

# Selective Serotonin Reuptake Inhibitors and Cytochrome P-450 Mediated Drug-Drug Interactions: An Update

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**Abstract:** The selective serotonin reuptake inhibitors (SSRIs) have become the most prescribed antidepressants in many countries. Although the SSRIs share a common mechanism of action, they differ substantially in their chemical structure, metabolism, and pharmacokinetics. Perhaps the most important difference between the SSRIs is their potential to cause drug-drug interactions through inhibition of cytochrome-P450 (CYP) isoforms.

This paper provides an update on both the *in vitro* and *in vivo* evidence with respect to CYP-mediated drug-drug interactions with this class of antidepressants.

The available evidence clearly indicates that the individual SSRIs display a distinct profile of cytochrome P450 inhibition. Fluvoxamine is a potent CYP1A2 and CYP2C19 inhibitor, and a moderate CYP2C9, CYP2D6, and CYP3A4 inhibitor. Fluoxetine and paroxetine are potent CYP2D6 inhibitors, whereas fluoxetine's main metabolite, norfluoxetine, has a moderate inhibitory effect on CYP3A4. Sertraline is a moderate CYP2D6 inhibitor; citalopram appears to have little effect on the major CYP isoforms. Fluoxetine deserves special attention as inhibitory effects on CYP-activity can persist for several weeks after fluoxetine discontinuation because of the long half-life of fluoxetine and its metabolite norfluoxetine.

Drug combinations with SSRIs should be assessed on an individual basis. Knowledge regarding the CYP-isoforms involved in the metabolism of the co-administered drug may help clinicians to anticipate and avoid potentially dangerous drug-drug interactions. Anticipated interactions can usually be managed by appropriate dose adjustment and titration of the object drug. In some cases, therapeutic drug monitoring can be useful. Equally well, an SSRI with limited interaction potential may be selected to treat depression in patients that receive other medications.

## INTRODUCTION

The selective serotonin reuptake inhibitors (SSRIs) have become an important component in the pharmacotherapeutic treatment of depression. Owing to their efficacy, good tolerability and relative safety, the SSRIs have become the most frequently prescribed antidepressant drugs [1,2].

While members of this class are remarkably similar in their antidepressant activity and side effect profile [1], they differ substantially in their chemical structure, metabolism, pharmacokinetics, and their inhibitory effect on the cytochrome P450-system (CYP).

Because many patients require long-term maintenance treatment with antidepressants, the SSRIs are frequently co-prescribed with other medications. Such polypharmacy may, however, lead to clinically important interactions with co-administered drugs. These interactions can be pharmacodynamic or pharmacokinetic. Pharmacokinetic interactions caused by metabolic inhibition of CYP-activity represent the majority of the reported interactions with the group of the SSRIs. Differences in their interaction potential

are related to differences in their inhibitory potency toward several important CYP-isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), involved in human drug metabolism.

In the past, several excellent reviews have been dedicated to this subject [3-12].

However, because of the rapid accumulation of the *in vitro* and *in vivo* data, there is the need to update the evidence on CYP-mediated drug-drug interactions with this class of antidepressants.

In this paper, the *in vitro* and *in vivo* evidence with respect to CYP-mediated drug-drug interactions with the SSRIs, as well as the evidence for and the clinical significance of these interactions will be reviewed.

## 1. THE CYTOCHROME P450 SYSTEM

Cytochrome P450 (CYP) describes a class of heme-containing proteins that represent the major enzymes responsible for the oxidation and reduction of numerous endogenous substrates and drugs [13].

The P450 enzymes have been classified based on their amino acid homology: enzymes with 40% greater sequence

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identity are included in the same family (designated by Arabic numerals, e.g. CYP2), and, within this family, enzymes with greater than 55% sequence identity are included in the same subfamily (designated by uppercase letters, e.g. CYP2D). Individual isoenzymes are designated by a second Arabic numeral (e.g. CYP2D6). To date, 17 CYP families have been identified in humans. Whereas families CYP1, CYP2, and CYP3 are implicated in the metabolism of xenobiotics, the other families are involved in the synthesis and metabolism of e.g. steroids, bile, and fatty acids. The liver is a crucial site for CYP isoenzymes, although also considerable metabolic activity has been found in the gut, kidney, and in the brain. Whereas liver and gut isoenzymes are mostly microsomal, brain isoenzymes are mostly mitochondrial. P450 mediated metabolism is associated with a limited degree of nonspecificity, i.e. one P450 isoenzyme can metabolize multiple substrates and most substrates can be metabolized by different P450 isoenzymes. However, many substrates have a high affinity for one particular P450 isoenzyme, which then becomes a major factor regulating its elimination.

CYP1A, CYP2A6, CYP2B6, CYP2C, CYP2D6, CYP2E1, and CYP3A enzymes account for approximately

70% of human liver CYP. Among these, CYP3A (CYP3A4 and CYP3A5) and CYP2C (CYP2C8, CYP2C9, CYP2C18, and CYP2C19) are the most abundant subfamilies, accounting for 30% and 20% of total CYP, respectively. Other isoforms are minor contributors to the total CYP: CYP1A2 at 13%, CYP2E1 at 7%, CYP2A6 at 4%, CYP2D6 at 2%, and CYP2B6 at 0.2% [13,14]. CYP3A participates in the metabolism of approximately 50% of all drugs, with CYP2D6 contributing to approximately 25%, CYP2C9 to approximately 15%, and CYP1A2 to approximately 5%. Therefore, these four isoforms participate in the metabolism of 95% of all drugs [15].

The activity of the major isoforms involved in drug metabolism *in vitro* can be quantified by the use of probe substrates [13,14,16,17]. Similarly, several probe drugs are suitable for the quantification of *in vivo* activity of specific isoforms [18,19]. Table (1) shows some important substrates, inhibitors, and inducers for the most important CYPs (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) with regard to drug metabolism in humans.

Genetic polymorphisms have been clearly identified in two CYP isoenzymes, CYP2C19 and CYP2D6. This genetic

**Table 1. Some Important Substrates, Inhibitors, and Inducers of the Major Human Liver Cytochrome P450 (CYP) Enzymes [13,14,16,17]**

Isoform	Drug substrate	Marker substrate/reaction	Inhibitor	Inducer
CYP1A2	Caffeine, clozapine, cyclobenzaprine, fluvoxamine, haloperidol, mexiletine, olanzapine, paracetamol, pentazocine, phenacetin, propranolol, tacrine, tamoxifen, theophylline	Caffeine N3-demethylation, 7-ethoxyresorufin O-deethylation, phenacetin O-deethylation	Ciprofloxacin, fluvoxamine, furafylline, -naphthoflavone, ofloxacin	Carbamazepine, charred food, omeprazole, rifampicine, tobacco
CYP2C9	Diclofenac, flurbiprofen, ibuprofen, losartan, phenytoin, piroxicam, (S)-warfarin, tienilic acid, tolbutamide, torasemide	Diclofenac 4-hydroxylation, tolbutamide 4-methylhydroxylation, (S)-warfarin 7-hydroxylation	Fluvastatin, sulphaphenazole	Phenobarbital, rifampicine
CYP2C19	Diazepam, (S)-mephenytoin, omeprazole, pentamidine, propranolol	(S)-mephenytoin 4'-hydroxylation	Fluconazole, fluvoxamine, omeprazole, ticlopidine	Rifampicine
CYP2D6	Bufuralol, codeine, debrisoquine, desipramine, dextromethorphan, encainide, fluoxetine, fluvoxamine, metoprolol, nortryptiline, paroxetine, perphenazine, propafenone, propranolol, risperidone, sparteine, thioridazine, timolol, venlafaxine	Bufuralol 1'-hydroxylation, debrisoquine 4-hydroxylation, dextromethorphan O-demethylation, metoprolol -hydroxylation	Fluoxetine, paroxetine, quinidine, ticlopidine	No potent inducers known
CYP2E1	Caffeine, chlorzoxazone, disulfiram, ethanol, enflurane, halothane, isoflurane, paracetamol	Aniline 4-hydroxylation, chlorzoxazone 6-hydroxylation	Disulfiram, dithiocarbamate	Chronic ethanol, isoniazid
CYP3A4	Alprazolam, alfentanil, benzphetamine, carbamazepine, cisapride, citalopram, clarithromycin, codeine, cortisol, cyclosporin, dapsone, diazepam, erythromycin, ethynylestradiol, felodipine, haloperidol, indinavir, losartan, lovastatin, midazolam, nefazodone, nifedipine, quinidine, ritonavir, saquinavir, sertraline, simvastatin, tacrolimus, taxol, testosterone, terfenadine, triazolam, zolpidem	Cyclosporin oxidation, erythromycin N-demethylation, midazolam 1' and 4'-hydroxylation, nifedipine oxidation, testosterone 6 - hydroxylation	Erythromycin, grapefruit juice, HIV protease inhibitors, itraconazole, ketoconazole, nefazodone, triacetyloleandomycin	Carbamazepine, dexamethasone, St.-Johns Wort, rifabutin, rifampicin, ritonavir

polymorphism divides the population in two sub-populations, i.e. one group of individuals with a normal catalytic function, so-called extensive metabolizers, and a group of individuals with a severely impaired catalytic capacity, so-called poor metabolizers [20]. The CYP2D6 poor metabolizer phenotype occurs at a frequency of approximately 5% to 10% in the Caucasian population. In other populations, however, the PM phenotype is considerably less frequent, only 2% in black Americans and < 1% in Orientals. The frequency of the CYP2C19 poor metabolizer phenotype in Caucasians is 2% to 5%, in Orientals a greater frequency of about 20% is observed [20].

Probe drugs can be used for phenotyping purposes to identify poor and extensive metabolizers of drugs exhibiting genetic polymorphism [18,19]. An individual can e.g. be phenotyped for CYP2D6 by the administration of a probe drug such as sparteine, debrisoquine, or dextromethorphan, followed by the collection of the urine for 8 to 12 hours. The ratio between the amount of unchanged (e.g. dextromethorphan) and the amount of metabolite formed via the pathway catalyzed by CYP2D6 (e.g. dextrorphan), excreted in the urine is a measure of the individual's CYP2D6 activity. This ratio has often been referred to as the metabolic ratio (MR) and is distributed bimodally in the Caucasian population. This phenotyping procedure is a real-time assessment of isoform specific activity. An individual's genetic capacity in enzyme specific activity can be determined by genotyping. In contrast to phenotyping, genotyping does not require the intake of a probe drug and the results are not influenced by environmental factors [20].

The clinical consequences of the PM phenotype depend upon the situation. When the parent drug is the active moiety and most of its clearance is effected by the polymorphically enzyme, PMs can experience exaggerated wanted and/or unwanted effects, with possibly toxicity as a consequence of too high parent drug concentrations. If the parent drug is a prodrug undergoing bioactivation via the polymorphically expressed enzyme, PM subjects can experience therapeutic failure. On the other hand, similar therapeutic responses are anticipated in EM and PM subjects when both parent drug and the metabolite formed by the polymorphically enzyme are equipotent with respect to pharmacological activity [21].

## 2. CYP-MEDIATED DRUG-DRUG INTERACTIONS

Multiple drug therapy is common therapeutic practice, particularly in patients with several diseases. Whenever two or more drugs are administered over similar or overlapping time periods, the possibility of drug interactions exists, at the pharmacokinetic level and/or at the pharmacodynamic level.

The ability of a single CYP isoenzyme to metabolize multiple substrates is responsible for the large number of documented drug interactions associated with CYP inhibition, because these substrates can compete for enzyme catalytic sites. Interactions with drugs exhibiting genetic polymorphism are restricted to EMs; inhibition of drug metabolism can be so extensive that the individual's metabolic capacity is impaired to such extent that he becomes a phenotypic poor metabolizer (phenocopying)

[13]. The inhibition of drug metabolism can result in undesirable elevations in plasma drug concentrations, and depending on the pharmacodynamic properties of the drug lead to exaggerated drug effects. In the case that the drug undergoes bioactivation through metabolism mediated by a specific isoform, inhibition of this isoform can lead to therapeutic failure [13]. Drug-drug interactions can also occur as a result of the induction of CYPs following drug treatment. In most cases, metabolites are pharmacologically less active than the parent compound and increased drug metabolism is expected to lead to a reduction in pharmacological response. In some cases, induction can lead to an increased production of reactive metabolites with increased toxicity as a result [13].

