich FP. Comparisons of catalytic selectivity of cytochrome P450 subfamily enzymes from different species. *Chem Biol Interact* 1997;**106**:161–82.
- 9 Nelson DR, Koymans L, Kamataki T et al. P450 superfamily: update on new sequences, gene mapping, accession numbers and nomenclature. *Pharmacogenetics* 1996;**6**:1–42.
- 10 Meyer UA. The molecular basis of genetic polymorphism of drug metabolism. *J Pharm Pharmacol* 1994;**46** (Suppl 1):409–15.
- 11 Rendic S, Di Carlo FJ. Human cytochrome P450 enzymes: a status report summarizing their reactions, substrates, inducers, and inhibitors. *Drug Metab Rev* 1997;**29**:413–580.
- 12 Liston HL, Markowitz JS, Devane L. Drug glucuronidation in clinical psychopharmacology. *J Clin Psychopharmacol* 2001;**21**:500–15.
- 13 Mackenzie PI, Owens IS, Burchell B et al. The UDP glycosyltransferase gene superfamily: recommended nomenclature update based on evolutionary divergence. *Pharmacogenetics* 1997;**7**:255–69.
- 14 de Leon J. Glucuronidation enzyme genes and psychiatry. *Int J Neuropsychopharmacol* 2003;**6**:57–72.
- 15 Lin JH, Lu AYH. Inhibition and induction of cytochrome P450 and the clinical implications. *Clin Pharmacokinet* 1998;**35**:361–90.
- 16 Thummel KE, Kunze KL, Shen DD. Metabolically-based drug-drug interactions: principles and mechanisms. In: Levy RH, Thummel KE, Trager WF, Hansten PD, Eichelbaum M (eds). *Metabolic Drug Interactions*. Lippincott Williams & Wilkins, Philadelphia, PA, 2000;3–19.
- 17 Skjelbo E, Brosen K. Inhibitors of imipramine metabolism by human liver microsomes. *Br J Clin Pharmacol* 1992;**34**:256–61.
- 18 Nielsen TL, Rasmussen BB, Flinois JP, Beaune P, Brosen K. *In vitro* metabolism of quinidine: the (3S)-3-hydroxylation of quinidine is a specific marker reaction for cytochrome P4503A4 activity in human liver microsomes. *J Pharmacol Exp Ther* 1999;**289**:31–7.
- 19 Armstrong SC, Cozza KL, Sandson NB. Six patterns of drug-drug interactions. *Psychosomatics* 2003;**44**:255–8.
- 20 Sproule BA, Naranjo CA, Bremner KE, Hassan PC. Selective serotonin reuptake inhibitors and CNS drug interactions: a critical review of the evidence. *Clin Pharmacokinet* 1997;**33**:454–71.
- 21 Ring BJ, Binkley SN, Vandenbranden M, Wright SA. *In vitro* interaction of the antipsychotic agent olanzapine with human cytochromes P450 CYP2C19, CYP2C10, CYP2D6, and CYP3A. *Br J Clin Pharmacol* 1996;**41**:181–6.
- 22 Shin JG, Soukhova N, Flockart DA. Effect of antipsychotic drugs on human liver cytochrome P450 (CYP) isoforms *in vitro*: preferential inhibition of CYP2D6. *Drug Metab Dispos* 1999;**27**:1078–84.
- 23 Mulsant BH, Foglia JP, Sweet RA, Rosen J, Lo KH, Pollock BJ. The effects of perphenazine on the concentration of nortriptyline and its hydroxymetabolites in older patients. *J Clin Psychopharmacol* 1997;**17**:318–21.
- 24 Prior TI, Chue PS, Tibbo P, Baker GR. Drug metabolism and atypical antipsychotics. *Eur Neuropsychopharmacol* 1999;**9**:301–9.
- 25 Caccia S. New antipsychotic agents for schizophrenia: pharmacokinetics and metabolism update. *Curr Opin Invest Drugs* 2002;**3**:1073–80.
- 26 Raggi MA, Mandrioli R, Sabbioni C, Pucci V. Atypical antipsychotics: pharmacokinetics, therapeutic drug monitoring and pharmacological implications. *Curr Med Chem* 2004;**11**:279–96.
- 27 Murray M. Role of CYP pharmacogenetics and drug-drug interactions in the efficacy and safety of atypical and other antipsychotic agents. *J Pharm Pharmacol* 2006;**58**:871–5.
- 28 Bertilsson L, Carrillo JA, Dahl ML et al. Clozapine disposition covaries with CYP1A2 activity determined by a caffeine test. *Br J Clin Pharmacol* 1994;**38**:471–3.

- 29 Dahl ML, Llerena A, Bondesson U, Lindstrom L, Bertilsson L. Disposition of clozapine in man: lack of association with debrisoquine and S-mephenytoin hydroxylation polymorphisms. *Br J Clin Pharmacol* 1994;**37**:71–4.
- 30 Eierman B, Engel G, Johansson I, Zanger UM, Bertilsson L. The involvement of CYP1A2 and CYP3A4 in the metabolism of clozapine. *Br J Clin Pharmacol* 1997;**44**:439–46.
- 31 Linnet K, Olesen OV. Metabolism of clozapine by cDNA-expressed human cytochrome P450 enzymes. *Drug Metab Dispos* 1997;**25**:1379–82.
