

Associate editor: H. Bönisch

## Pharmacokinetics of selective serotonin reuptake inhibitors

Christoph Hiemke\*, Sebastian Härter

Department of Psychiatry, University of Mainz, Untere Zahlbacher Str. 8, D-55101 Mainz, Germany

### Abstract

The five selective serotonin reuptake inhibitors (SSRIs), fluoxetine, fluvoxamine, paroxetine, sertraline, and citalopram, have similar antidepressant efficacy and a similar side effect profile. They differ, however, in their pharmacokinetic properties. Under steady-state concentrations, their half-lives range between 1 and 4 days for fluoxetine (7 and 15 days for norfluoxetine) and between 21 (paroxetine) and 36 (citalopram) hr for the other SSRIs. Sertraline and citalopram show linear and fluoxetine, fluvoxamine, and paroxetine nonlinear pharmacokinetics. SSRIs undergo an extensive metabolism with high interindividual variability, whereby cytochrome P450 (CYP) isoenzymes play a major role. Therefore, resulting blood concentrations are highly variable between individuals. Except for N-demethylated fluoxetine, metabolites of SSRIs do not contribute to clinical actions. Therapeutically effective blood concentrations are unclear so far, although there is evidence for minimal effective and upper-threshold concentrations that should not be exceeded. Paroxetine and, to a lesser degree, fluoxetine and norfluoxetine are potent inhibitors of CYP2D6 and fluvoxamine of CYP1A2 and CYP2C19. This can give rise to drug-drug interactions that may have no effect, lead to intoxication, or improve the therapeutic response. These different pharmacokinetic properties of the five SSRIs, especially their drug-drug interaction potential, should be considered when selecting a distinct SSRI for treatment of depression or other disorders with a suggested dysfunction of the serotonergic system in the brain. © 1999 Elsevier Science Inc. All rights reserved.

**Keywords:** Fluoxetine; Fluvoxamine; Paroxetine; Citalopram; Sertraline; Drug-drug interactions

**Abbreviations:** AUC, area under the concentration-time curve;  $C_{max}$ , maximum plasma concentration; CYP, cytochrome P450; EM, extensive metabolizers; NMRS, nuclear magnetic resonance spectroscopy; PM, poor metabolizers; SSRI, selective serotonin reuptake inhibitor;  $t_{1/2}$ , half-life; TCA, tricyclic antidepressant; TDM, therapeutic drug monitoring;  $V_d$ , volume of distribution.

### Contents

1. Introduction . . . . .	12
2. Fluoxetine . . . . .	13
2.1. Basic pharmacology . . . . .	13
2.2. Basic pharmacokinetic properties . . . . .	13
2.3. Metabolism . . . . .	13
2.4. Blood concentrations and clinical response . . . . .	14
2.5. Drug-drug interactions . . . . .	14
3. Fluvoxamine . . . . .	15
3.1. Basic pharmacology . . . . .	15
3.2. Basic pharmacokinetic properties . . . . .	15
3.3. Metabolism . . . . .	15
3.4. Blood concentrations and clinical response . . . . .	16
3.5. Drug-drug interactions . . . . .	16
4. Paroxetine . . . . .	17
4.1. Basic pharmacology . . . . .	17
4.2. Basic pharmacokinetic properties . . . . .	17
4.3. Metabolism . . . . .	17
4.4. Blood concentrations and clinical response . . . . .	18
4.5. Drug-drug interactions . . . . .	18
5. Sertraline . . . . .	19

\* Corresponding author. Tel.: +0049-6131-177131; fax: +0049-6131-176690.

E-mail address: hiemke@mail.uni-mainz.de (C. Hiemke)

5.1.	Basic pharmacology	19
5.2.	Basic pharmacokinetic properties	19
5.3.	Metabolism	19
5.4.	Blood concentrations and clinical response	19
5.5.	Drug-drug interactions	19
6.	Citalopram	20
6.1.	Basic pharmacology	20
6.2.	Basic pharmacokinetic properties	20
6.3.	Metabolism	21
6.4.	Blood concentrations and clinical response	22
6.5.	Drug-drug interactions	22
7.	Synopsis	22
	References	23

## 1. Introduction

In a manner similar to many psychotropic drugs, imipramine was the result of an accidental observation. It was first proposed as an antipsychotic drug. However, preclinical and clinical studies provided the first insight into the mechanisms likely to underlie therapeutic antidepressant actions, as well as the adverse reactions of imipramine and other tricyclic antidepressants (TCAs). Blockade of serotonin or noradrenaline uptake was related to antidepressant actions (Wong et al., 1975; Fuller et al., 1975) and blockade of neurotransmitter receptors to their side effects. Among the latter are unpleasant, but harmless, reactions, such as dry mouth or sedation, and severe toxic reactions, such as cardiac arrest or delir (Richelson, 1994; Cusack et al., 1994; Owens et al., 1997). Biochemical research, therefore, looked for safer drugs that selectively or exclusively block monoamine uptake sites. The selective serotonin reuptake inhibitors (SSRIs) with high affinity to serotonin uptake sites, low affinity to noradrenaline uptake sites (Fig. 1), and very low affinity for neurotransmitter receptors were the result of these efforts (Frazer, 1997). SSRIs are thus the first class of rationally designed therapeutic drugs in psychiatry.

After the introduction of fluvoxamine, in Great Britain in

1983, fluoxetine became widely available, followed by paroxetine, citalopram, and sertraline (Preskorn, 1996a). Based on clinical trials, SSRIs are regarded as an alternative to TCAs. In some countries, they have even replaced TCAs as first-choice antidepressant medication (Leonard & Tollefson, 1994; Preskorn, 1996a). With regard to therapeutic efficacy, SSRIs and TCAs are almost equipotent (Bech, 1988; Rickels & Schweizer, 1990; Cole, 1992). Due to the lack of receptor antagonism, SSRIs are almost devoid of life-threatening side effects, such as cardiotoxicity and CNS toxicity. SSRIs are safe (De Jonghe & Swinkels, 1992; Hotopf et al., 1996) and easy to handle (Leonard & Tollefson, 1994). In a Swedish survey consisting of 1202 reports describing adverse reactions to SSRIs, the most often reported events were neurological (22.4%), psychiatric (19.4%), and gastrointestinal (18%) symptoms (Spigset, 1999). The Swedish study was also aimed to assess possible risk factors associated with the occurrence of adverse events. It revealed differences in frequency and type of adverse reactions between male and female, old and young patients and between the different SSRIs.

Because of the advantageous safety profile of SSRIs, treatment of depression with antidepressant drugs could change from primarily hospitalized inpatients to outpatients

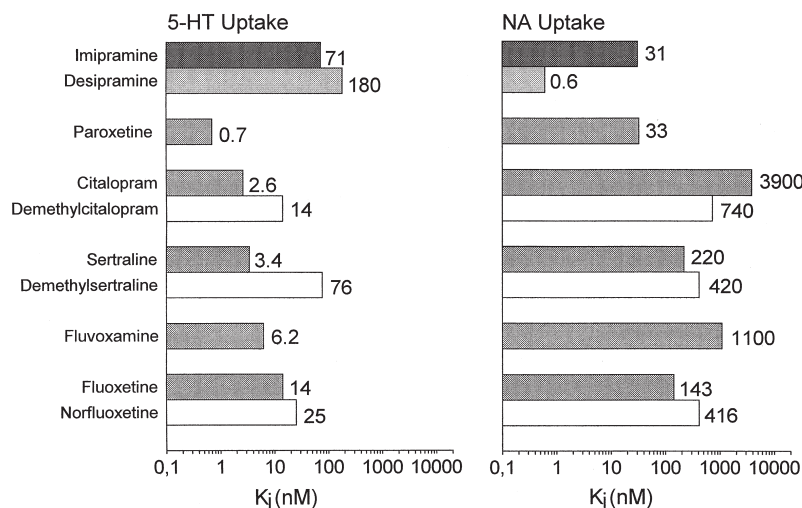


Fig. 1. Inhibitory constants ( $K_i$ ) for inhibition of monoamine uptake into rat brain tissue by imipramine, selective serotonin reuptake inhibitors, or N-demethylated metabolites. 5-HT, 5-hydroxytryptamine; NA, noradrenaline. Data from Richelson (1994) and Preskorn (1996a).