As pharmacokinetic interactions caused by metabolic inhibition of CYP-activity represent the majority of the interactions reported with the group of the SSRIs, this review focuses on pharmacokinetic interactions that stem from inhibition of cytochrome P450-activity.

## 3. THE SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

### 3.1 Basic Pharmacology and Therapeutic Use

Depression is believed to arise from a deficit in the availability of serotonin and/or noradrenalin. The SSRIs share a common mechanism of action in that they block the reuptake of serotonin from the synaptic junctions in the brain, hereby enhancing central serotonergic function. They have high affinity for serotonin uptake sites, low affinity for noradrenalin uptake sites, and very low affinity for neurotransmitter receptors [22].

The efficacy of the SSRIs has been established in numerous controlled double-blind studies and through vast clinical experience. Because of their high selectivity for serotonin uptake blockade, the SSRIs do not cause the unwanted blockade of peripheral and central adrenergic, cholinergic, and histaminergic receptors, that is characteristic of the tricyclic antidepressants (TCA) and the monoamine-oxidase inhibitors. As opposed to these older antidepressants, SSRIs are safe, even in overdose, and easy to handle [1,2].

Due to their aforementioned characteristics, the SSRIs are currently widely prescribed medications: over 35 million patients have been treated with SSRIs since their introduction in the mid-eighties [1].

In addition to being popular antidepressants, some SSRIs are indicated for the treatment of other disorders that are also thought to be associated with a dysfunctional state of the serotonin system, such as obsessive-compulsive [23-25], panic and anxiety disorders [26].

Although the members of this class are quite similar in terms of their neuropsychopharmacology, their efficacy, their tolerability, and their safety [1,2], they differ substantially in terms of chemical structure, pharmacokinetics, and their potential to cause drug-drug

interactions. These differences, with emphasis on the latter, will be discussed next.

### 3.2 Pharmacokinetics and Metabolism of the SSRIs

In this chapter a brief overview on the basic pharmacokinetic properties of the SSRIs is presented. For more detailed information the reader is referred to the references cited below and recent reviews on this subject [8,27-29].

Fig. (1) depicts the chemical structures of the SSRIs. Table (2), at the end of this section, summarizes the pharmacokinetic properties of the SSRIs relevant to their use.

#### 3.2.1. Citalopram

Citalopram is marketed as a racemate, but its pharmacological effect resides in the (S)-(+)-enantiomer [28]. Citalopram is administered orally and the usual effective antidepressant dose is 40 mg/day [30].

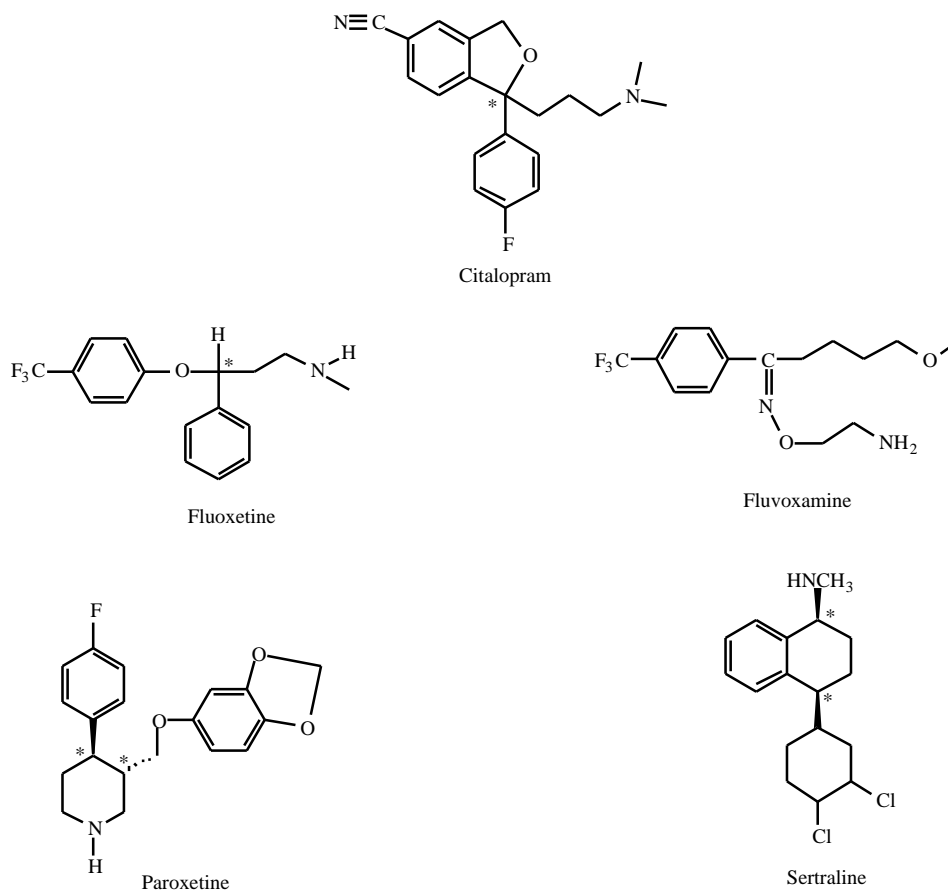
The absorption of citalopram from the gastro-intestinal tract is almost complete. With an absolute bioavailability of about 80%, first-pass metabolism seems to be of minor importance [31]. Protein binding amounts only to 80%; the volume of distribution is 14 l/kg [32]. A half-life of about 36 hours has been reported [32], with linear pharmacokinetics

over the therapeutic dose range [31], allowing steady-state to be reached after a week of treatment. Plasma concentrations of the (R)-enantiomers of citalopram and N-desmethylcitalopram are higher than those of the active (S)-enantiomers [28].

Citalopram is extensively metabolized in the liver. The main metabolic pathway in the metabolism of citalopram is N-demethylation to N-desmethylcitalopram, which is further N-demethylated to didesmethylcitalopram. An N-oxide and a propionic acid metabolite have also been identified. As plasma levels of N-desmethylcitalopram generally reach less than 50% of those of the parent compound, a meaningful contribution of this metabolite to the overall antidepressant activity is unlikely [31]. *In vitro*, formation of N-desmethylcitalopram from citalopram is dependent on both CYP2C19 and CYP3A, with a possible contribution of CYP2D6 [33-36]. Co-segregation of citalopram clearance with CYP2C19 phenotype has been described *in vivo* [37]. In addition, limited data indicates the contribution of CYP3A4 to the clearance of citalopram by accelerated metabolism of citalopram under concomitant carbamazepine treatment [38]. *In vivo* data show that further demethylation of N-desmethylcitalopram is mainly catalyzed by CYP2D6 [37].

#### 3.2.2. Fluoxetine

Fluoxetine is marketed as a racemic mixture of two active enantiomers ((S)- and (R)-fluoxetine) and is the only



**Fig. (1).** Chemical structures of the selective serotonin reuptake inhibitors. An asterisk denotes a chiral center.

SSRI that has a metabolite ((S)-norfluoxetine) with a significant contribution to the overall clinical activity [28]. Fluoxetine is administered orally and its minimal effective antidepressant dose is 20 mg/day [30].

After oral administration, fluoxetine is almost completely absorbed; oral bioavailability in humans is below 90% [29]. Fluoxetine is highly bound to plasma proteins (> 95%); it has a large volume of distribution, ranging from 14 to 100 l/kg [29,39]. Fluoxetine has a half-life ranging between 1 to 4 days, while that of its principal metabolite, norfluoxetine, ranges between 7 to 15 days. This implies that 6 to 8 weeks of treatment with fluoxetine are required to reach steady-state levels [40]. Fluoxetine exhibits non-linear kinetics as evidenced from dose-escalation studies and multiple-dose studies [40]. Under steady-state conditions, the concentrations of racemic norfluoxetine normally exceed those of racemic fluoxetine. For both fluoxetine and norfluoxetine, the plasma concentrations of the (S)-enantiomer are higher than for the (R)-enantiomer [28].

Fluoxetine undergoes extensive metabolic conversion, leading to the active metabolite norfluoxetine (major pathway), and multiple other metabolites [40]. Fluoxetine and its metabolites are excreted chiefly in the urine, with less than 10% excreted unchanged or as fluoxetine N-glucuronide [40]. The evidence is conflicting regarding the involvement of the different CYPs in the formation of norfluoxetine. *In vivo* clearance of fluoxetine co-segregates with the CYP2D6 polymorphic phenotype, suggesting that fluoxetine clearance is mediated by that isoform [41,42]. Recently, it has been shown that the clearance of (R)- and (S)-fluoxetine and that of (S)-norfluoxetine, but not that of (R)-norfluoxetine, strongly depend on CYP2D6 activity [43]. This was confirmed *in vitro* supporting a major role for CYP2D6, with an additional contribution of CYP2C9 and CYP3A4 [44]. One *in vitro* study, however, implicated CYP2C9 as the principal cytochrome involved in the N-demethylation of fluoxetine, with a possible contribution of CYP2C19 and CYP3A4 [45]. CYP2D6 involvement was found to be negligible [45,46], but these findings could be the result of the use of high substrate concentrations in these studies.

### 3.2.3. Fluvoxamine

Fluvoxamine is the only achiral SSRI. Fluvoxamine is administered orally and its usually effective antidepressant dose is 150 mg/day [30].

After oral administration, more than 90% of fluvoxamine is absorbed. Due to extensive hepatic first-pass metabolism the oral bioavailability is only about 50%. The plasma protein binding is low (77%); the volume of distribution of fluvoxamine is about 25 l/kg. Fluvoxamine exhibits non-linear kinetics in therapeutic dose range [47], with the  $t_{1/2}$  ranging between 8 and 28 hours (mean 15 hours). Steady-state is reached within a week of treatment [48].

Fluvoxamine's main route of elimination is through hepatic metabolism with only trace amounts excreted unchanged. The primary routes of metabolism are oxidative demethylation, oxidative deamination, =N-O bond cleavage, and N-acetylation. After oral intake, fluvoxamine and its

metabolites are mainly excreted in the urine. Most of these metabolites are weak acids and are unlikely to possess pharmacological activity [48].

From *in vivo* data, the disposition of fluvoxamine was found to be associated with CYP1A2 and CYP2D6 activity [49-51]. *In vitro* data are lacking.

### 3.2.4. Paroxetine

Paroxetine is a chiral SSRI but is marketed as its active (S)-enantiomer. Paroxetine is administered orally and its usually effective antidepressant dose is 20 mg/day [30].

The drug is efficiently absorbed from the gastrointestinal tract, but is readily metabolized during its first-pass through the liver, with a bioavailability of about 50% [52]. Its plasma protein binding is about 95%; the volume of distribution of paroxetine is 2 to 12 l/kg [53]. The half-life of paroxetine is variable, depending both on dose and duration of administration, indicating non-linear kinetics. At a multiple dosing regimen of 20 mg/day, the half-life is about 18 hours [53].

Paroxetine undergoes extensive metabolism with less than 1% excreted unchanged. Paroxetine's metabolism includes oxidative cleavage of the methylenedioxy bridge, resulting in an unstable catechol intermediate that is further methylated in meta-position to the meta-methoxyderivative (M1 metabolite) or in para-position to the para-methoxyderivative (M2 metabolite). Both metabolites are further conjugated with sulfuric acid or glucuronic acid. None of the metabolites is assumed to contribute to paroxetine's antidepressant activity [53]. Whereas the oxidative cleavage is probably mediated by CYP, the subsequent methylations are catalyzed by another enzyme system. The isoenzyme CYP2D6 is likely involved in the metabolism of paroxetine, as paroxetine's clearance co-segregates with the CYP2D6 phenotype *in vivo* [54,55], a finding supported by *in vitro* data [56]. CYP3A4 could also be involved in the oxidative degradation of paroxetine because co-treatment with carbamazepine, a potent CYP3A4 inducer, lowered paroxetine plasma concentrations in patients [57].