- 32 Olesen OV, Linnet K. Contributions of five human cytochrome P450 isoforms to the N-demethylation of clozapine *in vitro* at low and high concentrations. *J Clin Pharmacol* 2001;**41**:823–32.
- 33 Huang ML, van Peer A, Woestenborghs R et al. Pharmacokinetics of the novel antipsychotic agent risperidone and the prolactin response in healthy subjects. *Clin Pharmacol Ther* 1993;**54**:257–68.
- 34 Fang J, Bourin M, Baker GB. Metabolism of risperidone to 9-hydroxyrisperidone by human cytochrome P450 2D6 and 3A4. *Naunyn Schmiedebergs Arch Pharmacol* 1999;**359**:147–51.
- 35 Yasui-Furukori N, Hidestrand M, Spina E, Facciola G, Scordo MG, Tybring G. Different enantioselective 9-hydroxylation of risperidone by the two human CYP2D6 and CYP3A4 enzymes. *Drug Metab Dispos* 2001;**29**:1263–8.
- 36 Callaghan JT, Bergstrom RF, Ptak LR, Beasley CM. Olanzapine: pharmacokinetic and pharmacodynamic profile. *Clin Pharmacokinet* 1999;**37**:177–93.
- 37 Linnet K. Glucuronidation of olanzapine by cDNA-expressed human UDP-glucuronosyltransferases and human liver microsomes. *Hum Psychopharmacol* 2002;**17**:233–8.
- 38 Devane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine. *Clin Pharmacokinet* 2001;**40**:509–22.
- 39 Murdoch D, Keating GM. Sertindole: a review of its use in schizophrenia. *CNS Drugs* 2006;**20**:233–55.
- 40 Prakash C, Kamel A, Cui D, Whalen RD, Miceli JJ, Tweedie D. Identification of the major human liver cytochrome P450 isoform(s) responsible for the formation of the primary metabolites of ziprasidone and prediction of possible drug interactions. *Br J Clin Pharmacol* 2000;**49** (Suppl 1):35S–42S.
- 41 Swainston-Harrison T, Perry C. Aripiprazole: a review of its use in schizophrenia and schizoaffective disorder. *Drugs* 2004;**64**:1715–36.
- 42 Rosenzweig P, Canal M, Patat A, Bergougnan L, Zieleniuk I, Bianchetti G. A review of the pharmacokinetics, tolerability and pharmacodynamics of amisulpride in healthy volunteers. *Hum Psychopharmacol* 2002;**17**:1–13.
- 43 Boulton DW, Devane CL, Liston HL, Markowitz JS. *In vitro* P-glycoprotein affinity for atypical and conventional antipsychotics. *Life Sci* 2002;**71**:163–9.
- 44 Wang JS, Zhu HJ, Markowitz JS, Donovan JL, Devane CL. Evaluation of antipsychotic drugs as inhibitors of multidrug resistance transporters P-glycoprotein. *Psychopharmacology* 2006;**187**:415–23.
- 45 Wang JS, Ruan Y, Taylor RM, Donovan JL, Markowitz JS, Devane CL. The brain entry of risperidone and 9-hydroxyrisperidone is greatly limited by P-glycoprotein. *Int J Neuropsychopharmacol* 2004;**7**:415–9.
- 46 Simpson GM, Lindenmayer JP. Extrapyramidal symptoms in patients treated with risperidone. *J Clin Psychopharmacol* 1997;**17**:194–201.
- 47 Spina E, Avenoso A, Facciola G et al. Relationship between plasma risperidone and 9-hydroxyrisperidone concentrations and clinical response in patients with schizophrenia. *Psychopharmacology* 2001;**153**:238–43.
- 48 Freeman DJ, Oyewumi LK. Will routine therapeutic drug monitoring have a place in clozapine therapy? *Clin Pharmacokinet* 1997;**32**:93–100.
- 49 Kontaxakis VP, Havaki-Kontaxaki BJ, Stamouli SS, Christodoulou GN. Toxic interaction between risperidone and clozapine: a case report. *Prog Neuropsychopharmacol Biol Psychiatry* 2002;**26**:407–9.
- 50 Koreen AR, Lieberman JA, Kronig M, Cooper TB. Cross-tapering clozapine and risperidone. *Am J Psychiatry* 1995;**152**:1690.
- 51 Tyson SC, Devane CL, Risch SC. Pharmacokinetic interaction between risperidone and clozapine. *Am J Psychiatry* 1995;**152**:1401–2.
- 52 Henderson DC, Goff DC. Risperidone as an adjunct to clozapine therapy in chronic schizophrenics. *J Clin Psychiatry* 1996;**57**:395–7.
- 53 Raaska K, Raitasuo V, Neuvonen PJ. Therapeutic drug monitoring data: risperidone does not increase serum clozapine concentration. *Eur J Clin Pharmacol* 2002;**58**:587–91.
- 54 Potkin SG, Thyrum PT, Alva G et al. The safety and pharmacokinetics of quetiapine when coadministered with haloperidol, risperidone, or thioridazine. *J Clin Psychopharmacol* 2002;**22**:121–30.
- 55 Smith T, Risken J. Effect of clozapine on plasma nortriptyline concentration. *Pharmacopsychiatry* 1994;**27**:41–2.