(Lecrubier, 1992). Moreover, the use of SSRIs was extended from major depression to minor depression (Szegeedi et al., 1997) and other psychiatric disorders that are also suggested to be associated with a dysfunctional state of the serotonin system. This includes anxiety (den Boer et al., 1995), obsessive-compulsive disorders (Piccinelli et al., 1995; Leonard, 1997), or premenstrual dysphoric disorders (Redmond, 1997; Gunasekara et al., 1998). Thus, the use of SSRIs is a rational, mechanism-based therapy.

In addition to higher safety of SSRIs, the pharmacology of the new drugs was first regarded as being less complex than for TCAs. The metabolism of TCAs leads to multiple metabolites with pharmacological properties that are different from that of the parent drug. Imipramine, for example, is a preferential serotonin reuptake inhibitor, whereas its N-demethylated metabolite desipramine primarily interacts with noradrenaline uptake sites. Clomipramine exerts marked anticholinergic activity; its 8-hydroxylated metabolite is almost devoid of anticholinergic activity, but still has serotonin uptake blocking activity. With the exception of norfluoxetine and perhaps desmethylcitalopram or desmethylsertraline, SSRI metabolites do not exhibit pharmacological properties that are relevant in vivo. Moreover, the three metabolites are also preferential inhibitors of the uptake of serotonin.

Thus, after the introduction of SSRIs, little attention was given to their pharmacokinetics in depressed patients being treated with SSRIs. This view has changed completely. Differences in the pharmacokinetics, especially in drug-drug interactions, are now the major selection criteria to use a distinct SSRI (van den Berg, 1995; Baumann, 1996a; Brøsen, 1996). Some SSRIs inhibit cytochrome P450 (CYP) isoenzymes (Harvey & Preskorn, 1996; Preskorn, 1996b), a family containing more than 30 enzymes in humans that catalyze the oxidative metabolism of multiple drugs (Nelson et al., 1996; Gonzalez, 1992). The drug-drug interactions of SSRIs created a new estimation of a drug's pharmacokinetics in general for pharmacotherapy, since it became obvious that drug-drug interactions are not only a problem of SSRIs, but also of other drugs (Preskorn & Magnus, 1994; Harvey & Preskorn, 1995; Shader et al., 1996; Nemeroff et al., 1996).

Because of the high relevance of differences in the pharmacokinetic properties of SSRIs for antidepressant drug therapy, this review describes pharmacokinetic abnormalities of the different SSRIs, such as nonlinear kinetics, gender differences, and age dependencies, and clinically relevant drug-drug interactions. Moreover, special attention is given to the current knowledge of therapeutically effective concentrations of SSRIs in blood, which so far is poorly documented in the literature.

## 2. Fluoxetine

### 2.1. Basic pharmacology

In most countries, fluoxetine was the first SSRI that became available for clinical use (Preskorn, 1996a). It is a ra-

cemic mixture of two enantiomers, whereby the S-enantiomer is  $\sim 1.5$  times more potent in the inhibition of serotonin reuptake than the R-enantiomer (Gram, 1994). The pharmacological difference between enantiomers is even more pronounced for the active metabolite norfluoxetine, with the S-enantiomer having  $\sim 20$  times higher reuptake blocking potency than the R-enantiomer (Fuller et al., 1992). Under steady-state conditions, the concentration of racemic norfluoxetine normally exceeds the concentrations of racemic fluoxetine. In blood, the concentrations of the N-demethylated metabolite are higher for S-norfluoxetine than for R-norfluoxetine (Baumann & Rochat, 1995).

### 2.2. Basic pharmacokinetic properties

After oral administration, fluoxetine is almost completely absorbed. Due to hepatic first-pass metabolism, the oral bioavailability is below 90% (Catterson & Preskorn, 1996; van Harten, 1993). Similar to other lipophilic drugs, fluoxetine has a large volume of distribution ( $V_d$ ), between 14 and 100 L/kg, which indicates extensive accumulation in tissue. The  $V_d$  of fluoxetine is by far the highest among all SSRIs (Catterson & Preskorn, 1996). The accumulation is highest in lungs, an organ enriched with lysosomes. Lysosomal trapping is considered to play a role for the high  $V_d$  of fluoxetine (Daniel & Wójcikowski, 1997a, 1997b). In spite of the high  $V_d$ , which is similar to that of TCAs, accumulation in the brain is lower than for other SSRIs shown in vitro in brain slices (Daniel & Wójcikowski, 1997b) and in vivo in patients using fluorine-19 NMR spectroscopy (NMRS) (Renshaw et al., 1992). The brain to plasma ratio of fluoxetine in patients is only 2.6:1 compared with 24:1 for fluvoxamine (Strauss et al., 1997).

Fluoxetine has a long half-life ( $t_{1/2}$ ) of 1–4 days (Gram, 1994; Benfield et al., 1986). For norfluoxetine,  $t_{1/2}$  ranges even between 7 and 15 days (Gram, 1994; Benfield et al., 1986). Because of the long  $t_{1/2}$ , 1–22 months are required to achieve steady-state conditions (Catterson & Preskorn, 1996). Fluoxetine exhibits nonlinear kinetics, indicated by a disproportionate increase in its blood concentrations after dose escalation. Under multiple dosing, longer  $t_{1/2}$  and reduced oral clearance result, compared with single doses. In rats, the bioavailability increases with dose, pointing to a saturable first-pass metabolism of fluoxetine (Caccia et al., 1990). Abnormalities in the elimination of fluoxetine have not been noted for patients with renal impairment, whereas liver cirrhosis significantly reduces the plasma clearance of fluoxetine (Benfield et al., 1986).

### 2.3. Metabolism

Fluoxetine undergoes extensive metabolic conversion, leading to the active metabolite norfluoxetine and multiple other metabolites (Fig. 2).