### 3.2.5. Sertraline

Sertraline is a chiral SSRI but is marketed as its active (1S,4S)-enantiomer. Sertraline is administered orally; its usually effective antidepressant dose is 50 mg/day [30]. After oral intake, it is almost completely, but rather slowly, absorbed from the gastro-intestinal tract. No data on oral availability are available in humans. This SSRI is also extensively bound to plasma proteins (> 95%); the volume of distribution in humans exceeds 20 l/kg [58]. Sertraline has a half-life of about 26 hours and linear pharmacokinetics over the therapeutic dose range have been demonstrated [59].

Hepatic metabolism is the most important elimination pathway, with less than 1% of an oral dose excreted as unchanged drug in the urine. N-demethylation is the main metabolic pathway in the biotransformation of sertraline. Desmethylsertraline is more slowly eliminated with a half-life three times longer than that of the parent drug. Hence, its plasma concentrations are usually one to three times that of

sertraline. A meaningful contribution to the overall pharmacological effect of sertraline is not expected since this metabolite has only 5 to 10% serotonin reuptake inhibitor potency of sertraline [59]. The N-demethylation rate correlates with the activity of CYP3A4 *in vivo* [60]; *in vitro* data suggest that probably at least five CYPs (CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) are involved [61,62].

#### 4. CYP-MEDIATED DRUG-DRUG INTERACTIONS WITH SSRIs

The inhibitory effect of the SSRIs on CYP activity has been extensively studied both *in vitro* and *in vivo*. *In vitro* studies primarily used human hepatic microsomes; *in vivo* most data are from formal pharmacokinetic drug-drug interaction studies in healthy volunteers, although a number of studies have also been done in patients.

The *in vitro* studies permit the determination of the potency of a drug to inhibit a specific CYP isoform. However, because the potency of the inhibitor is not the sole determinant whether and to what extent both drugs interact *in vivo*, only a formal pharmacokinetic interaction study in healthy volunteers or patients can assess the magnitude and the clinical relevance of an interaction when the two interacting drugs are combined in man.

##### 4.1. *In Vitro*

The best measure of a drug's *in vitro* potency is the  $K_i$ , or inhibition constant. This is the concentration of inhibitor resulting in a 50% decrease in metabolite formation rate. A  $K_i$  is characteristic for each particular inhibitor and enzyme, and reflects theoretically the affinity of the inhibitor for a particular enzyme. Thus, the smaller the  $K_i$  value of the inhibitor, the greater the *in vitro* potency on a molar basis. The numerical value of the  $K_i$  is model-dependent, which means that it depends on the mechanism of inhibition, e.g. competitive, non-competitive, etc.

In Table (3) the inhibitory potency of the SSRIs and some of their metabolites for specific CYP isoforms, expressed as the  $K_i$  ( $\mu\text{M}$ ), is given, based on studies using

human liver microsomes. It should be noted that several studies evaluated some metabolites of SSRIs for their inhibitory effect on the activity of particular CYPs. These metabolites can contribute to the overall inhibitory effect of a compound *in vivo*.

As can be seen from Table (3), there is a substantial variation in the  $K_i$  values of the individual SSRIs for the different metabolic reactions used to probe the activity of a particular isoform. For the SSRIs, inhibition was in most cases explained by a competitive mechanism; in a few cases inhibition was consisted with non-competitive or mixed competitive/non-competitive inhibition. In principle, when the mechanism is purely competitive,  $K_i$  values should be identical across different substrates metabolized by that particular CYP. Experimental data show that this is not always so, probably because of *in vitro* experimental artefacts [14], and because of the fact that the underlying biochemical mechanisms are not entirely competitive. Artefacts include non-specific binding to microsomes and the fact that estimates of  $K_i$  may well be influenced by the number of data points analyzed, as well as the range of substrate and inhibitor concentrations [14,86]. Because the SSRIs are highly lipophilic drugs, futile binding to *in vitro* matrices such as human liver microsomes may be substantial [87-91]. Extensive non-specific binding has already been experimentally confirmed for fluoxetine [92] and paroxetine [93].

The SSRIs were classified potent, moderate, or weak inhibitors of specific isoforms based on their  $K_i$  value:  $K_i < 1 \mu\text{M}$ : potent,  $1 < K_i < 50 \mu\text{M}$ : moderate, and  $K_i > 50 \mu\text{M}$ : weak inhibitor.

##### • CYP1A2

The data sources clearly indicate that, among the SSRI studied, fluvoxamine is a potent inhibitor of this isoform. The other SSRIs have only a weak capacity to inhibit CYP1A2 *in vitro* [63-66].

##### • CYP2C9

Fluvoxamine is also a moderate inhibitor of CYP2C9-mediated metabolism *in vitro* [67,68]. One study demonstrated that certain other SSRIs, e.g. fluoxetine, had

**Table 2. Pharmacokinetic Properties of the Selective Serotonin Reuptake Inhibitors Relevant to Their Use**

Parameter [Ref]	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
Clinically relevant metabolites in terms of serotonin reuptake inhibition [28,31,48,53,59]	No	Norfluoxetine	No	No	No
Half-life (days) <sup>†</sup> [32,40,48,53,59]	1.5	2 to 4* (7 to 15)	0.5	1*	1
Time to steady-state (days) [32,40,48,53,59]	6 to 7	30 to 60*	3 to 5	4 to 5*	4 to 5
Linear pharmacokinetics [31,40,47,53,59]	Yes	No	No	No	Yes
Usual effective antidepressant dose (mg) [30]	40	20	150	20	50

<sup>†</sup>, when chronically given

\*, at their usually effective antidepressant dose

**Table 3. Inhibitory Potency of the SSRIs and their Metabolites for Specific CYP Isoforms, Expressed as the  $K_i$  ( $\mu\text{M}$ ), Based on In Vitro Studies Using Human Liver Microsomes**

Isoform	Substrate [Ref]	Reaction	Citalopram/ desmethylcitalopram	Fluoxetine/ norfluoxetine	Fluvoxamine	Paroxetine/ M2	Sertraline/ desmethylsertraline	
<b>CYP1A2</b>	Caffeine [63]	N3-Demethylation	> 100/NA	> 100/NA	0.08	> 100/NA	NA	
	Phenacetin [64]	O-Deethylation	> 100/> 100	> 100/> 100	0.2	45/NA	70/NA	
	Phenacetin [65]	O-Deethylation	NA	4.4/15.9	0.24	5.5/NA	8.8/9.5	
	Theophylline [66]	N1-Demethylation	> 100/> 100	> 100/> 100	0.2	50/NA	> 100/NA	
	Theophylline [66]	N3-Demethylation	> 100/> 100	> 100/> 100	0.2	50/NA	90/NA	
<b>CYP2C9</b>	Phenytoin [67]	p-Hydroxylation	NA	19/17	6.0	35/NA	33/66	
	Tolbutamide [68]	4-Methylhydroxylation	> 100/> 100	> 100/> 100	13.3	> 100/NA	> 100/> 30	
	(S)-Warfarin [68]	7-Hydroxylation	> 100/> 100	87/> 100	13.0	> 100/NA	> 100/> 30	
<b>CYP2C19</b>	(S)-Mephenytoin [69]	4'-Hydroxylation	87.3/55.8	5.2/1.1	NA	7.5/NA	2.0/NA	
	Proguanil [70]	Cycloguanil formation	> 100/NA	50/7.3	0.7	92/NA	40/NA	
<b>CYP2D6</b>	Clomipramine [71]	8-Hydroxylation	NA	0.24/0.33	1.3	0.86/NA	27/NA	
	Desipramine [72]	2-Hydroxylation	NA	3.0/3.5	16.6	2.0/NA	22.7/16.0	
	Desmethylclomipramine [71]	8-hydroxylation	NA	0.53/0.61	6.8	1.5/NA	16/NA	
	Dextromethorphan [73]	O-Demethylation	NA	0.15/0.19	1.8	0.07/NA	1.2/NA	
	Imipramine [74]	2-Hydroxylation	NA	1.6/NA	8.0	3.2/NA	24.7/NA	
	Imipramine [75]	2-Hydroxylation	19/1.3	0.92/0.33	3.9	0.36/NA	NA	
	Metoprolol [76]	-Hydroxylation	61/21	1.2/1.1	14	1.1/NA	19.5/21	
	Metoprolol [76]	O-Demethylation	27/26.5	1.4/1.4	13	1.35/NA	13.5/26.5	
	Oxycodone [77]	O-Demethylation	7/6	0.17/0.19	1.8	NA	1.5/NA	
	Propafenone [78]	5-Hydroxylation	NA	0.33/0.55	NA	0.54/NA	NA	
	Sparteine [79]	Hydroxylation	5.1/NA	0.60/0.43	8.2	0.15/0.50	0.70/NA	
	Venlafaxine [80]	O-Demethylation	NA	0.39/0.40	1.45	0.17/NA	1.15/4.32	
	<b>CYP3A4</b>	Alprazolam [72]	-Hydroxylation	NA	47.2/8.8	8.2	36.7/NA	159/56
		Alprazolam [72]	4-Hydroxylation	NA	83.3/11.1	10.2	39.4/NA	23.8/20.4
Midazolam [81]		-Hydroxylation	NA	65.7/19.1	NA	NA	64.4/48.1	
Midazolam [82]		-Hydroxylation	NA	11.5/1.44	NA	NA	NA	
Midazolam [82]		4-Hydroxylation	NA	67.3/17.0	NA	NA	NA	
Terfenadine [83]		N-Dealkylation	NA	30.0/2.2	17.6	15.8/NA	4.7/1.4	
Terfenadine [83]		Hydroxylation	NA	65.6/13.0	50.8	55.6/NA	30.1/7.5	
Terfenadine [84]		N-Dealkylation	NA	68/NA	NA	NA	10.0/NA	
Terfenadine [84]		Hydroxylation	NA	310/NA	NA	NA	67/NA	
Triazolam [85]		-Hydroxylation	NA	7.1/2.7	5.6	3.8/NA	3.5/3.5	
Triazolam [85]	4-Hydroxylation	NA	44.3/8.0	20.2	14.3/NA	20.3/10.7		

$K_i$ , inhibition constant, the smaller the value, the greater the potency on a molar basis; NA, data not available.

also some effect on CYP2C9 [67]. The other SSRIs have a weak CYP2C9 inhibitory capacity.

An explanation for the apparent discrepancy between the moderate effect of fluoxetine on phenytoin p-hydroxylation

[67], and its much smaller inhibitory effect on the 4-methylhydroxylation of tolbutamide or the 7-hydroxylation of (S)-warfarin [68], could be inhibition of the CYP2C19 component of phenytoin p-hydroxylation [94]. In addition, in this study it was demonstrated that the (R)-enantiomer of

fluoxetine is about five-fold more potent in inhibiting the p-hydroxylation of phenytoin than its (S)-enantiomer [67].

- **CYP2C19**

Fluvoxamine is also a potent inhibitor of CYP2C19 activity. Other SSRIs have moderate to weak effect on CYP2C19 activity, depending on the study [69,70].

- **CYP2D6**

Fluoxetine, its metabolite norfluoxetine, and paroxetine are potent inhibitors of CYP2D6 activity. The inhibitory potency of sertraline, desmethylsertraline, citalopram, desmethylcitalopram, and fluvoxamine is nearly an order of a magnitude lower [71-79]. Only one study found a similar CYP2D6 inhibitory potency of sertraline as compared to fluoxetine and paroxetine [79].

Stereoselective inhibition of CYP2D6-mediated metabolism by SSRIs is relatively unexplored. Paroxetine was reported to have similar  $K_i$ -values for inhibition of the 5-hydroxylation of the individual propafenone enantiomers, suggesting no stereoselective effect [78]. Paroxetine's inhibitory effect has also been studied on the oxidative metabolism of the metoprolol enantiomers using human liver microsomes [93]. Whereas no stereoselective inhibition by paroxetine was seen for the  $\beta$ -hydroxylation, a trend towards stereoselective inhibition of the metoprolol O-demethylation was observed: paroxetine preferentially inhibited the O-demethylation of the (R)-enantiomer.

Two studies also tested the individual enantiomers of fluoxetine and norfluoxetine for their inhibitory effect on CYP2D6 activity *in vitro*. Both studies showed that the (S)-enantiomers were an order of a magnitude more potent than their corresponding (R)-enantiomers [46,95].