- 56 Spina E, Scordo M, D'Arrigo C. Metabolic drug interactions with new psychotropic agents. *Fundam Clin Pharmacol* 2003;**17**:517–38.
- 57 Crewe HK, Lennard MS, Tucker GT, Woods FR, Haddock RE. The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. *Br J Clin Pharmacol* 1992;**34**:262–5.
- 58 Brosen K, Skielbo E, Rasmussen BB, Poulson HE, Loft S. Fluvoxamine is a potent inhibitor of cytochrome P4501A2. *Biochem Pharmacol* 1993;**45**:1211–4.
- 59 Kobayashi K, Yamamoto T, Chiba K, Tani M, Ishizaki T, Kuroiwa Y. The effects of selective serotonin reuptake inhibitors and their metabolites on S-mephenytoin 4'-hydroxylase activity in human liver microsomes. *Br J Clin Pharmacol* 1995;**40**:481–5.
- 60 Greenblatt DJ, von Moltke LL, Schmider J, Harmatz JS, Shader RI. Inhibition of human cytochrome P450–3A isoforms by fluoxetine and norfluoxetine: *in vitro* and *in vivo* studies. *J Clin Pharmacol* 1996;**36**:792–8.
- 61 Schmider J, Greenblatt DJ, von Moltke LL, Karsov D, Shader RI. Inhibition of CYP2C9 by selective serotonin reuptake inhibitors *in vitro*: studies of phenytoin p-hydroxylaton. *Br J Clin Pharmacol* 1997;**44**:495–8.
- 62 Centorrino F, Baldessarini RJ, Kando J, Frankenburg FR, Volpicelli SA, Flood JG. Serum concentrations of clozapine and its metabolites: effects of cotreatment with fluoxetine or valproate. *Am J Psychiatry* 1994;**151**:123–5.
- 63 Centorrino F, Baldessarini RJ, Frankenburg FR, Kando J, Volpicelli SA, Flood JG. Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. *Am J Psychiatry* 1996;**153**:820–3.
- 64 Spina E, Avenoso A, Facciola G et al. Effect of fluoxetine on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenia. *Int Clin Psychopharmacol* 1998;**13**:141–5.
- 65 McGinnity DF, Berry AJ, Kenny JR, Grime K, Riley RJ. Evaluation of time-dependent cytochrome P450 inhibition using cultured human hepatocytes. *Drug Metab Dispos* 2006;**34**:1291–300.
- 66 Bork J, Rogers T, Wedlund P, de Leon J. A pilot study of risperidone metabolism: the role of cytochrome P450 2D6 and 3A. *J Clin Psychiatry* 1999;**60**:469–76.
- 67 Spina E, Avenoso A, Scordo MG et al. Inhibition of risperidone metabolism by fluoxetine in patients with schizophrenia: a clinically relevant pharmacokinetic drug interaction. *J Clin Psychopharmacol* 2002;**22**:419–23.

- 68 Benazzi F. Gynecomastia with risperidone-fluoxetine combination. *Pharmacopsychiatry* 1999;**32**:41.
- 69 Bozikas V, Petrikis P, Karavatos A. Urinary retention caused after fluoxetine-risperidone combination. *J Psychopharmacol* 2001;**15**:142–3.
- 70 Bondolfi G, Eap CB, Bertschy G, Zullino D, Vermeulen A, Baumann P. The effect of fluoxetine on the pharmacokinetics and safety of risperidone in psychiatric patients. *Pharmacopsychiatry* 2002;**35**:50–6.
- 71 Gossen D, de Suray JM, Vandenhanden F, Onkelinx C, Gangji D. Influence of fluoxetine on olanzapine pharmacokinetics. *AAPS PharmSci* 2002;**4**:1–6.
- 72 Potkin SG, Thyrum PT, Alva G et al. Effect of fluoxetine and imipramine on the pharmacokinetics and tolerability of the antipsychotic quetiapine. *J Clin Psychopharmacol* 2002;**22**:174–82.
- 73 Spina E, Avenoso A, Salemi M et al. Plasma concentrations of clozapine and its major metabolites during combined treatment with paroxetine or sertraline. *Pharmacopsychiatry* 2000;**33**:213–7.
- 74 Wetzel H, Anghelescu I, Szegei A et al. Pharmacokinetic interactions of clozapine with selective serotonin reuptake inhibitors: differential effects of fluvoxamine and paroxetine in a prospective study. *J Clin Psychopharmacol* 1998;**18**:2–9.
- 75 Spina E, Avenoso A, Facciola G, Scordo MG, Ancione M, Madia A. Plasma concentrations of risperidone and 9-hydroxy-risperidone during combined treatment with paroxetine. *Ther Drug Monit* 2001;**23**:223–7.
- 76 Barnhill J, Susce MT, Diaz FJ, de Leon J. Risperidone half-life in a patient taking paroxetine: a case report. *Pharmacopsychiatry* 2005;**38**:223–5.
- 77 Saito M, Yasui-Furukori N, Nakagami T, Furukori H, Kaneko S. Dose-dependent interaction of paroxetine with risperidone in schizophrenic patients. *J Clin Psychopharmacol* 2005;**25**:527–32.
- 78 Hiemke C, Weighmann H, Hartter S, Dahmen N, Wetzel H, Muller H. Elevated serum levels of clozapine after addition of fluvoxamine. *J Clin Psychopharmacol* 1994;**14**:279–81.