After oral administration, fluoxetine is mainly excreted in urine, with less than 10% excreted unchanged or as fluoxetine N-glucuronide (Benfield et al., 1986). So far, only a

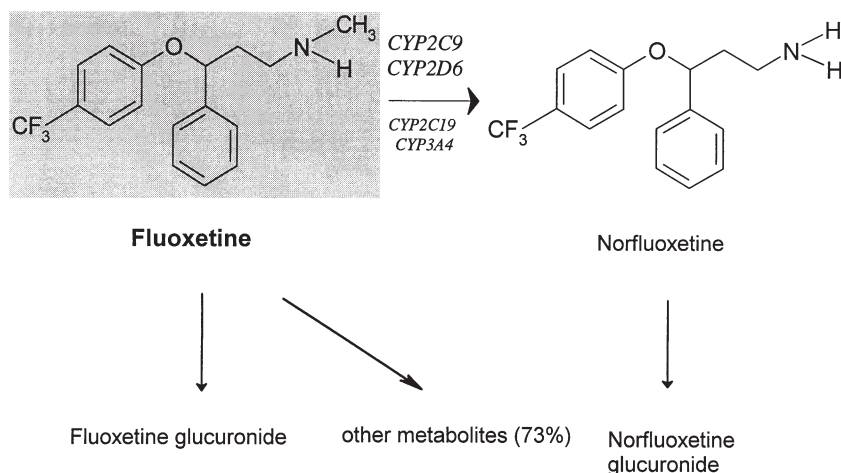


Fig. 2. Metabolism of fluoxetine and CYP isoenzymes, amine oxidase, and *N*-acetyltransferase, suggested to catalyze the Phase I reactions.

few studies have investigated the CYP isoenzymes responsible for the metabolism of fluoxetine, and the results have been inconclusive. Investigations have focused largely on the *N*-demethylation of fluoxetine. Hamelin and co-workers (1996) reported a meaningful contribution of CYP2D6 in the *N*-demethylation of fluoxetine in healthy volunteers, similar to Dominguez and co-workers (1996), who studied psychiatric patients whose medication was switched from fluoxetine to paroxetine. On the other hand, the pharmacokinetics of fluoxetine and norfluoxetine are not affected by paroxetine, a potent inhibitor of CYP2D6 (Harvey & Preskorn, 1995). Other enzymes that contribute to more than 70% of the biotransformation of fluoxetine so far are obscure.

From an *in vitro* study, it was suggested that CYP2C9 plays a pivotal role in the *N*-demethylation of fluoxetine with a possible contribution of the CYP2C19 and a CYP3A isoform, whereas the contribution of CYP2D6 was found to be negligible (von Moltke et al., 1997). It has been shown recently that the clearance of *R*- and *S*-fluoxetine and of *S*-norfluoxetine, but not of *R*-norfluoxetine, strongly depends on the CYP2D6 activity (Fjordside et al., 1999).

#### 2.4. Blood concentrations and clinical response

The relationship between blood concentrations of racemic fluoxetine and norfluoxetine and clinical outcome or adverse events was studied recently in a large number of patients (Amsterdam et al., 1997; Koran et al., 1996; Beasley et al., 1990). These studies could not find a relationship between clinical outcome and plasma concentrations of either fluoxetine or norfluoxetine or the sum of both. Since the enantiomers differ in their pharmacological potency, chiral analysis might give an association between the concentration or ratio of enantiomers and clinical outcome. As long as chiral analysis has not been conducted in conjunction with the assessment of clinical effects, a conclusion on the relationship between blood concentrations of fluoxetine or norfluoxetine and clinical response cannot be drawn. More-

over, a NMRS study has shown that plateau concentrations in the brain are not achieved before 6–8 months of treatment (Karlson et al., 1993). None of the studies aimed at the investigation of an association between blood level and clinical response were conducted over such a long period.

Although fluoxetine and its main metabolite norfluoxetine have low affinities to neurotransmitter receptors, such as serotonin 5-HT<sub>2A</sub> receptors, muscarinic acetylcholine receptors, dopamine D<sub>2</sub>-receptors, or  $\beta$ -adrenoreceptors (Stanford, 1996), some of the rare adverse events might be attributable to effects on receptor sites under conditions when high blood concentrations of fluoxetine and norfluoxetine are achieved. This may be relevant for patients with CYP2D6 deficiency (poor metabolizers [PM]), since the clearance of both fluoxetine enantiomers and of *S*-norfluoxetine depends on the activity of CYP2D6 (Fjordside et al., 1999). The extrapyramidal symptoms occasionally described in patients treated with fluoxetine (Leo, 1996), therefore, might be due to metabolic deficiency, which leads to high fluoxetine and norfluoxetine blood levels.

#### 2.5. Drug-drug interactions

One of the most prominent features of all SSRIs is their potential for pharmacokinetic drug interactions with other classes of drugs. Fluoxetine was the first SSRI for which interactions have been reported. Clinically relevant interactions have been observed for TCAs and neuroleptics (Aranow et al., 1989; Brøsen & Skjelbo, 1991; Vandel et al., 1992; Suckow et al., 1992; Rosenstein et al., 1991; Avenoso et al., 1997; Otton et al., 1993; Spina et al., 1998; Preskorn & Baker, 1997). The mechanism of these interactions could be ascribed to inhibitory effects of fluoxetine and norfluoxetine on the isoenzyme CYP2D6. The extent of inhibition correlated with the plasma concentrations of fluoxetine and norfluoxetine, respectively (Bergstrom et al., 1992). This suggests that fluoxetine and norfluoxetine can compete with other drugs for metabolism by CYP2D6. Similar to serotonin reuptake inhibition, the *S*-enantiomers of fluoxetine and

norfluoxetine were  $\sim 5$  times more potent in the inhibition of CYP2D6 than the respective R-enantiomer (Stevens & Wrighton, 1993).

Recently, a moderate inhibitory effect has been reported for norfluoxetine on CYP3A3/4 (Greenblatt et al., 1996). This can explain previously observed interactions of fluoxetine with the anxiolytic drug alprazolam (Greenblatt et al., 1992; Lasher et al., 1991) and the anticonvulsant drug carbamazepine (Levy, 1995; Ketter et al., 1991). Concomitant administration of fluoxetine to alprazolam medication elevates blood levels of alprazolam due to reduced clearance of alprazolam, and thus, may enhance psychomotor decrement. Similarly, blood levels of carbamazepine may increase when fluoxetine is co-administered (Levy, 1995; Ketter et al., 1991). The metabolism of both alprazolam and carbamazepine depends mainly on CYP3A isoenzymes (Kerr et al., 1994). In patients treated with fluoxetine and phenytoin, supertherapeutic plasma concentrations of phenytoin occurred with signs of intoxication (Jalil, 1992; Darley, 1994). This observation points to inhibition of CYP2C9, an isoenzyme mainly responsible for the metabolism of phenytoin (Shader et al., 1994).

Because of long half-lives of fluoxetine and norfluoxetine, therapeutic drug monitoring (TDM) can be applied to switch safely from fluoxetine to another antidepressant, especially to a TCA. Otherwise, an intoxication may arise from the drug interaction potential of fluoxetine and its metabolite, which can inhibit the metabolism of a TCA even weeks after discontinuation of fluoxetine (Baumann, 1996a, 1996b; unpublished observation).

### 3. Fluvoxamine

#### 3.1. Basic pharmacology

Fluvoxamine facilitates serotonergic transmission by potent and selective inhibition of serotonin reuptake into presynaptic neurons (Fig. 1). The selectivity for blocking the uptake of serotonin is markedly higher than for norepinephrine or dopamine (Richelson, 1994; Hyttel, 1993; Benfield & Ward, 1986).

#### 3.2. Basic pharmacokinetic properties

After oral application of fluvoxamine, more than 90% of the drug is absorbed (van Harten, 1995; DeVane & Gill, 1997). Due to rapid and extensive hepatic first-pass biotransformation, the amount of unchanged drug reaching the systemic circulation is much lower, reducing the bioavailability to  $\sim 53\%$  (van Harten et al., 1994).

Almost 100% of an oral dose is recovered in urine, but only negligible amounts are excreted unchanged (De Bree et al., 1983). The time to reach the maximum concentration is relatively long,  $\sim 5$  hr after a single oral dose, but independent of the dose (van Harten, 1995). The  $V_d$  of fluvoxamine is  $\sim 25$  L/kg, which is within the range of the other SSRIs except fluoxetine (van Harten, 1995). In contrast, the

accumulation in the brains of human patients, as evaluated by means of fluorine-19 NMRS, is higher than for fluoxetine (Strauss et al., 1997). In the NMRS study, it was also found that it takes  $\sim 3$  times longer to achieve steady-state concentrations in brain compared with plasma (3–10 days) (Strauss et al., 1997).