Recently, we have demonstrated that paroxetine, but none of the other SSRIs, causes a pre-incubation time dependent loss of CYP2D6 activity in NADPH-supplemented human liver microsomes, the hallmark of mechanism-based inhibition (unpublished observations). Among the SSRIs, paroxetine is the only compound with a methylenedioxyphenyl nucleus. This structure has been well documented to inactivate CYP-activity, through metabolic intermediate complex (MIC) formation [96,97].

- **CYP3A4**

Norfluoxetine and fluvoxamine are moderate inhibitors of CYP3A4, whereas the other SSRIs are moderate to weak inhibitors [72,81-85].

Mayhem *et al.* have demonstrated that fluoxetine, a secondary amine, mechanistically inactivates CYP3A4 through MIC formation. None of the other SSRIs were tested in this study [98].

- **CYP2E1**

Only citalopram and desmethylcitalopram have been evaluated for their inhibitory effect on CYP2E1 activity *in*

*vitro* and were found to be weak inhibitors of this isoform [35].

Despite the substantial variation in the experimental data of the different *in vitro* studies, the overall rank order of the various SSRIs for inhibition of the particular isoforms is rather well maintained.

*Summary points:* The *in vitro* data indicate that fluvoxamine is a potent CYP1A2 and CYP2C19 inhibitor, and a moderate CYP2C9, CYP2D6, and CYP3A4 inhibitor. Fluoxetine and paroxetine are potent CYP2D6 inhibitors, whereas fluoxetine's main metabolite, norfluoxetine, has a moderate inhibitory effect on CYP3A4. Sertraline is moderate CYP2D6 inhibitor whereas citalopram has little effect on the major CYP isoforms.

Recent data indicates that paroxetine and fluoxetine inactivate CYP2D6 and CYP3A4, respectively, through mechanism-based inhibition.

#### 4.2. *In Vivo*

The *in vivo* extent of a metabolic drug-drug interaction is not only dependent on the potency of the metabolic inhibitor, as reflected by the  $K_i$  value, but also on the concentration of the inhibitor at the enzyme *in vivo*. In addition, the fraction of the drugs clearance affected by the metabolic inhibitor needs to represent a major contribution to its overall clearance. The individual's inherent enzyme activity will also be of importance for the extent of interaction *in vivo*, because in general, subjects with the highest baseline metabolic activity often display the largest inhibitory effects. Interactions for CYP2D6 and CYP2C19 are also phenotype dependent, since they are restricted to extensive metabolizers. Therefore, only a formal pharmacokinetic interaction study in humans can assess the magnitude of interaction. All SSRIs, with the possible exception of fluvoxamine, have metabolites that inhibit various CYP isoforms *in vitro*, with, in some cases, a potency similar or greater than that of the parent compound. However, only fluoxetine produces a metabolite (norfluoxetine) that reaches sufficiently high plasma and tissue concentrations to contribute to CYP inhibition *in vivo*. By virtue of its long half-life, it requires in general about one month to reach steady-state concentrations for fluoxetine and its N-demethylated metabolite. This also implicates that drug-drug interactions mediated by this metabolite can persist for weeks after fluoxetine discontinuation.

Tables (4) to (8) contain the available data on the effect of the SSRIs on specific CYP isoforms *in vivo*, as determined by substrates whose clearance is chiefly dependent on metabolism by one particular CYP. The remaining studies have been summarized in Table (9). In these tables, only formal pharmacokinetic studies in healthy volunteers or patients in which the SSRIs were multiple-dosed, have been compiled. Case reports were not considered, as the extent of interaction may be confounded by problems such as compliance and concomitant medications. Steady-state conditions for the SSRI were almost always reached, except for some studies with

fluoxetine because of the long half-life of fluoxetine and norfluoxetine. In an effort to overcome this problem several studies have employed a loading dose strategy, e.g. fluoxetine 60 mg/day for 8 days, to achieve fluoxetine and norfluoxetine concentrations comparable to those attained at 20 mg/day in steady-state. Nevertheless, using such loading dose approach, fluoxetine's inhibitory effect is most likely somewhat underestimated as norfluoxetine concentrations probably did not reach steady-state. The attainment of steady-state fluoxetine and norfluoxetine concentrations is of particular importance for the effect of fluoxetine towards CYP2D6 and CYP3A4 activity because norfluoxetine is equipotent to fluoxetine in inhibiting CYP2D6 activity, and substantially more potent than fluoxetine in inhibiting CYP3A4.

Two different dosing strategies have been used with regard to the administration of the substrate. In the single dose approach the substrate is administered once without and once with the SSRI at steady-state. In the multiple-dose approach, the substrate is administered sufficiently long enough so that its steady-state is achieved, prior to the addition of the SSRI. The majority of the interaction studies listed in Tables (4) to (9) have been performed with a single dose of the substrate, because a multiple-dose strategy is more time-consuming, more expensive, and, in some cases, presents serious risks. This latter approach, however, more closely imitates clinical practice than does the single dose approach. All drugs mentioned in these tables were given orally, unless otherwise stated.

Only a minority of the studies assessed possible changes in pharmacodynamics associated with changes in pharmacokinetics. This is, however, important for the determination of the clinical relevance of the interaction.

Furthermore, it is important to compare the effects of the various SSRI on different CYP isoforms at their recommended antidepressant dose, as this dose is optimal for most patients. Some patients, however, require higher doses. As the SSRI inhibit CYP-activity in a concentration-dependent manner [8], this is especially important for the SSRI that display non-linear pharmacokinetics (fluoxetine, fluvoxamine, and paroxetine) where an increase in dose will result in a disproportionate increase in plasma concentrations.

The inhibitory effect of the SSRI *in vivo* was considered to be substantial, moderate, mild, or having no effect based on the percentage change in AUC at the usual effective antidepressant dose: substantial (> 150% change), moderate (50 – 150% change), mild (< 50% change), and no effect (0% change) [8].

• **CYP1A2 (Table (4))**

Neither citalopram nor fluoxetine have been adequately tested for their inhibitory effect on CYP1A2 activity *in vivo*.

Treatment with fluvoxamine, under steady-state conditions, has been shown to substantially elevate the plasma concentrations of tacrine [99,102]. Similarly, concomitant administration of fluvoxamine markedly increased the plasma levels of caffeine [101] and theophylline [103]. The inhibitory effect of several SSRI on CYP1A2 *in vivo* has also been assessed using the urinary caffeine metabolic ratio (CMR), at present the most reliable caffeine-based urinary index of CYP1A2 activity [19]. In three studies a significant decrease in CMR after administration of fluvoxamine was observed [100,101,104].

**Table 4. Summary of Formal Pharmacokinetic Interaction Studies Between SSRI and CYP1A2 Substrates**

SSRI	SSRI treatment	Substrate [Ref]	(n)	Substrate dosing	Change in AUC*	Change in MR*	Change in PD
<b>Citalopram</b>	NA						
<b>Fluoxetine</b>	NA						
<b>Fluvoxamine</b>	50 mg/day for 5 days	Tacrine [99]	(9)	Single dose	614%		NA
	100 mg/day for > 5 days	Caffeine [100]	(8)	Single dose		47% (1)	NA
	100 mg/day for 8 days	Caffeine [101]	(8)	Single dose	410%	36% (1)	NA
	100 mg/day for 5 days	Tacrine [99]	(9)	Single dose	567%		NA
	100 mg/day for 6 days	Tacrine [102]	(13)	Single dose	730%		NA
	100 mg/day for 5 days	Theophylline [103]	(12)	Single dose	233%		NA
	150 mg/day for 28 days	Caffeine [104]	(20)	Single dose		44% (1)	NA
<b>Paroxetine</b>	20 mg/day for > 5 days	Caffeine [100]	(13)	Single dose		0% (1)	NA
<b>Sertraline</b>	94 mg/day for >5 days	Caffeine [105]	(20)	Single dose		0% (1)	NA

\*, calculated as  $(AUC_{SSRI} - AUC_{baseline}) / AUC_{baseline} \times 100$  or  $(MR_{SSRI} - MR_{baseline}) / MR_{baseline} \times 100$ ;

NA, not available;

(1), caffeine metabolic urinary ratio = [5-acetyl-amino-6-formyl-amino-3-methyluracil+1-methylxanthine+1-methylurate]/1,7-methylurate (CYP1A2)

In contrast, neither paroxetine nor sertraline intake under steady-state dosing conditions, significantly altered the CMR, indicating that they have little effect on CYP1A2 *in vivo* [100,105].

**Summary points:** In agreement with the *in vitro* results, fluvoxamine is a potent inhibitor of CYP1A2 activity *in vivo*. Paroxetine and sertraline have no effect on this isoform *in vivo*. Although there are no formal *in vivo* studies on the effect of citalopram and fluoxetine on CYP1A2 activity, these SSRIs are expected to produce only a minimal inhibitory effect towards this isoform, based on their low *in vitro* potency.

- **CYP2C9 (Table (5))**

Citalopram administration did not affect the plasma levels of both warfarin enantiomers [106]. Whereas the clearance of the pharmacologically active (S)-enantiomer is mainly dependent on CYP2C9 activity, the (R)-enantiomer is metabolized by several isoforms including CYP1A2 and CYP3A4. The results of this study therefore suggest a negligible effect of citalopram on CYP2C9 activity.

Coadministration of fluoxetine 30 mg/day for 8 days, which is an inappropriate loading dose strategy, did not significantly alter tolbutamide plasma concentrations [107]. It has also been shown that fluoxetine 20 mg/day, at steady-state, did not affect the hypoprothrombinemic response of warfarin in patients chronically anticoagulated, suggesting that fluoxetine's effect on CYP2C9 is negligible [114].

Low-dose fluvoxamine (50 mg/day) resulted in a 65% increase in racemic warfarin plasma concentrations, associated with a prolongation of prothrombin time [108]. This suggests elevated plasma levels of (S)-warfarin, which may in turn be explained by inhibition of CYP2C9. A recent

paper reported a mild increase in tolbutamide plasma levels after treatment with fluvoxamine [109].

The effect of paroxetine intake on CYP2C9 activity *in vivo* has been investigated in three studies. Two studies demonstrated paroxetine's lack of effect on the pharmacokinetics of phenytoin [53,110], whereas a third showed no effect of paroxetine on the plasma concentrations of racemic warfarin [111].

Sertraline's effect on CYP2C9 activity has only been studied at its maximum recommended antidepressant dose, i.e. 200 mg/day. One study indicated that sertraline did not affect the clearance of phenytoin [112], whereas another showed a mild increase in plasma tolbutamide concentrations [113]. In addition, a slight increase in prothrombin time and unbound warfarin concentrations was observed after 26 days of treatment with sertraline 200 mg/day [115]. As these changes were considered to be clinically insignificant, these data confirm the notion that sertraline appears to have little effect on the CYP2C9 enzyme, even at its maximum recommended antidepressant dose.

**Summary points:** The evidence presented here indicates that fluvoxamine has a mild to moderate inhibitory effect on CYP2C9 *in vivo*. The other SSRIs appear to have little effect on CYP2C9 function.