- 79 Jerling M, Lindstrom L, Bondesson U, Bertilsson L. Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. *Ther Drug Monit* 1994;**16**:368–74.
- 80 Dequardo JM, Roberts M. Elevated clozapine levels after fluvoxamine initiation. *Am J Psychiatry* 1996;**153**:840–1.
- 81 Dumortier G, Lochu A, Colen de Melo P et al. Elevated clozapine plasma concentrations after fluvoxamine initiation. *Am J Psychiatry* 1996;**153**:738–89.
- 82 Koponen HJ, Leinonen E, Lepola U. Fluvoxamine increases the serum clozapine levels significantly. *Eur Neuropsychopharmacol* 1996;**6**:69–71.
- 83 Szegei A, Anghelescu I, Wiesner J et al. Addition of low-dose of fluvoxamine to low-dose clozapine monotherapy in schizophrenia: drug monitoring and tolerability data from a prospective clinical trial. *Pharmacopsychiatry* 1999;**32**:148–53.
- 84 Fabrizio M, La Pia S, Monteleone P et al. Fluvoxamine increases plasma and urinary levels of clozapine and its major metabolites in a time- and dose-dependent manner. *J Clin Psychopharmacol* 2000;**20**:708–10.
- 85 Kuo FJ, Lane HY, Chang WH. Extrapyramidal symptoms after addition of fluvoxamine to clozapine. *J Clin Psychopharmacol* 1998;**18**:483–4.
- 86 Shader RI, Greenblatt DJ. Clozapine and fluvoxamine, a curious complexity. *J Clin Psychopharmacol* 1998;**18**:101–2.
- 87 Olesen OV, Linnet K. Fluvoxamine-clozapine drug interaction: inhibition *in vitro* of five cytochrome P450 isoforms involved in clozapine metabolism. *J Clin Psychopharmacol* 2000;**20**:35–42.
- 88 Szegei A, Wiesner J, Hiemke C. Improved efficacy and fewer side effects under clozapine treatment after addition of fluvoxamine. *J Clin Psychopharmacol* 1995;**15**:141–3.
- 89 Lammers CH, Deuschle M, Weighmann H et al. Coadministration of clozapine and fluvoxamine in psychotic patients: clinical experience. *Pharmacopsychiatry* 1999;**2**:76–7.
- 90 Weighmann H, Gerek S, Zeisig A, Muller M, Hartter S, Hiemke C. Fluvoxamine but not sertraline inhibits the metabolism of olanzapine: evidence from a therapeutic drug monitoring service. *Ther Drug Monit* 2001;**23**:410–3.
- 91 de Jong J, Hoogenboom B, van Troostwijk LD, de Haan L. Interaction of olanzapine with fluvoxamine. *Psychopharmacology* 2001;**155**:219–20.
- 92 Hiemke C, Avi P, Jabarin M et al. Fluvoxamine augmentation of olanzapine in chronic schizophrenia: pharmacokinetic interactions and clinical effects. *J Clin Psychopharmacol* 2002;**22**:502–6.
- 93 D'Arrigo C, Migliardi G, Santoro V et al. Effect of fluvoxamine on plasma risperidone concentrations in patients with schizophrenia. *Pharmacol Res* 2005;**52**:497–501.
- 94 Reeves RR, Mack JE, Beddingfield JJ. Neurotoxic syndrome associated with risperidone and fluvoxamine. *Ann Pharmacother* 2002;**36**:440–3.
- 95 Chong SA, Tan CH, Lee HS. Worsening of psychosis with clozapine and selective serotonin reuptake inhibitor combination: two case reports. *J Clin Psychopharmacol* 1997;**17**:68–9.
- 96 Pinninti NR, de Leon J. Interaction of sertraline with clozapine. *J Clin Psychopharmacol* 1997;**17**:119–20.
- 97 Spina E, D'Arrigo C, Migliardi G et al. Plasma risperidone concentrations during combined treatment with sertraline. *Ther Drug Monit* 2004;**26**:386–90.
- 98 Taylor D, Ellison Z, Ementon Shaw L, Wickham H, Murray R. Co-administration of citalopram and clozapine: effect on plasma clozapine levels. *Int Clin Psychopharmacol* 1998;**13**:19–21.
- 99 Avenoso A, Facciola G, Scordo MG et al. No effect of citalopram on plasma concentrations of clozapine, risperidone and their active metabolites in patients with chronic schizophrenia. *Clin Drug Invest* 1998;**16**:393–8.
- 100 Borba C, Henderson D. Citalopram and clozapine: potential drug interaction. *J Clin Psychiatry* 2000;**61**:301–2.
- 101 Amchin J, Zarycranski W, Taylor KP, Albano D, Klockowski PM. Effect of venlafaxine on the pharmacokinetics of risperidone. *J Clin Pharmacol* 1999;**39**:297–309.
- 102 Schmitter J, Greenblatt DJ, von Moltke LL, Hartz J, Shader RI. Inhibition of cytochrome P450 by nefazodone *in vitro*: studies of dextromethorphan O- and N-demethylation. *Br J Clin Pharmacol* 1996;**41**:339–43.
- 103 Khan A, Preskorn S. Increase in plasma levels of clozapine and nortclozapine after administration of nefazodone. *J Clin Psychiatry* 2001;**62**:375–6.