The plasma protein binding is low (77%), which makes protein binding interaction with restrictively protein-bound drugs such as valproic acid unlikely to occur (van Harten, 1995).

In healthy young male volunteers,  $t_{1/2}$  ranged between 8 and 28 hr (mean  $\sim 15$  hr) after administration of a single oral dose of 25–100 mg fluvoxamine maleate (de Vries et al., 1993). This relatively short  $t_{1/2}$  indicates that steady-state conditions should be attained within 1 week. Fluvoxamine, however, exhibits nonlinear kinetics, which becomes most prominent after multiple dosing of dosages  $> 50$  mg fluvoxamine maleate/day (de Vries et al., 1992; Spigset et al., 1997b; Härtter et al., 1998a). After increasing dosages up to 100 mg b.i.d., the  $t_{1/2}$  was found to be  $32 \pm 11$  hr, an almost 100% increase in  $t_{1/2}$  (Spigset et al., 1997b). Therefore, sometimes steady-state conditions may not be reached before 10 days of continuous treatment with fluvoxamine. Another recent study of Spigset and co-workers (1998) confirmed the nonlinear kinetics within the therapeutic dose interval. The reason for nonlinearity is not ascribed to Michaelis-Menten saturation kinetics, but rather to a complex involvement of multiple parallel pathways.

Blood concentrations of fluvoxamine in patients with severe renal impairment treated with 100 mg/day fluvoxamine maleate were similar to those observed in healthy volunteers, indicating that the pharmacokinetics of fluvoxamine do not primarily depend on the renal function (van Harten, 1995). In contrast, in patients with hepatic cirrhosis, the area under the concentration-time curve (AUC) and  $t_{1/2}$  were significantly increased compared with healthy controls (van Harten et al., 1993). Pharmacokinetics were found to be similar in elderly (mean age 73 years) and young subjects (mean age 28 years) (de Vries et al., 1992). On the other hand, marked sex differences recently were reported, with female patients developing higher serum concentrations at a dosage of 100 mg/day. The gender difference disappeared after the dosage to 200 mg/day was doubled. This points to a saturable enzyme that is more active in male than in female subjects (Härtter et al., 1998a).

#### 3.3. Metabolism

Similar to other SSRIs, fluvoxamine's main route of elimination is through hepatic metabolism. It includes oxidative demethylation and oxidative deamination (Overmars et al., 1983). After ingestion of fluvoxamine, 11 metabolites have been detected in urine, 9 of which could be structurally identified (Overmars et al., 1983) (Fig. 3). Most of these metabolites were weak acids. They are unlikely to possess pharmacological activity (Claassen, 1983).

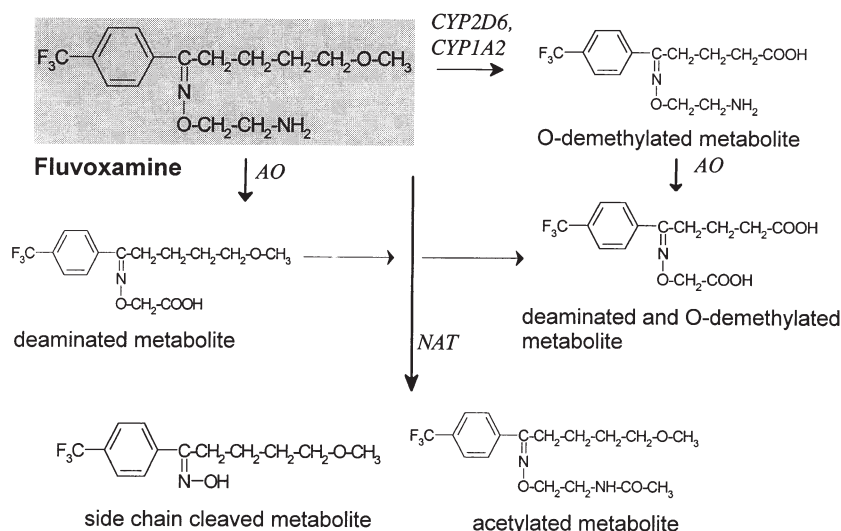


Fig. 3. Metabolism of fluvoxamine and enzymes suggested to catalyze the Phase I reactions: CYP isoenzymes, amine oxidase (AO), and *N*-acetyltransferase (NAT).

Recent reports have tried to identify CYP isoenzymes involved in the hepatic biotransformation of fluvoxamine (Carrillo et al., 1996; Spigset et al., 1995, 1997a, 1998). All these investigations were performed in healthy volunteers. In vitro studies are still lacking. The disposition of fluvoxamine was found to be associated with the polymorphic CYP2D6 and also the CYP1A2 activity (Carrillo et al., 1996; Spigset et al., 1995). Under the chosen conditions, the other polymorphic isoenzyme CYP2C19 did not play a role (Spigset et al., 1995). The studies, however, did not reflect clinical conditions, since they used a low single dose of 50 mg and young, healthy volunteers instead of a mixed-patient population. Moreover, some results are inconsistent, perhaps because of the use of different phenotyping approaches. The use of debrisoquine to phenotype CYP2D6 pointed to a meaningful contribution of CYP2D6 (Carrillo et al., 1996), whereas another study that used dextromethorphan as a probe indicated a moderate role of CYP2D6 (Spigset et al., 1997a).

#### 3.4. Blood concentrations and clinical response

As for other drugs with a high first-pass metabolism, fluvoxamine concentrations in blood are difficult to predict from any given dose. A relationship between blood concentrations and clinical effects or a "therapeutic window" has not been established (Walczak et al., 1996; Kasper et al., 1993; de Wilde & Doogan, 1982). This may be due to the inappropriate experimental design in studies that allowed dose titration and focused on side effects. Most of these studies used final dosages  $\geq 200$  mg/day that might have masked an association between blood concentrations and clinical response (Kasper et al., 1993). In contrast, side effects were suggested to correlate more directly with serum concentrations of fluvoxamine (Kasper et al., 1993), supporting the notion that there is a U-shaped relationship between drug concentrations and therapeutic response. There is so far no evidence for therapeutic

benefits of high doses (De Wilde & Doogan, 1982). In addition, in a fixed-dose pilot study on 20 depressed patients who were treated with 100 mg fluvoxamine for 14 days, we recently found that responders had serum concentrations of fluvoxamine below 85 ng/mL, and no responder was above this threshold (Härtter et al., 1998b). Assuming an upper blood concentration threshold and high interindividual variability of blood concentrations after a given dose, TDM might be helpful to improve therapy with fluvoxamine. Additional fixed-dose studies involving a sufficiently great number of patients are urgently needed to verify or falsify a possible therapeutic benefit of low fluvoxamine blood concentrations.

#### 3.5. Drug-drug interactions

Fluvoxamine is the only SSRI that potently interacts with an isoenzyme different from CYP2D6, namely CYP1A2 (Brøsen et al., 1993). CYP1A2 is an inducible P450 isoenzyme that is important for bioactivation of procarcinogens such as the heterocyclic arylamine food mutagens (Gonzales, 1992). This has led to the assumption of a protective function of continuous fluvoxamine administration (Shen, 1997).

On the other hand, CYP1A2 is involved in the *N*-demethylation of numerous xenobiotics such as TCAs (Bertschy et al., 1991; Rasmussen et al., 1995; Härtter et al., 1993; Seifritz et al., 1994; Becquemont et al., 1996; Daniel et al., 1994; Wetzel et al., 1998).