- **CYP2C19 (Table (6))**

The effect of SSRIs on CYP2C19 *in vivo* has been studied using diazepam and (S)-mephenytoin as substrates. Because both CYP2C19 and CYP3A4 contribute to the clearance of diazepam, this drug is not an ideal substrate for CYP2C19. Nevertheless, diazepam may be useful to explore the effect of SSRI treatment on CYP2C19 since this isoform is mainly responsible for the clearance of diazepam at low diazepam

**Table 5. Summary of Formal Pharmacokinetic Interaction Studies Between SSRIs and CYP2C9 Substrates**

SSRI	SSRI treatment	Substrate [Ref]	(n)	Substrate dosing	Change in AUC*	Change in PD
<b>Citalopram</b>	40 mg/day for 21 days	Warfarin [106]	(12)	Single dose	(R): 0%; (S): 0%	
<b>Fluoxetine</b>	30 mg/day for 8 days†#	Tolbutamide [107]	(NA)	Single dose	4%	
<b>Fluvoxamine</b>	50 mg/day for 14 days	Warfarin [108]	(NA)	Chronic	65%	
	75 mg/day for 5 days	Tolbutamide [109]	(7)	Single dose	23%	NA
	150 mg/day for 5 days	Tolbutamide [109]	(7)	Single dose	49%	NA
<b>Paroxetine</b>	30 mg/day for 14 days	Phenytoin [53]	(12)	Single dose	0%	NA
	30 mg/day for 10 days	Phenytoin [110]	(6)	Chronic	0%	NA
	30 mg/day for 28 days	Warfarin [111]	(14)	14 Days	0%	
<b>Sertraline</b>	200 mg/day for 10 days	Phenytoin [112]	(14)	10 Days	0%	
	200 mg/day for 28 days	Tolbutamide [113]	(11)	Single dose	19%	NA

\*, calculated as  $(AUC_{SSRI} - AUC_{baseline}) / AUC_{baseline} \times 100$ ;

NA, not available;

†, loading dose strategy to achieve (nor)fluoxetine concentrations comparable to those at 20 mg/day in steady-state;

#, steady-state not reached

**Table 6. Summary of Formal Pharmacokinetic Interaction Studies Between SSRIs and CYP2C19 Substrates**

SSRI	SSRI treatment	Substrate [Ref]	(n)	Substrate dosing	Change in AUC*	Change in MR*	EMs to PMs	Change in PD
<b>Citalopram</b>	40 mg/day for 10 days	Mephenytoin [37]	(18)	Single dose		0% (1)	0%	NA
<b>Fluoxetine</b>	30 mg/day for 7 days†#	Diazepam [107]	(NA)	Single dose	0%			NA
	60 mg/day for 8 days†	Diazepam [116]	(6)	Single dose	50%			
<b>Fluvoxamine</b>	100 mg/day for 14 days	Mephenytoin [117]	(8)	Single dose		244% (1)	0%	NA
	106 ± 32 mg/day for 16 days	Diazepam [118]	(8)	Single dose (IV)	316%			NA
<b>Paroxetine</b>	NA							
<b>Sertraline</b>	200 mg/day for 21 days	Diazepam [119]	(20)	Single dose	15%			NA

\*, calculated as  $(AUC_{SSRI}-AUC_{baseline})/AUC_{baseline} \times 100$  or  $(MR_{SSRI}-MR_{baseline})/MR_{baseline} \times 100$ ;

NA, not available;

†, loading dose strategy to achieve (nor)fluoxetine concentrations comparable to those at 20 mg/day in steady-state;

#, steady-state not reached;

IV, intravenous administration;

(1), (S)/(R)-mephenytoin urinary ratio (CYP2C19)

concentrations. The four studies in which the inhibitory effect of an SSRI was studied on the pharmacokinetics of diazepam, all employed a low diazepam dose (10 mg), suggesting that CYP2C19 was largely responsible for its clearance [107,116,118,119].

Fluoxetine did not alter the pharmacokinetics of diazepam after only 7 days of treatment with fluoxetine 30 mg/day [107]. In this study, the combined fluoxetine and norfluoxetine levels were expected to be less than 50% of those encountered at steady-state on 20 mg/day. In another fluoxetine-diazepam interaction study, fluoxetine increased plasma diazepam levels by 50%, when fluoxetine was given at 60 mg/day for 8 days [116].

In contrast, diazepam plasma levels were significantly more elevated (316%) after fluvoxamine administration on 100 mg/day [118].

On the other hand, sertraline, at a dose of 200 mg/day and under steady-state conditions, produced only a small net increase of 15% in the AUC of diazepam relative to placebo [119].

The effect of citalopram and fluvoxamine on CYP2C19 has been evaluated using the (S)/(R)-mephenytoin urinary excretion ratio, an established CYP2C19 phenotyping measure [18,19]. Whereas citalopram did not alter the urinary (S)/(R) mephenytoin ratio [37], fluvoxamine produced a marked increase in this ratio [117]. In spite of this, none of the eight extensive metabolizers of CYP2C19 was converted to a phenotypic poor metabolizer after fluvoxamine intake [117].

Paroxetine has not been adequately tested for its effect on CYP2C19 activity *in vivo*.

**Summary points:** At their usual effective antidepressant dose, fluvoxamine is an effective inhibitor of CYP2C19 *in vivo*, whereas fluoxetine appears to exert a milder effect on

this isoform. Sertraline is expected to have little effect on CYP2C19 when dosed at its minimal effective antidepressant dose of 50 mg/day. Similarly, citalopram, at its usual antidepressant dose, has no effect on CYP2C19 *in vivo*. Because of the absence of studies, no comment can be made about the potential effect of paroxetine on CYP2C19.

• **CYP2D6 (Table (7))**

Of all the CYP enzymes, CYP2D6 has been most thoroughly studied with respect to the inhibitory effects of the SSRIs on its functional activity.

With the exception of imipramine, amitriptyline, trazodone, and nefazodone (see also Table (9)), all substrates listed in this table undergo clearance mainly by metabolism via CYP2D6. Their respective metabolites (desipramine, nortriptyline, and meta-chlorophenylpiperazine (m-CCP)), however, display CYP2D6 dependent metabolism.

The effect of citalopram (40 mg/day) was investigated on the pharmacokinetics of imipramine and its main metabolite desipramine, after imipramine intake. Whereas no significant effect was seen on the disposition of imipramine, a mild increase in desipramine plasma concentrations was found [120]. Neither perphenazine nor zuclopentixol plasma levels were altered by citalopram treatment [121].

Fluoxetine (20 mg/day) produced a 50% increase in the plasma concentrations of both propafenone enantiomers after 10 days of treatment with this SSRI [122]. The extent of the interaction was, however, most likely substantially underestimated because steady-state was not reached. In addition, a stereoselective effect of fluoxetine on the disposition of propafenone was suggested as the peak levels of (R)-propafenone were increased more than those of (S)-propafenone. Two studies investigated the effect of fluoxetine on the plasma levels of desipramine, under dosing conditions that would have approximated steady-state fluoxetine and norfluoxetine concentrations on fluoxetine

**Table 7. Summary of Formal Pharmacokinetic Interaction Studies Between SSRIs and CYP2D6 Substrates**

SSRI	SSRI treatment	Substrate [Ref]	(n)	Substrate dosing	Change in AUC*	Change in MR*	EMs to PMs	Change in PD
<b>Citalopram</b>	40 mg/day for 10 days	Imipramine [120]	(8)	Single dose	(IMI 0%)			NA
					DMI 47%			
	40 mg/day for 11 weeks	Perphenazine [121]	(4)	Chronic	0%			NA
	40 mg/day for 10 days	Sparteine [37]	(16)	Single dose		161% (1)	0%	NA
	40 mg/day for 11 weeks	Zuclopentixol [121]	(11)	Chronic	0%			NA
<b>Fluoxetine</b>	20 mg/day for 10 days#	Propafenone [122]	(9)	Single dose	(R): 50%; (S): 51%	185% (2)	0%	
	20 mg/day for > 3 weeks	Amitriptyline [123]	(15)	Chronic	(AMI 80%) NOR 820%			NA
	20 mg/day for 21 days	Desipramine [124]	(9)	21 Days	380%			NA
	20 mg/day for > 28 days	Dextromethorphan [125]	(10)	Single dose		493% (2)	10%	NA
	60 mg/day for 8 days†#	Desipramine [126]	(6)	Single dose	640%			NA
	60 mg/day for 8 days†#	Dextromethorphan [127]	(8)	Single dose		3484% (2)	63%	NA
	60 mg/day for 8 days†#	Dextromethorphan [128]	(12)	Single dose		2530% (2)	42%	NA
	60 mg/day for 8 days†#	Imipramine [126]	(6)	Single dose	(IMI 235%) DMI 430%			NA
	80 mg/day for 14 days†#	Nefazodone [129]	(6)	7 Days	(NF 0%) m-CPP 300%			
	20 mg/day for 27 days	Tolterodine [130]	(9)	2.5 Days	560%			NA
	20 mg/day for 28 days	Trazodone [131]	(11)	28 Days	(TR 65%) m-CPP 820% ( 270%) ¶			
	37 ± 17 mg/day for 21 days	Dextromethorphan [77]	(19)				95% (2)	NA
	<b>Fluvoxamine</b>	100 mg/day for 10 days	Desipramine [132]	(6)	Single dose	14%		
100 mg/day for > 5 days		Dextromethorphan [100]	(8)	Single dose		0% (2)	0%	NA
100 mg/day for 8 days		Dextromethorphan [127]	(8)	Single dose		6% (2)	0%	NA
100 mg/day for 14 days		Metoprolol [117]	(8)	Single dose		0% (3)	0%	NA
150 mg/day for 28 days		Dextromethorphan [104]	(20)	Single dose		123% (2)	0%	NA
<b>Paroxetine</b>	20 mg/day for 14 days	Amitriptyline [133]	(9)	Chronic	(AMI 58%) NOR 143%			NA
	20 mg/day for 8 days	Desipramine [134]	(9)	Single dose	363%			NA
	20 mg/day for 9 days	Desipramine [135]	(17)	9 Days	421%			NA
	20 mg/day for > 5 days	Dextromethorphan [100]	(13)	Single dose		1312% (2)	0%	NA
	20 mg/day for 8 days	Dextromethorphan [127]	(8)	Single dose		3943% (2)	50%	NA
	20 mg/day for 8 days	Dextromethorphan [128]	(12)	Single dose		5054% (2)	83%	NA
	20 mg/day for 7 days	Dextromethorphan [136]	(10)	Single dose		697% (2)	40%	NA
	20 mg/day for 14 days	Imipramine [133]	(5)	Chronic	(IMI 34%) DMI 233%			NA

(Table 7) contd....

SSRI	SSRI treatment	Substrate [Ref]	(n)	Substrate dosing	Change in AUC*	Change in MR*	EMs to PMs	Change in PD
	20 mg/day for 7 days	Metoprolol [137]	(8)	Single dose	(R): 693%; (S): 408%	3247% (3)	12.5%	
	20 mg/day for 10 days	Perphenazine [138]	(8)	Single dose	595%			NA
	30 mg/day for 4 days#	Imipramine [139]	(9)	Single dose	(IMI 74%) DMI 327%			NA
	30 mg/day for 14 days	Sparteine [54]	(9)	Single dose			22% (1)	NA
<b>Sertraline</b>	50 mg/day for 21 days	Desipramine [124]	(9)	21 Days	23%			NA
	50 mg/day for 9 days	Desipramine [135]	(17)	9 Days	37%			NA
	50 mg/day for 7 days	Imipramine [140]	(4)	7 Days	(IMI 0%) DMI 0%			
	50 mg/day for > 5 days	Nortryptiline [141]	(13)	Chronic	4%			NA
	94 ± 26 mg/day for > 5 days	Dextromethorphan [105]	(9)	Single dose		6% (2)	0%	NA
	100 mg/day for 8 days	Dextromethorphan [127]	(7)	Single dose		28% (2)	0%	NA
	100 mg/day for 8 days	Dextromethorphan [128]	(12)	Single dose		60% (2)	0%	NA
	108 ± 49 mg/day for 21 days	Dextromethorphan [142]	(6)	Single dose		56% (2)	0%	NA
	150 mg/day for 8 days	Desipramine [143]	(6)	Single dose	54%			NA
	150 mg/day for 29 days	Desipramine [144]	(13)	Single dose	70%			NA

\*. calculated as  $(AUC_{SSRI} - AUC_{baseline}) / AUC_{baseline} \times 100$  or  $(MR_{SSRI} - MR_{baseline}) / MR_{baseline} \times 100$ ;

NA, not available; AMI, amitriptyline; DMI, desipramine; IMI, imipramine; m-CPP, meta-chlorophenylpiperazine; NF, nefazodone; NOR, nortryptiline; TR, trazodone;

†, loading dose strategy to achieve (nor)fluoxetine concentrations comparable to those at 20 mg/day in steady-state;

#, steady-state not reached;

(1), sparteine/2- + 5-dehydrosparteine urinary ratio (CYP2D6);

(2), dextromethorphan/dextrorphan urinary ratio (CYP2D6);

(3), metoprolol/ -hydroxymetoprolol urinary ratio (CYP2D6);

¶, if the highest two increases are excluded, the average was 270 %

20 mg/day. Both studies demonstrated that treatment with fluoxetine substantially increased the plasma levels of desipramine (380% and 640%) [124,126]. The latter study also reported a similar increase in desipramine plasma concentrations when imipramine was given after fluoxetine treatment [126]. In another study, the plasma concentrations of amitriptyline's active metabolite, nortryptiline, were markedly elevated when amitriptyline was given with fluoxetine [123]. Coadministration of nefazodone or trazodone with fluoxetine increased the plasma concentrations of m-CCP, an active metabolite, by an average of 430% and 820%, respectively [129,131]. Co-therapy of tolterodine and fluoxetine produced a more than six-fold increase in tolterodine plasma levels [130].