- 104 Taylor D, Bodani M, Hubbeling A, Murray R. The effect of nefazodone on clozapine plasma concentrations. *Int Clin Psychopharmacol* 1999;**14**:185–7.
- 105 Spina E, Avenoso A, Scordo MG, Ancione M, Madia A, Levita A. No effect of reboxetine on plasma concentrations of clozapine, risperidone and their active metabolites. *Ther Drug Monit* 2001;**23**:675–8.
- 106 Zoccali R, Muscatello MR, La Torre D et al. Lack of pharmacokinetic interaction between mirtazapine and the newer antipsychotics clozapine, risperidone and olanzapine in patients with chronic schizophrenia. *Pharmacol Res* 2003;**48**:411–4.
- 107 Klimke A, Klieser E. Sudden death after intravenous application of lorazepam in a patient treated with clozapine. *Am J Psychiatry* 1994;**151**:780.
- 108 Besag FMC, Berry D. Interactions between antiepileptic and antipsychotic drugs. *Drug Saf* 2006;**29**:95–118.



- 109 Spina E, Perucca E. Clinical significance of pharmacokinetic interactions between antiepileptic and psychotropic drugs. *Epilepsia* 2002;**43** (Suppl 2):37–44.
- 110 Junghan U, Albers M, Woggon B. Increased risk of hematological side-effect in psychiatric patients treated with clozapine and carbamazepine? *Pharmacopsychiatry* 1993;**26**:262.
- 111 Tiihonen J, Vartiainen H, Hakola P. Carbamazepine-induced changes in plasma levels of neuroleptics. *Pharmacopsychiatry* 1995;**28**:26–8.
- 112 de Leon J, Bork J. Risperidone and cytochrome P4503A. *J Clin Psychiatry* 1997;**58**:450.
- 113 Spina E, Avenoso A, Facciola G et al. Plasma concentrations of risperidone and 9-hydroxyrisperidone: effect of comedication with carbamazepine or valproate. *Ther Drug Monit* 2000;**22**:481–5.
- 114 Ono S, Mihara K, Suzuki A et al. Significant pharmacokinetic interaction between risperidone and carbamazepine: its relationship with CYP2D6 genotypes. *Psychopharmacology* 2002;**162**:50–4.
- 115 Spina E, Scordo MG, Avenoso A, Perucca E. Adverse drug interaction between risperidone and carbamazepine in a patient with chronic schizophrenia and deficient CYP2D6 activity. *J Clin Psychopharmacol* 2001;**21**:108–9.
- 116 Lucas RA, Gilfillan DJ, Bergstrom RF. A pharmacokinetic interaction between carbamazepine and olanzapine: observations on possible mechanisms. *Eur J Clin Pharmacol* 1998;**54**:639–43.
- 117 Olesen OV, Linnet K. Olanzapine serum concentrations in psychiatric patients given standard doses: the influence of comedication. *Ther Drug Monit* 1999;**21**:87–90.
- 118 Licht RW, Olesen OV, Friis P, Laustsen T. Olanzapine serum concentrations lowered by concomitant treatment with carbamazepine. *J Clin Psychopharmacol* 2000;**20**:110–2.
- 119 Linnet K, Olesen OV. Free and glucuronidated olanzapine serum concentrations in psychiatric patients: influence of carbamazepine comedication. *Ther Drug Monit* 2002;**24**:512–7.
- 120 Skogh E, Reis M, Dahl ML, Lundmark J, Bengtsson F. Therapeutic drug monitoring data on olanzapine and its N-demethyl metabolite in the naturalistic clinical setting. *Ther Drug Monit* 2002;**24**:518–26.
- 121 Grimm SW, Richtand NM, Winter HR, Stams KR, Reece SB. Effects of cytochrome P450 3A modulators ketoconazole and carbamazepine on quetiapine pharmacokinetics. *Br J Clin Pharmacol* 2005;**61**:58–69.
- 122 Fitzgerald B, Okos A. Elevation of carbamazepine-10, 11-epoxide by quetiapine. *Pharmacotherapy* 2002;**22**:1500–3.
- 123 Miceli JJ, Anziano RJ, Robarge L, Hansen RA, Laurent A. The effect of carbamazepine on the steady-state pharmacokinetics of ziprasidone in healthy volunteers. *Br J Clin Pharmacol* 2000;**49** (Suppl 1):65S–70S.
- 124 Finley P, Warner D. Potential impact of valproic acid therapy on clozapine disposition. *Biol Psychiatry* 1994;**36**:487–8.
- 125 Costello L, Suppes TA. A clinically significant interaction between clozapine and valproate. *J Clin Psychopharmacol* 1995;**15**:139–40.
- 126 Longo LP, Salzman C. Valproic acid effects on serum concentrations of clozapine and norclozapine. *Am J Psychiatry* 1995;**152**:650.
- 127 Facciola G, Avenoso A, Scordo MG et al. Small effects of valproic acid on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenic or affective disorders. *Ther Drug Monit* 1999;**21**:341–5.
- 128 Gex-Fabry M, Balant-Gorgia AE, Balant LP. Therapeutic drug monitoring of olanzapine: the combined effect of age, gender, smoking, and comedication. *Ther Drug Monit* 2003;**25**:46–53.