From *in vivo* investigations, fluvoxamine (or one of its metabolites) was found also to be an inhibitor of CYP2C19 (Xu et al., 1996), CYP3A4 (Fleishaker & Hulst, 1994), and possibly CYP2C9 (Schmider et al., 1997). CYP2D6 is only slightly affected by fluvoxamine *in vitro*. In a recent study on healthy volunteers receiving a common therapeutic dosage of 150 mg fluvoxamine/day, however, the urinary dextromethorphan/dextrorphan ratio as a measure of CYP2D6 activity was more than doubled, pointing to a significant inhibitory

effect of fluvoxamine on CYP2D6 under therapeutic conditions (Kashuba et al., 1998). The widespread inhibitory effects of fluvoxamine point to a common inhibitory mechanism, perhaps by interaction of fluvoxamine or one of its metabolites, with the heme moiety of the cytochromes, as has been shown for cimetidine (Levine & Bellward, 1995).

The potent inhibition of several CYP isoenzymes by fluvoxamine indicates that drug-drug interactions are clinically more critical than those of fluoxetine or paroxetine, which is directed more selectively to the inhibition of a single isoenzyme. This suggestion is supported by dramatic effects of fluvoxamine on blood concentrations of tertiary amine antidepressants (Bertschy et al., 1991; Härtter et al., 1993; Seifritz et al., 1994) or the neuroleptic clozapine (Hiemke et al., 1994; Jerling et al. 1994; Taylor, 1997), which might reflect the concerted action of fluvoxamine on more than a single CYP isoenzyme.

On the other hand, it should be emphasized that the concomitant use of fluvoxamine gives the opportunity to improve therapeutic effects of psychotropic drugs. A pharmacokinetic augmentation strategy has been proposed for the co-administration of fluvoxamine with the atypical neuroleptic clozapine (Szegedi et al., 1995; Silver et al., 1995; Silver & Shmuglikov, 1998; Bender & Eap, 1998), the typical neuroleptic haloperidol (Silver & Nassar, 1992), the TCA clomipramine (Szegedi et al., 1996), or the analgesic methadone (Bertschy et al., 1994). The observed improved responses may be due to a reduced formation rate of toxic metabolites that decreases the occurrence of side effects or prolongation of  $t_{1/2}$ , resulting in persistent optimal blood concentrations of the drug and thus, reducing the differences between minimal and maximal drug concentrations (Bender & Eap, 1998). However, besides pharmacokinetic interactions, the pharmacological properties of fluvoxamine also must be considered.

## 4. Paroxetine

### 4.1. Basic pharmacology

Paroxetine is the most potent serotonin reuptake blocker clinically available, but has a lower selectivity for the serotonin reuptake site than either fluvoxamine or sertraline (Fig. 1). In addition, it blocks muscarinic acetylcholine receptors to almost the same degree as the TCAs imipramine or doxepin, and even more effectively than desipramine or maprotiline (Owens et al., 1997). In spite of this property, anticholinergic side effects are likely to be restricted to toxic doses of paroxetine that are much higher than those required for therapeutic actions.

### 4.2. Basic pharmacokinetic properties

Paroxetine is a chiral SSRI that is marketed as a pure enantiomer (Dechant, 1991). This makes the pharmacokinetics more uniform when compared with racemic SSRIs, such as fluoxetine or citalopram. Paroxetine is efficiently absorbed from the gastrointestinal tract, but is readily me-

tabolized during its first pass through the liver (Kaye et al., 1989). Considerable amounts of paroxetine (~36%) are excreted in the feces, but less than 1% of this is unchanged paroxetine (Kaye et al., 1989). The  $V_d$  of 2–12 L/kg is similar to that of fluvoxamine; the  $t_{1/2}$  is variable, depending on both dose and duration of administration (van Harten, 1993). After 15 days of oral administration of 20 mg/day,  $t_{1/2}$  increases by ~12% (16.4–18.3 hr) and by more than 100% (9.8–21.0 hr) after oral administration of 30 mg paroxetine/day (Kaye et al., 1989). The time dependency becomes more pronounced when comparing the AUC after a single dose and after multiple dosing (Lund et al., 1979; Sindrup et al., 1992a). Even for the lower dosage of 20 mg/day, the AUC increased from 191 ng/hr/mL to 1481 ng/hr/mL. In accordance, the bioavailability reported to be less than 50% after single dose is remarkably higher after multiple doses. Taken together, these findings point to a saturable first-pass metabolism.

The nonlinear pharmacokinetics of paroxetine are best described by two distinct processes, a low-capacity/high-affinity process and a high-capacity/low-affinity linear process (Sindrup et al., 1992a). This, however, holds true only for extensive metabolizers (EM) of CYP2D6 (Sindrup et al., 1992a).

Plasma concentrations at steady-state and the elimination  $t_{1/2}$  are generally prolonged in elderly subjects (Lundmark et al., 1989; Bayer et al., 1989). While renal impairment has almost no effect on the pharmacokinetics of paroxetine, hepatic dysfunction may reduce the clearance of paroxetine (Doyle et al., 1989; Dalhoff et al., 1991).

### 4.3. Metabolism

Like other lipophilic psychotropic drugs, paroxetine undergoes extensive metabolism in the liver to form more hydrophilic excretable compounds. The 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 or in para-position to the para-methoxyderivative. Both metabolites are further conjugated with sulfuric acid or glucuronic acid (Fig. 4). None of the metabolites is assumed to contribute to the pharmacological effects of paroxetine (Kaye et al., 1989).

While the oxidative cleavage is probably catalyzed by CYP isoenzymes, methylations require other enzymes. The O-methylation is most probably catalyzed by catechol-O-methyltransferase, an enzyme involved in the deactivation of catecholamines and catechol estrogens. Interestingly, the *meta-O*-methyl metabolite or glucuronide and sulfate, respectively, was found in much lower amounts in urine of PM (Sindrup et al., 1992b), whereas the glucuronic acid conjugate of the *para-O*-methyl metabolite was found in similar amounts in EM and PM (Sindrup et al., 1992b). However, PM are able to form the *meta-O*-methyl metabolite. Differences between EM and PM, therefore, are more likely caused by different capabilities to form the catechol intermediate than by different methylation activities.

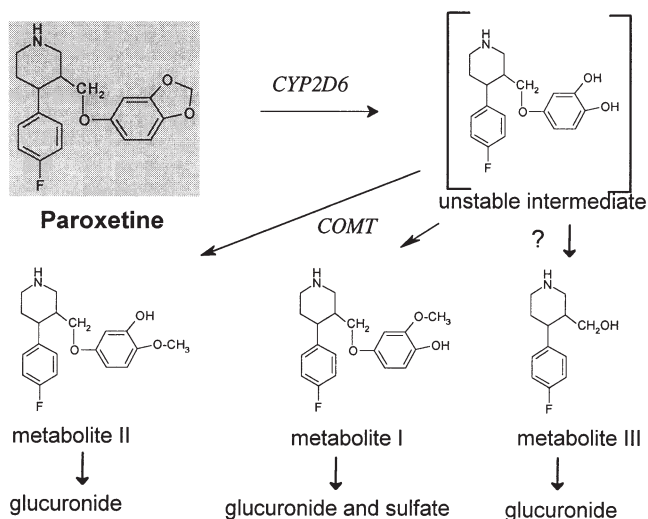


Fig. 4. Metabolism of paroxetine and enzymes suggested to catalyze the Phase I reactions: CYP2D6 and catechol-*O*-methyltransferase (COMT).