Fluvoxamine, 100 mg/day, caused only a small increase in desipramine plasma concentrations [132].

Paroxetine (20 mg/day), like fluoxetine, markedly elevated desipramine plasma levels four- to five-fold [134,135]. Similarly, desipramine plasma concentrations were increased three- to four-fold in two other studies when

imipramine was given after paroxetine intake [133,139]. As 4 days of paroxetine 30 mg/day employed in the study by Alberts et al. [139] would have resulted in paroxetine concentrations comparable to those achieved on 20 mg/day at steady-state [133], both studies evaluated essentially the same effect. Paroxetine treatment (20 mg/day) resulted in an eightfold and fivefold increase in mean AUC of (R)-metoprolol and (S)-metoprolol (the active enantiomer), respectively [137]. Paroxetine coadministration also abolished the stereoselectivity in metoprolol pharmacokinetics. These findings are in line with *in vitro* data from human liver microsomes that showed a stereoselective inhibition of the metoprolol O-demethylation, metoprolol's major metabolic pathway, by this SSRI. Paroxetine preferentially inhibited (R)-metoprolol O-demethylation. In another study it was demonstrated that paroxetine increased perphenazine plasma levels to a similar extent [138].

Sertraline's effect on the pharmacokinetics of desipramine has been evaluated in the three separate studies in which sertraline was dosed at its usually effective

antidepressant dose under steady-state conditions [124,135,140]. A mild increase in desipramine plasma concentrations was found after desipramine intake and no change in desipramine levels was seen after imipramine intake [124,135,140]. In addition, sertraline had no effect on nortriptyline plasma concentrations [141]. Sertraline is the only SSRI that has been extensively tested above its usual effective antidepressant dose with respect to its inhibitory effect on CYP2D6 *in vivo*. At 150 mg/day, which is three times its usual therapeutic dose, sertraline only mildly increased desipramine concentrations by 54% to 70% [143,144].

The inhibitory effects of the SSRIs on CYP2D6 status *in vivo* have also been studied by evaluating their effect on metabolic ratios (MR) such as the dextromethorphan/dextrorphan, the metoprolol/-hydroxymetoprolol, and the sparteine/dehydrosparteine urinary excretion ratio. At their usually effective antidepressant dose and at steady-state, both fluoxetine and paroxetine significantly increased the CYP2D6 metabolic ratios, indicating potent inhibition of CYP2D6-activity *in vivo* [100,125,127,128,136,137]. Sertraline's effect on the dextromethorphan MR has been studied in four different studies. At twice its usual antidepressant dose, sertraline only modestly inhibited CYP2D6 function [105,127,128,142]. Both citalopram and fluvoxamine increased the MR mildly, a finding in line with the mild increases in AUC of CYP2D6 substrates [37,100,104,117,127].

Another way of evaluating the relative effects of the SSRIs on CYP2D6 activity *in vivo*, is calculating what percentage of the phenotypic CYP2D6 EMs are converted to phenotypic PMs. At their usual therapeutic dose, fluoxetine and paroxetine are able to convert a substantial proportion of the EMs to PMs, whereas fluvoxamine (150 mg/day) and sertraline (100 mg/day) produce no conversions. However, it is of interest to note that the percentage conversions seen after fluoxetine or paroxetine intake is highly variable: e.g. 10% to 95% for fluoxetine (see Table (7)). This may be related to the baseline activity of the study population: EM subjects with a lower baseline CYP2D6-activity are more likely to be converted to phenocopies of PMs.

*Summary points:* The results of the *in vivo* studies show that fluoxetine and paroxetine, at their usual effective antidepressant dose, substantially inhibit CYP2D6 *in vivo*. Sertraline has a more modest effect, even at dosages of 150 mg/day. Although citalopram and fluvoxamine have been less extensively studied, they appear to have only a mild to no effect.

- **CYP3A4 (Table (8))**

No data on the effect of citalopram are available with respect to this isoform.

In two studies, the effect of fluoxetine on the pharmacokinetics of alprazolam was studied. In the first study, in which a fluoxetine loading dose strategy of 40 mg/day for 7 days was used, combined fluoxetine and norfluoxetine concentrations were about 75% of those typically encountered under steady-state dosing conditions of

20 mg/day. Therefore, the 26% increase in alprazolam plasma concentrations, is a somewhat underestimation of the extent of interaction that would occur under steady-state dosing conditions [149]. In a second study, a 33% increase in alprazolam plasma levels occurred after only 4 days of treatment with fluoxetine 60 mg/day [150]. The loading dose strategy applied in this study did, however, not allow steady-state (nor)fluoxetine concentrations to be reached, and thus also underestimated the magnitude of interaction. On the other hand, fluoxetine was reported not to increase the plasma concentrations of triazolam [152]. The decrease in the AUC of terfenadine is probably explained by mechanisms other than an increase in CYP-activity [148]. Fluoxetine 20 mg/day for 8 days also exerted no significant effect on the pharmacokinetics of the reboxetine enantiomers [148], but in this study steady-state conditions were not reached and therefore fluoxetine's full interaction potential was not explored. Although fluoxetine also did not affect the plasma levels of nefazodone, a CYP3A4 substrate, the four-fold increase in m-CPP concentrations caused by CYP2D6 inhibition, requires consideration [129]. Several studies addressed the interaction between SSRIs and carbamazepine. Because carbamazepine induces its own metabolism as well as that of other coadministered drugs, it is not a CYP3A4 model substrate. This, of course, hampers the interpretation of such studies. Two separate studies investigated the effect of fluoxetine 20 mg/day under steady-state conditions on the pharmacokinetics of carbamazepine. Whereas one study reported a 40% increase [147], the other found no change in carbamazepine plasma levels after the addition of fluoxetine [146]. Elevated carbamazepine plasma concentrations (27%) were also observed in a study in which fluoxetine was insufficiently long dosed (20 mg/day for only 7 days) [145].

Fluvoxamine (100 mg/day) produced a 100% increase in alprazolam plasma levels [153], but carbamazepine plasma concentrations remained unaffected [146]. At 150 mg/day, fluvoxamine increased the plasma concentrations of midazolam after IV administration by 50% [104].

Concurrent paroxetine administration had no effect on the pharmacokinetics of terfenadine [145] and carbamazepine [110].

Sertraline did not alter the disposition of alprazolam [155,156], carbamazepine [157], and terfenadine [60].

*Summary points:* Fluoxetine and fluvoxamine, at their usual therapeutic dose, are able to produce mild to moderate increases in AUC of CYP3A4 substrates, although the evidence is not clear-cut. Paroxetine and sertraline exert no effect on this isoform whereas citalopram has not been adequately tested.

- **Interaction studies with drugs whose clearance is not mainly dependent on metabolism via one particular CYP-isoform (Table (9))**

In this Table, the interaction studies with drugs whose clearance does not chiefly depend on the activity of a single CYP isoform, are compiled.

Table 8. Summary of Formal Pharmacokinetic Interaction Studies Between SSRIs and CYP3A4 Substrates

SSRI	SSRI treatment	Substrate [Ref]	(n)	Substrate dosing	Change in AUC*	Change in PD
<b>Citalopram</b>	NA					
<b>Fluoxetine</b>	20 mg/day for 7 days#	Carbamazepine [145]	(6)	7 Days	27%	NA
	20 mg/day for 21 days	Carbamazepine [146]	(8)	Chronic	0%	NA
	20 mg/day for > 30 days	Carbamazepine [147]	(7)	Chronic	40%	NA
	20 mg/day for 8 days#	Reboxetine [148]	(30)	8 Days	(R): 0%; (S): 0%	
	40 mg/day for 7 days†#	Alprazolam [149]	(12)	Single dose	26%	NA
	60 mg/day for 4 days†#	Alprazolam [150]	(20)	4 Days	33%	
	60 mg/day for 9 days†#	Terfenadine [151]	(12)	Single dose	42%	
	60 mg/day for 8 days†#	Triazolam [152]	(24)	Single dose	0%	NA
	80 mg/day for 14 days†#	Nefazodone [129]	(6)	7 Days	0%	
<b>Fluvoxamine</b>	100 mg/day for 6 days	Alprazolam [153]	(20)	4 Days	100%	
	100 mg/day for 21 days	Carbamazepine [146]	(7)	Chronic	0%	NA
	150 mg/day for 28 days	Midazolam [104]	(20)	Single dose (IV)	52%	NA
<b>Paroxetine</b>	20 mg/day for 15 days	Terfenadine [154]	(11)	7 Days	0%	
	30 mg/day for 16 days	Carbamazepine [110]	(6)	Chronic	0%	NA
<b>Sertraline</b>	50 mg/day for 14 days	Alprazolam [155]	(12)	Single dose	0%	NA
	50, 100, 150 mg/day for >14 days	Alprazolam [156]	(6,4,6)	Single dose	0%	
	200 mg/day for 10 days	Carbamazepine [157]	(14)	10 Days	0%	
	200 mg/day for 24 days	Terfenadine [60]	(20)	10 Days	0%	

\*, calculated as  $(AUC_{SSRI} - AUC_{baseline}) / AUC_{baseline} \times 100$ ;

NA, not available;

†, loading dose strategy to achieve (nor)fluoxetine concentrations comparable to those at 20 mg/day in steady-state;

IV, intravenous administration;

#, steady-state not reached

As can be expected from the lack of substantial inhibitory effects by citalopram on drugs that are more or less specific substrates for a particular CYP, citalopram had no effect on the disposition of chlorpromazine [121], clozapine [158], haloperidol [121], levopromazine [120,121], thioridazine [121], and the enantiomers of warfarin [106]. Furthermore, citalopram did not affect the plasma levels of imipramine, and only mildly increased those of its main metabolite, desipramine (see CYP2D6, Table (7)) [120]. The small, but statistically significant decrease in selegiline AUC after citalopram coadministration is unexplained [159].

Fluoxetine was reported not to interact with almotriptan [160] and zolpidem [170,171]. As for the fluoxetine-trazodone combination, the moderate elevation in trazodone concentrations was accompanied with substantially increased m-CPP levels (see CYP2D6, Table (7)) [131].