- 129 Aichhorn W, Marksteiner J, Walch T, Zernig G, Saria A, Kemmler G. Influence of age, gender, body weight and valproate comedication on quetiapine plasma concentrations. *Int Clin Psychopharmacol* 2006;**21**:81–5.
- 130 Citrome L, Josiassen R, Bark N, Salazar DE, Mallikaarjun S. Pharmacokinetics of aripiprazole and concomitant lithium and valproate. *J Clin Pharmacol* 2005;**45**:89–93.
- 131 Facciola G, Avenoso A, Spina E, Perucca E. Inducing effect of phenobarbital on clozapine metabolism in patients with chronic schizophrenia. *Ther Drug Monit* 1998;**20**:628–30.
- 132 Lane HY, Su KP, Chang WH, Jann MW. Elevated plasma clozapine concentrations after phenobarbital discontinuation. *J Clin Psychiatry* 1998;**59**:131–3.
- 133 Miller DD. Effect of phenytoin on plasma clozapine concentrations in two patients. *J Clin Psychiatry* 1991;**52**:23–5.
- 134 Wong YWJ, Yeh C, Thyrum PT. The effects of concomitant phenytoin administration on the steady-state pharmacokinetics of quetiapine. *J Clin Psychopharmacol* 2001;**21**:89–93.
- 135 Reimers A, Skogvoll E, Kutschera Sund J, Spigset O. Drug interactions between lamotrigine and psychoactive drugs: evidence from a therapeutic drug monitoring service. *J Clin Psychopharmacol* 2005;**25**:342–8.
- 136 Sidhu J, Job S, Bullman J et al. Pharmacokinetics and tolerability of lamotrigine and olanzapine coadministered to healthy subjects. *Br J Clin Pharmacol* 2006;**61**:420–6.
- 137 Kossen M, Selten JP, Kahn RS. Elevated clozapine plasma level with lamotrigine. *Am J Psychiatry* 2001;**158**:1930.
- 138 Bienentreu SD, Kronmuller KTH. Increase in risperidone plasma level with lamotrigine. *Am J Psychiatry* 2005;**162**:811–2.
- 139 Castberg I, Spigset O. Risperidone and lamotrigine: no evidence of a drug interaction. *J Clin Psychiatry* 2006;**67**:1159.
- 140 Tiihonen J, Hallikainen T, Ryyanen OP et al. Lamotrigine in treatment-resistant schizophrenia: a randomized placebo-controlled crossover trial. *Biol Psychiatry* 2003;**54**:1241–8.
- 141 Spina E, D'Arrigo C, Migliardi G et al. Effect of adjunctive lamotrigine treatment on the plasma concentrations of clozapine, risperidone and olanzapine in patients with schizophrenia or bipolar disorder. *Ther Drug Monit* 2006;**28**:599–602.
- 142 Jann MW, Hon YY, Shamsi SA, Zheng J, Awad EA, Spratlin V. Lack of pharmacokinetic interactions between lamotrigine and olanzapine in healthy volunteers. *Pharmacotherapy* 2006;**26**:627–33.
- 143 Muscatello MR, Pacetti M, Cacciola M et al. Plasma concentrations of risperidone and olanzapine during coadministration with oxcarbazepine. *Epilepsia* 2005;**46**:771–4.
- 144 Tiihonen J, Halonen P, Wahlbeck K et al. Topiramate add-on in treatment-resistant schizophrenia: a randomized, double-blind, placebo-controlled, crossover trial. *J Clin Psychiatry* 2005;**66**:1012–5.
- 145 Migliardi G, D'Arrigo C, Santoro V et al. Effect of topiramate on plasma concentrations of clozapine, olanzapine, risperidone and quetiapine in patients with psychotic disorders. *Clin Neuropharmacol* (in press).
- 146 Magnuson TM, Keller BK, Burke WJ. Extrapyramidal side effects in a patient treated with risperidone plus donepezil. *Am J Psychiatry* 1998;**155**:1457–9.
- 147 Liu HC, Lin SK, Sung SM. Extrapyramidal side-effect due to drug combination of risperidone and donepezil. *Psychiatry Clin Neurosci* 2002;**56**:479.
- 148 Zhao Q, Xie C, Pesco-Koplowitz L, Jia X, Parier JL. Pharmacokinetic and safety assessments of concurrent administration of risperidone and donepezil. *J Clin Pharmacol* 2003;**43**:180–6.
- 149 Reyes JF, Preskorn SH, Khan A et al. Concurrent administration of donepezil HCl and risperidone in patients with schizophrenia: assessment of pharmacokinetic changes and safety following multiple oral doses. *Br J Clin Pharmacol* 2004;**58** (Suppl 1):50–7.

- 150 Weiser M, Rotmensch HH, Korczyn AD, Hartman R, Cicin-Sain A, Anand R. A pilot, randomized, open-label trial assessing safety and pharmacokinetic parameters of co-administration of rivastigmine with risperidone in dementia patients with behavioral disturbances. *Int J Geriatr Psychiatry* 2002;**17**:343–6.
- 151 Huang F, Lasseter KC, Janssens L, Verhaeghe T, Lau H, Zhao Q. Pharmacokinetic and safety assessments of galantamine and risperidone after the two drugs are administered alone and together. *J Clin Pharmacol* 2002;**42**:1341–51.