Nonlinear kinetics have been shown for EM when comparing single and multiple dosing (Sindrup et al., 1992a). However, differences between EM and PM in kinetics, metabolite formation, and paroxetine blood concentrations are not measurable under steady-state conditions. CYP2D6 probably is involved as a low-capacity and high-affinity enzyme (Sindrup et al., 1992a, 1992b) that has also been shown in vitro (Bloomer et al., 1992). The saturability of the process might be caused by substrate inhibition, since paroxetine is a potent inhibitor of CYP2D6 (Lane, 1996) and thus, of its own metabolism. The contribution of other CYP isoenzymes besides CYP2D6 have so far not been documented. A recent analysis of a database of 1715 patients under paroxetine therapy revealed 55% lower blood concentrations in patients who were under carbamazepine co-medication ( $n = 94$ ) compared with patients under paroxetine without carbamazepine (Kuss & Hegerl, 1998). Since carbamazepine is a well-known inducer of CYP3A4, it may be concluded that CYP3A4 is also involved in the degradation of paroxetine.

#### 4.4. Blood concentrations and clinical response

Similar to the findings for other SSRIs, studies to date on paroxetine do not give evidence for the existence of a relationship between blood concentrations and clinical effects (Danish University Antidepressant Group, 1990; Kuhs et al., 1992). In a study of 94 depressed inpatients, however, there were only 50% responders when paroxetine plasma levels were below 10 ng/mL vs. 76% responders at paroxetine plasma levels between 40 and 120 ng/mL (Tasker et al., 1989). In another study of 271 outpatients, the latter were initially treated with 20 mg (Benkert et al., 1997). Patients with an inadequate response after 3 weeks were randomized either to continuation of the 20 mg dose or to 40 mg. A dose of 20 mg was found optimal for the majority of patients.

Taken together, the observations indicate that there is a lower and an upper threshold of drug concentration in blood for optimal response to paroxetine.

In PM of CYP2D6, high blood concentrations of paroxetine may result and lead to anticholinergic side effects (van den Berg, 1995). Anticholinergic properties have also been discussed to explain symptoms occurring after abrupt discontinuation of paroxetine (Barr et al., 1994).

#### 4.5. Drug-drug interactions

Paroxetine is the most potent inhibitor of CYP2D6 among all SSRIs (Preskorn, 1996a; Harvey & Preskorn, 1995; Shader et al., 1996; Nemeroff et al., 1996). The average  $K_i$  for inhibition of CYP2D6 is in the nanomolar range ( $K_i = 150$  nM) (Harvey & Preskorn, 1995). This is close to that of quinidine ( $K_i = 30$  nM), the most potent inhibitor of CYP2D6 found thus far (Ching et al., 1995).

Most studies or case reports where the inhibitory potency was examined measured inhibition of the metabolism of TCAs, such as imipramine (Albers et al., 1996; Härtter et al., 1994), desipramine (Alderman et al., 1997; von Moltke et al., 1995), or trimipramine (Leinonen et al., 1995). The inhibition is much more pronounced for N-demethylated metabolites (Albers et al., 1996; Härtter et al., 1994) of TCAs (e.g., desipramine) than for the tertiary amines. This is consistent with the finding that CYP2D6 plays a most pivotal role in the clearance of secondary amines, whereas its importance is reduced in the metabolic clearance of tertiary amines (Brøsen & Gram, 1988; Breyer-Pfaff et al., 1992). The magnitude of CYP2D6 inhibition correlates with the plasma concentrations of paroxetine (Ereshefsky et al., 1996; Jeppesen et al., 1996). This may explain the inconsistent findings of two investigations on the effect of paroxetine on the pharmacokinetics of the atypical neuroleptic clozapine. Applying dosages above 20 mg/day (mean = 31 mg/day) produced a substantial increase in clozapine plasma concentrations (Centorrino et al., 1996), while a fixed dose of 20 mg paroxetine/day could not find significant effects on the concentrations of clozapine (Wetzel et al., 1998).

Comparing fluvoxamine, fluoxetine, and paroxetine with regard to their interaction potential from a clinical point of view, paroxetine may be regarded as the least problematic of the three SSRIs, despite its potent inhibition of CYP2D6. Paroxetine inhibits almost exclusively CYP2D6, and the inhibition lasts only as long as paroxetine is in the body in a sufficient concentration (3–7 days). Its para-*O*-methylated metabolite is a potent inhibitor of CYP2D6 in vitro (Lane, 1996). The metabolite, however, is unlikely to contribute to the enzyme inhibition of paroxetine in vivo due to its very fast conjugation and excretion in urine (Sindrup et al., 1992b). Thus, the magnitude and duration of inhibition is easier to handle in a clinical setting for paroxetine than for either fluoxetine (due to its long  $t_{1/2}$ ) or fluvoxamine (due to nonselectivity).



## 5. Sertraline

### 5.1. Basic pharmacology

Sertraline is the second most potent inhibitor of serotonin reuptake and the second most selective blocker of serotonin over noradrenaline uptake (Fig. 1). It is the only SSRI that binds to dopamine transporters (Richelson, 1994). With the exception of an  $\alpha_1$ -adrenoceptor blocking potential (Owens et al., 1997), the affinity of sertraline for neurotransmitter receptors is low and without clinical relevance. Since chronic administration of sertraline to rats attenuates phenylclidine-induced locomotor hyperactivity, effects of sertraline on dopaminergic neurons should be considered (Redmond et al., 1999). The clinical relevance of interactions with the dopaminergic system, however, is still obscure.

### 5.2. Basic pharmacokinetic properties

Like paroxetine, sertraline possesses two chiral centers. Only one (1S, 4S) enantiomer of sertraline is contained in the marketed formulation (Murdoch & McTavish, 1992).

Absorption from the gastrointestinal tract is almost complete, but rather slow, with a time to reach the maximum plasma concentrations ( $C_{max}$ ) of 6–8 hr (Warrington et al., 1992). The reason for this delay is not clear, but the enterohepatic cycle may play a role (van Harten, 1993). The  $V_d$  in humans exceeds 20 L/kg, which points to extensive nonspecific binding to tissue (Levine et al., 1994). At least in rats, brain concentrations of sertraline are 40 times higher than in plasma.

Linear pharmacokinetics is suggested for sertraline (Preskorn, 1993). After single doses between 50 and 200 mg,  $t_{1/2}$  is similar for single dose and steady-state conditions (Warrington et al., 1992). The elimination rate constant is higher in young males than in females or subjects >65 years (0.031/hr vs. 0.022/hr for young females vs. 0.019/hr in the elderly). In young men,  $t_{1/2}$  is ~30% shorter (22.4 hr) than in females or aged patients (32.1–36.7 hr) (Ronfeld et al., 1997). This suggests sex- and age-dependent differences either in the tissue distribution (lower relative fat volume in young men) or in the metabolism of sertraline. Similar age and sex differences have been shown for the N-demethylated metabolite (Ronfeld et al., 1997).

The pharmacokinetics are not significantly different between healthy controls and patients suffering from renal impairment (Wilner et al., 1996a). In patients with liver cirrhosis, the clearance of sertraline is markedly reduced (Wilner et al., 1996b). This is consistent with the finding that the main route of sertraline clearance is hepatic metabolism.