Under dosing conditions that would have approximated steady-state fluoxetine and norfluoxetine concentrations at 20 mg/day, fluoxetine significantly elevated the plasma levels of the tertiary amine TCAs amitriptyline [123] and

imipramine [126]. In addition, the substantial increases in AUC of their respective active metabolites, the secondary TCAs desipramine and nortriptyline, should be taken into account (see Table (7)). Whereas tertiary amine TCAs are metabolized by ring hydroxylation via CYP2D6 and by N-demethylation via CYP2C19 (principal isoform), CYP1A2, and CYP3A4, the secondary amine TCAs resulting from such N-demethylation process, are almost exclusively hydroxylated by CYP2D6 [186]. As described earlier, fluoxetine potently inhibits CYP2D6, and moderately inhibits CYP2C19 and CYP3A4 activity *in vivo*. Therefore, the increase in imipramine and amitriptyline plasma levels by fluoxetine coadministration is likely explained by inhibition of these isoforms, while those of desipramine and nortriptyline by inhibition of CYP2D6. As can be expected from the greater involvement of CYP2D6 in the metabolism of the secondary amine TCAs, the rise in the plasma concentrations of their metabolites was more substantial compared to that of the parent compounds. Fluoxetine coadministration resulted in a 77% and 35% increase in the AUC of (R)- and (S)-carvedilol, respectively [125]. The

**Table 9. Summary of Formal Pharmacokinetic Interaction Studies Between SSRIs and Drugs Whose Clearance is not Mainly Dependent on Metabolism Via one Particular CYP-Isoform**

SSRI	SSRI treatment	Substrate [Ref]	(n)	Substrate dosing	CYPs involved in substrate metabolism	Change in AUC*	Change in PD
<b>Citalopram</b>	20 mg/day for > 14 days	Clozapine [158]	(5)	Chronic	1A2, 2C9, 2C19, 2D6, 3A4	0%	NA
	20 mg/day for 14 days	Selegiline [159]	(12)	4 Days	1A2, 2D6, 3A4	29%	
	40 mg/day for 11 weeks	Chlorpromazine [121]	(13)	Chronic	1A2, 2D6, 3A4	0%	NA
	40 mg/day for 11 weeks	Haloperidol [121]	(5)	Chronic	1A2, 2D6, 3A4	0%	NA
	40 mg/day for 10 days	Imipramine [120]	(8)	Single dose	1A2, 2C19, 2D6, 3A4	0%	NA
	40 mg/day for 11 weeks	Levopromazine [121]	(9)	Chronic	?	0%	NA
	40 mg/day for 10 days	Levopromazine [120]	(8)	Single dose	?	0%	NA
	40 mg/day for 11 weeks	Thioridazine [121]	(14)	Chronic	2C19, 2D6	0%	NA
	40 mg/day for 21 days	Warfarin [106]	(12)	Single dose	(R): 1A2, 2C19, 3A4; (S): 2C9	(R): 0%; (S): 0%	
<b>Fluoxetine</b>	60 mg/day for 8 days†	Almotriptan [160]	(14)	Single dose	2D6, 3A4	0%	
	20 mg/day for > 3 weeks	Amitriptyline [123]	(15)	Chronic	1A2, 2C19, 2D6, 3A4	80%	NA
	20 mg/day for >28 days	Carvedilol [125]	(10)	Chronic	(R): 2C9, 2D6; (S): 2C9, 2D6	(R): 33%; (S): 0%	
	20 mg/day for 8 weeks	Clozapine [161]	(10)	Chronic	1A2, 2C9, 2C19, 2D6, 3A4	58% NORCLZ 36%	
	36 ± 12 mg/day for > 7 days#	Clozapine [162]	(6)	Chronic	1A2, 2C9, 2C19, 2D6, 3A4	76% NORCLZ 52%	NA
	20 mg/day for 6 weeks	Fluphenazine [163]	(15)	Chronic (IV)	1A2, 2D6	65%	
	20 mg/day for 12 weeks	Haloperidol [164]	(13)	Chronic	1A2, 2D6, 3A4	35%	
	20 mg/day for 7-10 days#	Haloperidol [165]	(8)	Chronic	1A2, 2D6, 3A4	20%	
	60 mg/day for 8 days†#	Imipramine [126]	(6)	Single dose	1A2, 2C19, 2D6, 3A4	235%	NA
	20 mg/day for > 4 weeks	Methadone [166]	(9)	Chronic	(R) and (S): 2C9, 2C19, 3A4	0%	NA
	20 mg/day for > 28 days	Methadone [167]	(7)	Chronic	(R) and (S): 2C9, 2C19, 3A4	(R): 33%; (S): 0%	NA
	40 mg/day for 7 days, then 20 mg/day for 15 days†	Moclobemide [168]	(12)	Single dose	2C9, 2C19, 2D6	52%	
	60 mg/day for 7 days†#	Ritonavir [169]	(16)	Single dose	2D6, 3A4	19%	NA
	20 mg/day for 28 days	Trazodone [131]	(11)	28 Days	1A2, 2D6, 3A4	65%	
	<b>Fluvoxamine</b>	20 mg/day for 18 days#	Zolpidem [170]	(27)	Single dose	1A2, 2C9, 2C19, 2D6, 3A4	0%
20 mg/day for 24 days		Zolpidem [171]	(29)	Single dose	1A2, 2C9, 2C19, 2D6, 3A4	0%	
50 mg/day for 28 days		Clozapine [172]	(18)	28 Days	1A2, 2C9, 2C19, 2D6, 3A4	130% NORCLZ 82%	
50 mg/day for 2 days#		Ropivacaine [173]	(12)	Single dose (IV)	1A2, 3A4	210%	NA
50 mg/day for 7 days	Thioridazine [174]	(10)	Chronic	2C19, 2D6	225%	NA	
100 mg/day for 5 days	Buspirone [175]	(10)	Single dose	3A4 + ?	140%		

(Table 9). contd....

SSRI	SSRI treatment	Substrate [Ref]	(n)	Substrate dosing	CYPs involved in substrate metabolism	Change in AUC*	Change in PD
	100 mg/day for 5 days	Bromazepam [176]	(12)	Single dose	?	137%	
	100 mg/day for 14 days	Clozapine [177]	(9)	Single dose	1A2, 2C9, 2C19, 2D6, 3A4	185% NORCLZ 19%	NA
	100 mg/day for 10 days	Imipramine [132]	(6)	Single dose	1A2, 2C19, 2D6, 3A4	260%	NA
	104 ± 75/day for > 7 days	Methadone [167]	(6)	Chronic	(R) and (S): 2C9, 2C19, 3A4	(R): 43%; (S): 31%	NA
	100 mg/day for 7 days	Mexiletine [178]	(7)	Single dose	1A2, 2D6	55%	NA
	100 mg/day for 8 days	Proguanil [179]	(6)	Single dose	1A2, 2C19, 3A4	65%	NA
	100 mg/day for 14 days	Propranolol [108]	(NA)	Single dose	1A2, 2C19, 2D6	400%	
	100 mg/day for 5 days	Quinidine [180]	(6)	Single dose	3A4 + ?	41%	NA
	150 mg/day for 14 days	Clozapine [181]	(16)	Chronic	1A2, 2C9, 2C19, 2D6, 3A4	188% NORCLZ 163%	NA
<b>Paroxetine</b>	20 mg/day for 14 days	Amitryptiline [133]	(9)	Chronic	1A2, 2C19, 2D6, 3A4	58%	NA
	20 mg/day for 14 days	Clozapine [181]	(14)	Chronic	1A2, 2C9, 2C19, 2D6, 3A4	0% NORCLZ 0%	NA
	20-40 mg/day for 3 weeks	Clozapine [182]	(9)	Chronic	1A2, 2C9, 2C19, 2D6, 3A4	31% NORCLZ 20%	NA
	20 mg/day for 14 days	Imipramine [133]	(5)	Chronic	1A2, 2C19, 2D6, 3A4	34%	NA
	20 mg/day for 14 days	Rizatriptan [183]	(12)	Single dose	?	0%	
	30 mg/day for 4 days	Imipramine [139]	(9)	Single dose	1A2, 2C19, 2D6, 3A4	76%	NA
<b>Sertraline</b>	50-100 mg/day for 3 weeks	Clozapine [182]	(8)	Chronic	1A2, 2C9, 2C19, 2D6, 3A4	0% NORCLZ 0%	NA
	50 mg/day for 8 weeks	Haloperidol [184]	(18)	Chronic	1A2, 2D6, 3A4	0%	
	50 mg/day for 7 days	Imipramine [140]	(4)	7 Days	1A2, 2C19, 2D6, 3A4	0%	
	100 mg/day for 10 days	Clonazepam [185]	(13)	10 Days	3A4	0%	
	150 mg/day for 8 days	Imipramine [143]	(6)	Single dose	1A2, 2C19, 2D6, 3A4	68%	NA

\* , calculated as  $(AUC_{SSRI} - AUC_{baseline}) / AUC_{baseline} \times 100$  or  $(MR_{SSRI} - MR_{baseline}) / MR_{baseline} \times 100$ ;

NA, not available; NORCLZ, norclozapine;

†, loading dose strategy to achieve (nor)fluoxetine concentrations comparable to those at 20 mg/day in steady-state;

IV, intravenous administration;

#, steady-state not reached;

greater involvement of CYP2D6 in the metabolism of (R)-carvedilol is probably the reason why the plasma concentrations of this enantiomer were more increased after fluoxetine intake when compared to (S)-carvedilol. The interaction between fluoxetine and clozapine was explored in several studies. With respect to clozapine, it is also important to consider changes in norclozapine levels because this major metabolite is thought to contribute to the overall effect of the drug. Fluoxetine administration at 20 mg/day significantly increased mean plasma concentrations of clozapine by 58%, with a less pronounced increase for norclozapine [161]. Similar findings were reported in another study in which fluoxetine was dosed at 36 mg/day for at least seven days [162]. A third study reported a trend

towards higher (29.6%) clozapine plus norclozapine concentrations after concurrent treatment with this SSRI at a dose of 40 mg/day under steady-state conditions [187]. Several CYP-isoforms are implicated in the complex oxidative metabolism of clozapine. Of these isoforms, primary roles for CYP1A2 and CYP3A4 have been suggested whereas CYP2C19 contribution may also be significant [188]. As fluoxetine has little effect on CYP1A2 activity, the interaction may be explained by inhibition of CYP3A4 and possibly also CYP2C19. It has been speculated that the rise in norclozapine plasma concentrations may be attributed to the fact that fluoxetine also interferes with the degradation of this metabolite [161]. A 65% increase in serum fluphenazine concentrations was seen in patients

receiving fluphenazine and fluoxetine polytherapy [163]. No interaction mechanism was suggested. Adjunctive use of fluoxetine (20 mg/day) in patients stabilized on haloperidol resulted in a mild increase in the plasma levels of the neuroleptic [164,165]. The metabolism of haloperidol is complex and to date existing evidence indicates that CYP3A4 plays the most important role, whereas CYP2D6 may also be involved but to a smaller extent [189]. By inference, the mechanism of interaction between fluoxetine and haloperidol may be inhibition of CYP3A4 and possibly also CYP2D6 by fluoxetine. While one study found no effect of fluoxetine on racemic methadone concentrations [166], another study showed increased (R)-methadone (the active enantiomer) concentrations after fluoxetine intake. (S)-methadone levels remained unaffected [167]. The isoforms involved in this interaction have not yet been elucidated. Fluoxetine markedly inhibited the metabolism of moclobemide, yielding a 52% increase in moclobemide AUC [168]. CYP2C19, the principal isoform implicated in the metabolism of moclobemide, is probably the target of fluoxetine's inhibitory effect. Therapeutic concentrations of fluoxetine and norfluoxetine produced a small effect on the AUC of ritonavir [169]; this was largely ascribed to inhibition of CYP2D6, although effects on CYP3A4 could not be excluded.

The interaction between fluvoxamine and clozapine has been the subject of three investigations showing substantially elevated clozapine plasma levels (130% to 188%) [172,177,181]. Except for the study by Chang *et al.*, norclozapine plasma concentrations also rose, but to a smaller extent. This apparent discrepancy was explained by differences in study design: the study by Chang *et al.* employed a single clozapine dose, which did not allow for the detection of significant changes in metabolite levels [177]. Fluvoxamine's effect on clozapine pharmacokinetics is probably due to potent inhibition of CYP1A2 and CYP2C19, and moderate inhibition of CYP3A4. As with fluoxetine, the degradation of norclozapine may as well be inhibited by treatment with this SSRI. Ropivacaine plasma levels were increased more than three-fold after only 2 days of low-dose (50 mg/day) fluvoxamine coadministration [173]. Due to the short treatment period, steady-state was not reached and hence, the extent of interaction was likely substantially underestimated. The authors attribute the interaction to inhibition of ropivacaine's CYP1A2-mediated metabolism [173]. Comedication of thioridazine with low-dose fluvoxamine led to a more than three-fold elevation in thioridazine concentrations [174]. It was proposed that fluvoxamine interfered with the CYP2C19-mediated metabolism of thioridazine, although inhibition of CYP1A2 could also have been involved. van Harten *et al.* demonstrated a moderate (137%) increase in bromazepam plasma levels, following the coadministration of fluvoxamine (100 mg/day) relative to those after bromazepam alone [176]. The specific isoforms involved have not yet been identified. Fluvoxamine also interferes with the metabolism of tertiary TCAs, e.g. imipramine [132]. This effect is the result of a significant inhibition of the N-demethylation process by fluvoxamine [290]. A similar effect of fluvoxamine has also been demonstrated for amitriptyline and clomipramine [190,191]. Fluvoxamine's inhibitory effect on the N-demethylation process is probably

explained by potent inhibition of CYP2C19, the major isoform involved in this metabolic step; effects on CYP1A2 and CYP3A4 cannot be excluded [186]. Fluvoxamine also considerably increased the buspirone AUC (2.4-fold) [175]. Quinidine plasma concentrations rose only mildly (41%) after fluvoxamine intake [180]. The mechanism of both interactions is most likely explained by inhibition of the CYP3A4-mediated metabolism of buspirone and quinidine by fluvoxamine. Here also, effects on other CYP-isoforms could not be ruled out [175,180]. In contrast to fluoxetine, fluvoxamine mildly increased the plasma concentrations of both methadone enantiomers, with a more pronounced effect on (R)-methadone, the active enantiomer [167]. Here also, the exact mechanism of interaction is not known. Concomitant fluvoxamine was also found to increase the mexiletine AUC by 55%, an effect that was likely explained by inhibition of CYP1A2. CYP2D6, the major isoform implicated in the metabolism of mexiltine was probably not inhibited [190]. Fluvoxamine was reported to increase proguanil AUC by 65% in healthy volunteers, phenotyped as extensive metabolizer of the (S)-mephenytoin oxidation polymorphism [179]. CYP1A2, CYP2C19, and CYP3A4 have been identified as the isoforms implicated in the oxidative metabolism of proguanil, but their relative contributions *in vivo* remain to be determined [192]. Therefore, impairment of proguanil clearance by fluvoxamine is probably caused by a combined effect on these three isoforms. Following the coadministration of fluvoxamine, plasma concentrations of propranolol rose about five-fold [108]. Several isoforms (CYP1A2, CYP2D6, and CYP2C19) involved in the metabolism of propranolol could be inhibited.