- 152 Farren CK, Famedi FA, Rosen ME, Woods S, Jatlow P, Kosten TR. Significant interaction between clozapine and cocaine in cocaine addicts. *Drug Alcohol Depend* 2000;**59**:153–63.
- 153 Bano MD, Mico JA, Agujetas M, Lopez ML, Guillen JL. Olanzapine efficacy in the treatment of cocaine abuse in methadone maintenance patients: interaction with plasma levels. *Actas Esp Psiquiatr* 2001;**29**:215–20.
- 154 Fuhr U, Anders EM, Mahr G, Sorgel F, Staib AH. Inhibitory potency of quinolone antibacterial agents against cytochrome P450IA2 *in vivo* and *in vitro*. *Antimicrob Agents Chemother* 1992;**36**:942–8.
- 155 Raaska K, Neuvonen PJ. Ciprofloxacin increases serum clozapine and N-desmethylclozapine: a study in patients with schizophrenia. *Eur J Clin Pharmacol* 2000;**56**:585–9.
- 156 Markowitz JS, Devane CL. Suspected ciprofloxacin inhibition of olanzapine resulting in increased plasma concentrations. *J Clin Psychopharmacol* 1999;**19**:289–91.
- 157 Letsas K, Sideris A, Kounas SP, Efremidis M, Korantzopoulos P, Kardaras F. Drug-induced QT interval prolongation after ciprofloxacin administration in a patient receiving olanzapine. *Int J Cardiol* 2005;**109**:273–4.
- 158 Yamazaki H, Shimada T. Comparative studies of *in vitro* inhibition of cytochrome P450 3A4-dependent testosterone 6beta-hydroxylation by roxithromycin and its metabolites, troleandomycin, and erythromycin. *Drug Metab Dispos* 1998;**26**:1053–7.
- 159 Funderburg LG, Vertrees JE, True JE, Miller AL. Seizure following addition of erythromycin to clozapine treatment. *Am J Psychiatry* 1994;**151**:1840–1.
- 160 Cohen LG, Chesley S, Eugenio L, Flood JG, Fisch J, Goff DC. Erythromycin-induced clozapine toxic reaction. *Arch Intern Med* 1996;**156**:675–7.
- 161 Hagg S, Spigset O, Mjorndal T, Granberg K, Persbo-Lundqvist G, Dahlqvist R. Absence of interaction between erythromycin and a single dose of clozapine. *Eur J Clin Pharmacol* 1999;**55**:221–6.
- 162 Li KY, Li X, Cheng ZN, Zhang BK, Peng WX, Li HD. Effects of erythromycin on metabolism of quetiapine in Chinese suffering from schizophrenia. *Eur J Clin Pharmacol* 2005;**60**:791–5.
- 163 Wong SL, Cao G, Mack RJ, Granneman GR. The effect of erythromycin on the CYP3A component of sertindole clearance in healthy volunteers. *J Clin Pharmacol* 1997;**37**:1056–61.
- 164 Reinach B, de Sousa G, Dostert P, Ings R, Gugenheim J, Rahmani R. Comparative effects of rifabutin and rifampicin on cytochromes P450 and UDP-glucuronosyl-transferases expression in fresh and cryopreserved human hepatocytes. *Chem Biol Interact* 1999;**121**:37–48.
- 165 Joos AAB, Frank UG, Kaschka WP. Pharmacokinetic interaction of clozapine and rifampicin in a forensic patient with an atypical mycobacterial infection. *J Clin Psychopharmacol* 1998;**18**:83–5.
- 166 von Moltke LL, Greenblatt DJ, Schmider J et al. Midazolam hydroxylation by human liver microsomes *in vitro*: inhibition by fluoxetine, norfluoxetine, and by azole antifungal agents. *J Clin Pharmacol* 1996;**36**:783–91.
- 167 Raaska K, Neuvonen PJ. Serum concentrations of clozapine and N-desmethylclozapine are unaffected by the potent CYP3A4 inhibitor itraconazole. *Eur J Clin Pharmacol* 1998;**54**:167–70.
- 168 Jung SM, Kim KA, Cho HK et al. Cytochrome P450 3A inhibitor itraconazole affects plasma concentrations of risperidone and 9-hydroxyrisperidone in schizophrenic patients. *Clin Pharmacol Ther* 2005;**78**:520–8.
- 169 Miceli JJ, Smith M, Robarge L, Morse T, Laurent A. The effects of ketoconazole on ziprasidone pharmacokinetics: a placebo-controlled crossover study in healthy volunteers. *Br J Clin Pharmacol* 2000;**49** (Suppl 1):71S–76S.
- 170 Kubo M, Koue T, Inaba A et al. Influence of itraconazole co-administration and CYP2D6 genotype on the pharmacokinetics of the new antipsychotic aripiprazole. *Drug Metab Pharmacokinet* 2005;**20**:55–64.
- 171 Unadkat JD, Wang Y. Protease inhibitors. In: Levy RH, Thummel KE, Trager WF, Hansten PD, Eichelbaum M (eds). *Metabolic Drug Interactions*. Lippincott Williams & Wilkins, Philadelphia, PA, 2000:647–52.
- 172 Jover F, Cuadrado JM, Andreu L, Merino J. Reversible coma caused by risperidone-ritonavir interaction. *Clin Neuropharmacol* 2002;**25**:251–3.