### 5.3. Metabolism

Although the hepatic metabolism is the most important elimination pathway, with only 0.2% of an oral dose being excreted unchanged in the urine (Murdoch & McTavish, 1992), information on the metabolism of sertraline is rather

limited. N-demethylation is the main metabolic step in the biotransformation of sertraline (Rudorfer & Potter, 1997). The N-demethylated metabolite is more slowly eliminated and has a 3 times longer  $t_{1/2}$  (60–100 hr) (Rudorfer & Potter, 1997) than its parent drug. Hence, the plasma concentration of N-desmethylsertraline is 1–3 times that of sertraline. Since N-desmethylsertraline has only 5–10% of the serotonin reuptake inhibitor potency of sertraline (Owens et al., 1997), a contribution to clinical effects of sertraline can be neglected. The N-demethylation correlates with the activity of CYP3A4 (Preskorn, 1997), suggesting that this enzyme is involved. Conclusive data on enzymes responsible for the metabolism of sertraline, however, are still lacking. Because it is a substrate of a CYP3A, the metabolism of sertraline in the gut may be important. However, the gut metabolism of sertraline has not been examined and little has been reported on other pathways, including oxidation at the side chain to a carbamaic acid and oxidative deamination to a ketone derivative (Fig. 5).

Compared to other SSRIs, a relevant portion of oral sertraline is excreted in the feces (~50%) (Warrington et al., 1992). This points to an extensive transport of metabolites or their conjugates into the bile or fecal elimination from the enterohepatic circle.

### 5.4. Blood concentrations and clinical response

To date, there have been few reports on studies on a blood concentration and clinical effect relationship for sertraline. There are, however, indications similar to the finding mentioned in Sections 3.4 and 4.4 on fluvoxamine and paroxetine that low concentrations might be advantageous. Doses of 50 mg/day are at least as effective as higher dosages, which was mainly ascribed to a reduced side effect burden (Preskorn & Lane, 1995; Stock & Kofoed, 1994). Whether the upper-threshold plasma concentrations or the dosages are more important for optimal response needs to be established. Several well-designed studies support the idea that TDM improves therapy with sertraline. This has been shown recently for geriatric patients where the therapeutic outcome was improved and clinical costs were reduced by means of TDM (Bengtsson et al., 1997).

Highly variable plasma concentrations, resulting after a given dose of sertraline (Gupta & Dziurdzy, 1994), are consistent with the involvement of the highly variably expressed CYP3A4 in the clearance of sertraline.

### 5.5. Drug-drug interactions

Interaction studies with sertraline indicate that pharmacokinetic interactions with other drugs are of minor clinical importance (Murdoch & McTavish, 1992; Rapeport et al., 1996a, 1996b; Ziegler & Wilner, 1996; Wilner et al., 1992), although the 8.9% increase in prothrombin time reported after combination with warfarin may be significant (Apseloff et al., 1997). In vitro studies on possible inhibition of CYP2D6 by sertraline and/or its N-demethylated metabolite

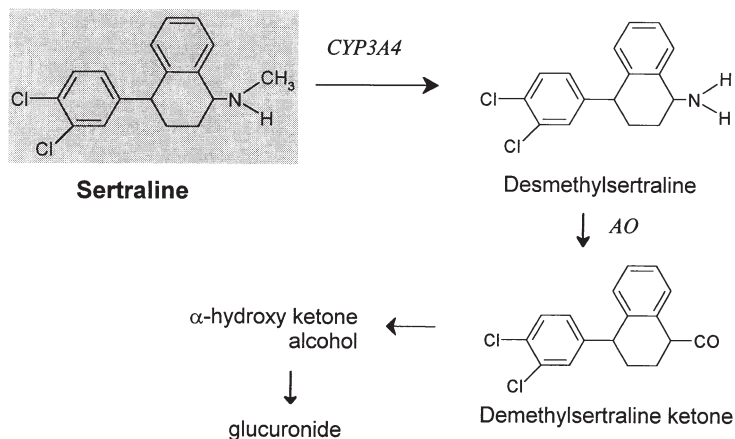


Fig. 5. Metabolism of sertraline and enzymes suggested to catalyze Phase I reactions: CYP3A4 and amine oxidase (AO).

detected a high inhibitory potency ( $K_i = 0.7 \mu\text{M}$ ) (Crewe et al., 1992). Studies on patients, however, have failed to show clinical relevance (Preskorn et al., 1994; Sproule et al., 1997; Kurz et al., 1997; Harvey & Lane, 1996). Using desipramine, a meaningful inhibitory effect of sertraline was not observed (Preskorn et al., 1994; Sproule et al., 1997; Kurz et al., 1997), even under high, chronic doses (Kurz et al., 1997). A modest inhibitory property was found for individuals with high baseline CYP2D6 activity (Solai et al., 1997).

Sertraline is a substrate of CYP3A4 (Rapeport et al., 1996a), which suggests the potential for drug interactions at this isoenzyme. An effect on the pharmacokinetics of either carbamazepine (Rapeport et al., 1996a; Preskorn et al., 1997; Harvey et al., 1996) or midazolam (in vitro) (Ring et al., 1995), which are substrates of CYP3A4, has not been observed. Just two recent case reports give evidence for significant inhibition of clozapine's metabolism by sertraline. Under 600 mg clozapine and 300 mg sertraline, the serum concentration of clozapine was 1300 ng/mL, and it decreased by 40% after discontinuation of sertraline (Pinninti & de Leon, 1997). A similar observation was described by Chong and co-workers (1997), who found that in a patient taking 175 mg clozapine, there was a 2.1-fold increase in clozapine serum concentration after addition of 50 mg sertraline, which disappeared after discontinuation of the SSRI. These case reports give evidence for in vivo inhibition of CYP3A4. Interactions of sertraline with phenytoin point to an involvement of CYP2C9 (Schmider et al., 1997).

## 6. Citalopram

### 6.1. Basic pharmacology

Citalopram has by far the highest selectivity for inhibiting serotonin reuptake (Fig. 1) over noradrenaline reuptake (Owens et al., 1997; Baumann, 1996a; Hyttel et al., 1995). It is marketed as a racemate, but its pharmacological effects

are almost exclusively ascribed to the S-(+) enantiomer (Hyttel et al., 1992). The main metabolite of citalopram, measurable in plasma, is *N*-desmethylcitalopram, which is also an SSRI showing the same enantiomeric differential as its parent drug (Baumann & Larsen, 1995). In addition to its ability to inhibit serotonin reuptake, citalopram has some affinity to  $\alpha_1$ -adrenoceptors and a slight histamine  $H_1$ -receptor blocking potency (Owens et al., 1997).

### 6.2. Basic pharmacokinetic properties

As for other lipophilic drugs, the absorption of citalopram from the gastrointestinal tract is almost complete. In contrast to the other SSRIs, the first-pass effect of citalopram seems to be of minor importance (Baumann & Larsen, 1995; Gonzales, 1992; van Harten, 1993), which is in line with an absolute bioavailability of  $\sim 80\%$ . Since only 50% of the dose is excreted in urine (Milne & Goa, 1991), a significant fecal elimination is suggested (van Harten, 1993), which is supported by unaltered  $C_{\text{max}}$  in patients with hepatic insufficiency (Baumann & Larsen, 1995).

The elimination in healthy volunteers was found to be biphasic, with a  $t_{1/2}$  at steady-state of  $\sim 36$  hr (Kragh-Sørensen et al., 1981). The  $t_{1/2}$  of the *N*-demethylated metabolites is  $\sim 2$ – $3$  times longer (Kragh-Sørensen et al., 1981). Despite that, *N*-desmethylcitalopram normally does not exceed the plasma concentration of its parent drug (Rudorfer & Potter, 1997; Baumann, 1996b; Kragh-Sørensen et al., 1981; Foglia et al., 1997). This also indicates the relatively poor contribution of metabolism to the overall clearance of citalopram.