Paroxetine did not interact with rizatriptan [183]. The plasma concentrations of the tertiary amine TCAs amitriptyline [133] and imipramine [133,139] were mildly to moderately elevated after paroxetine treatment; more considerable increases were seen for their respective metabolites, nortriptyline, and desipramine (see Table (7)). Because paroxetine nearly exclusively inhibits CYP2D6, only the hydroxylation of the tertiary TCAs is thought to be compromised when paroxetine is administered concurrently. The effect of paroxetine on the pharmacokinetics of clozapine was investigated in three studies and yielded contradictory results. Whereas one study reported no interaction between both drugs [181], a mild increase in clozapine and norclozapine plasma levels was found in the other [182]. The latter findings are in line with those of another study that reported significantly (56.6%) elevated clozapine plus norclozapine concentrations after add-on therapy with this SSRI [187]. It has been speculated that the small increase was due to inhibition of CYP2D6, one of the minor isoforms involved in the metabolism of clozapine.

Sertraline coadministration had no effect on the disposition of clonazepam [185], clozapine [182], and haloperidol [184]. Two studies reported on the effect of sertraline on the pharmacokinetics of imipramine. Sertraline 50 and 150 mg/day yielded 0% [140] and 68% [143] increases in imipramine concentrations, respectively, a finding consistent with sertraline's mild inhibitory effects on CYP2C19 and CYP2D6.

**Summary points:** The magnitude of these interactions is obviously dependent on which isoforms are implicated in the metabolism of the substrate and their contribution to the overall clearance of the drug. Nevertheless, the data indicate that fluvoxamine has the greatest potential to interact with drugs whose clearance is not solely dependent on the activity of a single CYP because this SSRI inhibits several CYP-isoforms.

The effect of the selective serotonin reuptake inhibitors in inhibiting various CYP isoforms *in vivo*, at the usual effective therapeutic dose has been summarized in Table (10). This Table shows that fluoxetine and paroxetine are potent CYP2D6 inhibitors *in vivo*, whereas fluvoxamine potently inhibits CYP1A2 and CYP2C19. Sertraline is, at its best, a moderate CYP2D6 inhibitor and citalopram has little effect on the major CYP isoforms *in vivo*. These conclusions are in keeping with the conclusions concerning the *in vitro* data.

**4.3. Clinical relevance of CYP-Mediated Drug-Drug Interactions with the SSRIs**

The clinical relevance of a metabolic drug-drug interaction will depend on a number of factors [13].

First, the probability of concurrent use is an important factor. Combination drug therapy is common in clinical practice, particularly in psychiatry, but it has also become increasingly usual for SSRIs to be combined with non-psychotropics. This latter situation has arisen because the treatment of depression is often long-term, and a number of patients need to be treated for concurrent illnesses. A second factor relates to the therapeutic window and concentrations-effect relationship of the drug whose metabolism is affected. For drugs with a narrow therapeutic window and/or a steep concentration-effect relationship, the likelihood of clinically significant consequences from altered concentrations is high. A third factor concerns the presence of active metabolites: when they are formed by the metabolic pathway(s) inhibited by a particular SSRI, the impact may be reduced. Fourth, some individuals have higher risks of experiencing adverse effects. In this respect, the elderly may be more at risk than the young [13].

The clinical relevance of the drug-drug interactions with the SSRIs listed in Tables (4) to (9) will be discussed next.

• **Fluoxetine**

Clinically significant interactions have been described between the tricyclic antidepressants (amitryptiline [123], desipramine [124,126], and imipramine [126]) and fluoxetine in that these drug combinations may produce tricyclic antidepressant toxicity. A tricyclic antidepressant dose reduction is therefore strongly advocated. The interaction of fluoxetine with nefazodone [129] and trazodone [131] resulted in substantial increase in meta-chlorophenylpiperazine levels that could be responsible for an augmentation of clinical efficacy, and probably also for an increase in adverse effects. Despite the marked increase in tolterodine concentrations when combined with fluoxetine, this interaction is probably not clinically important, because the increased levels of tolterodine are compensated by the decreased concentrations of the active metabolite [130]. Fluoxetine is able to produce some increase in carbamazepine plasma concentrations [145,147], but this has not been found in all studies [146]. Careful monitoring of the carbamazepine plasma concentrations is advised when fluoxetine is co-administered. Co-treatment of alprazolam and fluoxetine resulted in greater reductions in psychomotor performance and memory, suggesting that the dosage of alprazolam should be reduced when this drug is given together with fluoxetine [149,150].

Fluoxetine did not affect the disposition of triazolam. However, because the results with respect to fluoxetine's effect on CYP3A4 activity *in vivo* are not consistent, it is also advised that triazolam therapy is closely monitored when fluoxetine is coadministered [152]. Inhibition of propafenone metabolism by fluoxetine did not lead to changes in electrocardiographic parameters, as can be expected from the fact that an increase in propafenone concentrations was compensated by decreased concentrations of its active metabolite 5-hydroxypropafenone. However, this interaction may be of clinical relevance for propafenone-induced side effects, such as -blockade, a property associated with the (S)-enantiomer of the parent drug [122].

**Table 10. Summary of the Effect of the Selective Serotonin Reuptake Inhibitors in Inhibiting Various CYP Isoforms, Based on *in vivo* Studies.**

CYP isoform	Citalopram	Fluoxetine	Fluvoxamine	Paroxetine	Sertraline
CYP1A2	NA	NA	+++	-	-
CYP2C9	-	-	+ / ++	-	- / +
CYP2C19	-	+	++ / +++	NA	- / +
CYP2D6	- / +	+++	+	+++	+
CYP3A4	NA	+	+	-	-

NA, not available; - = no effect; + = < 50% change; ++ = 50 - 150% change; +++ = > 150% change (in plasma levels)

- **Fluvoxamine**

The clinical implications of the fluvoxamine-tacrine interaction remain unclear. First, gastrointestinal side effects may be more frequent when combined with fluvoxamine due to high parent drug concentrations. Second, with regard to hepatotoxicity, the effects of fluvoxamine treatment will depend on whether this hepatotoxicity is caused by the parent drug or by one or more reactive metabolites formed through CYP1A2. Further clinical investigations are required to establish the consequences of concomitant prescription of tacrine and fluvoxamine [99,102]. When caffeine intake is combined with fluvoxamine, caffeine consumption should be restricted since a combined intake could lead to caffeine intoxication [100,101]. Similarly, when fluvoxamine is co-administered with theophylline, it is strongly recommended that the dose of theophylline should be reduced and that the serum levels of theophylline be closely monitored [103].

Fluvoxamine also produces a clinically relevant interaction with warfarin, and when fluvoxamine is added to a stable warfarin therapy, a warfarin dose reduction is advised combined with close monitoring of the anticoagulant effect [108]. The effect of fluvoxamine on the disposition of diazepam is also of considerable clinical significance, requiring a diazepam dose reduction [118]. The interactions between fluvoxamine and alprazolam [153], amitriptyline [190], bromazepam [176], clomipramine [191], clozapine [172,177,181], imipramine [132], mexiletine [178], propranolol [108], ropivacaine [173], and thioridazine [174] are considered clinically significant, requiring a dose reduction when fluvoxamine is co-administered. This may also hold true for midazolam [104] and carbamazepine [146], when fluvoxamine is given concurrently. The fluvoxamine-proguanil combination is not recommended because fluvoxamine treatment inhibits the bioactivation of proguanil, a prodrug, most likely leading to a lowered efficacy of the drug [179].

- **Paroxetine**

A number of clinically important interactions between paroxetine and the tricyclic antidepressants (desipramine [134,135], imipramine [133,139], and amitriptyline [133]) have been reported, requiring close monitoring and tricyclic antidepressant dose reduction. Paroxetine also caused an increase in central nervous system (CNS) side effects of perphenazine when both drugs were co-administered. In order to prevent CNS side effects, a reduction of the perphenazine dose seems to be required [138]. Intake of multiple-dose paroxetine affected the pharmacokinetics and pharmacodynamics of the cardioselective  $\beta$ -blocker metoprolol in healthy volunteers [137]. Although the therapeutic concentration range of  $\beta$ -blockers such as metoprolol is large, to high plasma concentrations may lead to unwanted effects such as bradycardia and/or loss of cardioselectivity. A metoprolol dose adaptation may be required to prevent untoward effects.

- **Sertraline**

Sertraline causes less important interactions with tricyclic antidepressants (desipramine [124,135,143,144], imipramine

[140,143], and nortriptyline [141]), but, nonetheless, caution is warranted when sertraline is added to a tricyclic antidepressant regimen.

The other interactions listed in Tables (4) to (9), are of minor or no clinical importance.

In conclusion, when fluvoxamine is co-administered with a drug whose metabolism is mainly dependent on CYP1A2, CYP2C9, CYP2C19, CYP3A4, or on a combination of these isoforms, caution is advised. An appropriate dose reduction may be needed in order to prevent exaggerated effects or untoward effects, depending on the drug's pharmacodynamics. In some cases, therapeutic drug monitoring can be useful. This is also mandatory when paroxetine or fluoxetine, and possibly sertraline, are combined with drugs mainly metabolized by CYP2D6. In addition, this may also be needed for certain CYP3A4 substrates, when fluoxetine is co-administered. Citalopram seems to have little interaction potential.

## CONCLUSION

A large amount of knowledge has now been gained on the effect of this class of antidepressants on the cytochrome P450-system. The *in vitro* and *in vivo* data presented here clearly provides evidence for a distinct profile of cytochrome P450 inhibition by individual SSRIs.

Fluvoxamine potentially inhibits CYP1A2 and CYP2C19, and has a mild to moderate inhibitory effect on CYP2C9, CYP2D6, and CYP3A4. Both fluoxetine and paroxetine potentially inhibit CYP2D6 and the first also exerts a moderate effect on CYP3A4-activity. Sertraline has a modest effect on CYP2D6. The current knowledge on citalopram suggests little interaction potential with co-administered drugs.

Special attention should be given to fluoxetine: inhibitory effects on CYP-activity can persist for several weeks after fluoxetine discontinuation because of the long half-life of fluoxetine and its metabolite norfluoxetine.

Drug combinations with SSRIs should be assessed on a case-by-case basis. In this respect, knowledge regarding the CYP-isoforms involved in the metabolism of the co-administered drug may help clinicians to anticipate and avoid potentially detrimental drug-drug interactions that may occur through modification of CYP-mediated drug metabolism. When an interaction is anticipated, this does not necessarily mean that both drugs cannot be co-administered: problems can usually be managed by careful monitoring and appropriate dose adjustments and titration. Conversely, a SSRI with limited interaction potential, e.g. citalopram or sertraline, may be selected for the treatment of depression in patients receiving other medications.

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