- 173 Kelly DV, Beique LC, Bowmer MI. Extrapyramidal symptoms with ritonavir/indinavir plus risperidone. *Ann Pharmacother* 2002;**36**:827–30.
- 174 Penzak SR, Hon YY, Lawhorn WD, Shirley KL, Spratlin V, Jann MW. Influence of ritonavir on olanzapine pharmacokinetics in healthy volunteers. *J Clin Psychopharmacol* 2002;**22**:366–70.
- 175 Rogers T, de Leon J, Atcher D. Possible interaction between warfarin and quetiapine. *J Clin Psychopharmacol* 1999;**19**:382–3.
- 176 Furst BA, Champion KM, Pierre JM, Wirshing DA, Wirshing WC. Possible association of QTc interval prolongation with coadministration of quetiapine and lovastatin. *Biol Psychiatry* 2002;**51**:264–5.
- 177 Giner V, Munoz R, Redon J. Risperidone and severe cervicostatin-induced rhabdomyolysis. *J Intern Med* 2002;**251**:177–8.
- 178 Webber MA, Mahmud W, Lightfoot JD, Shekhar A. Rhabdomyolysis and compartment syndrome with coadministration of risperidone and simvastatin. *J Psychopharmacol* 2004;**18**:432–4.
- 179 Szymanski S, Lieberman JA, Picou D, Masiar S, Cooper T. A case report of cimetidine-induced clozapine toxicity. *J Clin Psychiatry* 1991;**52**:21–2.
- 180 Strakowski SM, Kech PE, Wong YWJ, Thyrum PT, Yeh C. The effect of multiple doses of cimetidine on the steady-state pharmacokinetics of quetiapine in men with selected psychotic disorders. *J Clin Psychopharmacol* 2002;**22**:201–5.
- 181 Wilner KD, Hansen RA, Folger CJ, Geoffroy P. The pharmacokinetics of ziprasidone in healthy volunteers treated with cimetidine or antacid. *Br J Clin Pharmacol* 2000;**49** (Suppl 1): 57S–60S.
- 182 Frick A, Kopitz J, Bergemann N. Omeprazole reduces clozapine plasma concentrations. A case report. *Pharmacopsychiatry* 2003;**36**:121–3.
- 183 Mookhoek EJ, Loonen AJ. Retrospective evaluation of the effect of omeprazole on clozapine metabolism. *Pharm World Sci* 2004;**26**:180–2.
- 184 Gabbay V, O'Dowd MA, Mamamtavrisvili M, Asnis GM. Clozapine and oral contraceptives: a possible drug interaction. *J Clin Psychopharmacol* 2002;**22**:621–2.
- 185 Zevin S, Benowitz NL. Drug interactions with tobacco smoking: an update. *Clin Pharmacokinet* 1999;**36**:425–38.
- 186 Haring C, Fleischhacker WW, Schett P, Humpel C, Barnas C, Saria A. Influence of patient-related variables on clozapine plasma levels. *Am J Psychiatry* 1990;**147**:1471–5.

- 187 Hasegawa M, Guiterrez R, Way L, Meltzer HI. Relationship between clinical efficacy and clozapine concentration in plasma in schizophrenia: effect of smoking. *J Clin Psychopharmacol* 1993;**13**:383–90.
- 188 Carrillo JA, Herraiz AG, Ramos SI, Gervasini G, Vizcaino S, Benitez J. Role of smoking-induced cytochrome P450 (CYP) 1A2 and polymorphic CYP2D6 in steady-state concentration of olanzapine. *J Clin Psychopharmacol* 2003;**23**:119–27.
- 189 de Leon J. Atypical antipsychotic dosing: the effect of smoking and caffeine. *Psychiatr Serv* 2004;**55**:491–3.
- 190 McCarthy R. Seizure following smoking cessation in a clozapine responder. *Pharmacopsychiatry* 1994;**27**:210–1.
- 191 Meyer JM. Individual changes in clozapine levels after smoking cessation: results and a predictive model. *J Clin Psychopharmacol* 2001;**21**:569–74.
- 192 Hagg S, Spigset O, Mjorndal T, Dahlqvist R. Effect of caffeine on clozapine pharmacokinetics in healthy volunteers. *Br J Clin Pharmacol* 2000;**49**:59–63.
- 193 Vainer JL, Chouinard G. Interaction between caffeine and clozapine. *J Clin Psychopharmacol* 1994;**14**:284–5.
- 194 Carrillo JA, Herraiz AG, Ramos SI, Benitez J. Effect of caffeine withdrawal from the diet on the metabolism of clozapine in schizophrenic patients. *J Clin Psychopharmacol* 1998;**18**:311–6.
- 195 Raaska K, Raitasuo V, Laitila J, Neuvonen PJ. Effect of caffeine-containing versus decaffeinated coffee on serum clozapine concentrations in hospitalised patients. *Basic Clin Pharmacol Toxicol* 2004;**94**:13–8.
- 196 Vandel S, Netillard C, Perault M, Bel AM. Plasma levels of clozapine and desmethylclozapine are unaffected by concomitant ingestion of grapefruit juice. *Eur J Clin Pharmacol* 2000;**56**:347–8.
- 197 Lane HY, Jann MW, Chang YC et al. Repeated ingestion of grapefruit juice does not alter clozapine's steady-state plasma levels, effectiveness, and tolerability. *J Clin Psychiatry* 2001;**62**:812–7.