A linear relationship between citalopram dosage and plasma concentration has been reported under steady-state conditions (Baumann and Larsen, 1995; Fredricson-Overø, 1987). The interindividual variability, however, also increases with dose, which might be due to saturation of an elimination pathway.

Protein binding amounts only to  $\sim 80\%$  (Milne & Goa, 1991), which makes interactions at specific protein-binding sites quite unlikely.

As for the hepatic impairment, the  $C_{\max}$  in patients with renal impairment was unchanged compared with that of healthy volunteers (Baumann & Larsen, 1995). The  $t_{1/2}$  was significantly increased to  $\sim 50$  hr and the renal clearance of citalopram and desmethylcitalopram was significantly lower (Baumann & Larsen, 1995). These effects, however, are regarded as clinically not important.

Interestingly, the clearance and N-demethylation are significantly reduced in elderly patients (Foglia et al., 1997; Fredricson-Overø et al., 1985), the latter suggesting the contribution of an isoenzyme whose activity decreases with age (George et al., 1995). Therefore, lower doses are recommended for elderly patients than for young ones.

### 6.3. Metabolism

The metabolism of citalopram leads to two pharmacologically active metabolites (Fig. 6) with two enantiomers for each (Baumann & Larsen, 1995). As for citalopram, only the S-(+) enantiomer of each metabolite has serotonin reuptake inhibitory properties (Hyttel et al., 1992). Since plasma levels of the metabolites observed under steady-state conditions reach  $< 50\%$  of those measured for the parent compound (Kragh-Sørensen et al., 1981; Fredricson-Overø, 1982; Øyehaug & Østensen, 1984), the role of the metabolites for the overall activity of citalopram can be neglected.

The main metabolic step is N-demethylation to N-desmethylcitalopram, which is further N-demethylated to didesmethylcitalopram (Baumann & Larsen, 1995). Plasma concentrations of the nonactive R-(−) enantiomer (Rochat et al., 1995a) are higher than those of the S-(+) enantiomer (Rochat et al., 1995b). The mean S/R enantiomer ratio of citalopram in patients is 0.56 and that of desmethylcitalopram is 0.72. This points to a stereoselective metabolism of

citalopram, possibly due to a higher affinity of S-(+) citalopram to particular metabolizing isoenzymes.

Besides the N-demethylated metabolites, an N-oxide and a propionic acid derivative have also been identified. However, only N-desmethylcitalopram is detectable in the blood in substantial amounts (Baumann & Larsen, 1995; Kragh-Sørensen et al., 1981). This main metabolite reaches only  $\sim 50\%$  the concentration of the parent drug in blood (Øyehaug & Østensen, 1984).

Recently, it has been shown that CYP2C19 and CYP2D6, both polymorphically expressed isoenzymes, play a role in the biotransformation of citalopram (Sindrup et al., 1993). The N-demethylation correlates with mephenytoin hydroxylase activity; and in PM of mephenytoin that lack CYP2C19 activity, the total clearance and N-demethylation clearance are lower than in EM of CYP2C19 (Sindrup et al., 1993). Furthermore, it was suggested that the S/R ratio of the citalopram enantiomers might be indicative of the activity of CYP2C19, with CYP2C19-deficient patients having an almost doubled citalopram S/R ratio of  $\geq 1$  (Rochat et al., 1995b). The N-demethylation of desmethylcitalopram to didesmethylcitalopram depends on CYP2D6, as didesmethylcitalopram was never detectable in PM of sparteine and AUCs of desmethylcitalopram were about one-third higher in PM than in EM (Sindrup et al., 1993). This is of particular interest because desmethylcitalopram would be the first primary amine substrate of CYP2D6.

From in vitro analysis, it has been concluded that CYP3A4 is involved in the N-demethylation of citalopram (Rochat et al., 1997; Kobayashi et al., 1997). The contribution of CYP3A4 to the clearance of citalopram is also indicated by accelerated metabolism of citalopram under concomitant treatment with carbamazepine (Leinonen et al., 1996).

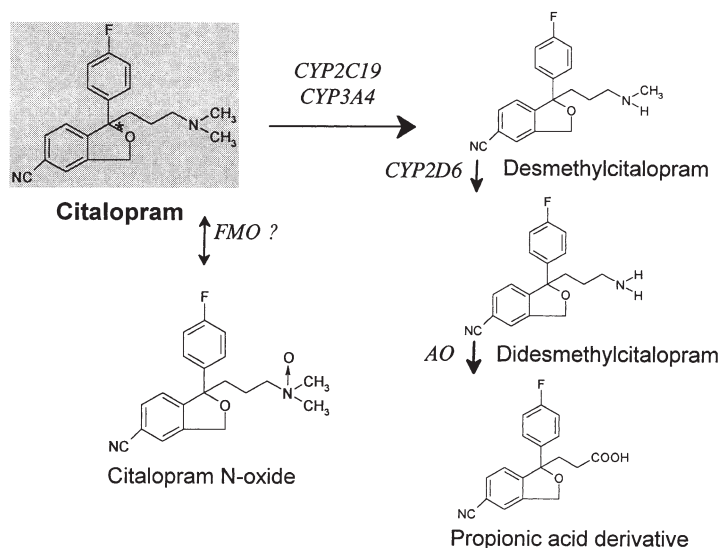


Fig. 6. Metabolism of citalopram and enzymes suggested to catalyze Phase I reactions: CYP2C19, CYP3A4, CYP2D6, amine oxidase (AO), and flavine monooxygenase (FMO).

#### 6.4. Blood concentrations and clinical response

There have been few studies on SSRI concentration-effect relationships, and this is particularly the case for citalopram. As shown by Rochat et al. (1995a), the steady-state levels of the citalopram metabolites will never exceed those of the parent drug. Together with their lower serotonin reuptake blocking potency, they probably will not contribute to the overall effect of citalopram. Determination of metabolites, therefore, is not necessary for drug monitoring. In a study by Bjerkenstedt and co-workers (1985), who did not consider the pharmacological differences between the R-(–) and S-(+) enantiomers, no correlation was found between clinical effect and citalopram serum concentrations. Possible relationships between clinical outcome and serum concentrations might have been masked by the lack of stereospecific analysis. Bjerkenstedt and co-workers suggested a better efficacy or tolerability at low citalopram blood levels, consistent with the previously mentioned reports on fluvoxamine, paroxetine, and sertraline (see Sections 3.4, 4.4, and 5.4), and perhaps a common feature of all SSRIs.

#### 6.5. Drug-drug interactions

Since CYP2C19 and CYP2D6 possibly are involved in the catabolism of citalopram, effects on the activity of these isoenzymes may be expected. After chronic treatment with citalopram, the activity of CYP2D6 is slightly reduced, which probably is due to inhibitory properties of *N*-desmethylcitalopram (Baumann & Larsen, 1995; Gram et al., 1993). No significant effect of citalopram has been found so far on the pharmacokinetics of substrates of CYP2C19 (Kobayashi et al., 1995). On the other hand, co-medication with phenothiazine neuroleptics such as levomepromazine increases steady-state trough concentrations of citalopram by ~30% without clinical consequences. Levomepromazine, a known inhibitor of CYP2D6, particularly increased the steady-state concentrations of desmethylcitalopram (Gram et al., 1993). Chronic treatment with high doses of cimetidine (800 mg/day) decreased the oral clearance of citalopram by 29% and increased the blood concentration of citalopram by 43% (Priskorn et al., 1997).

With other psychotropic drugs, including TCAs (Baettig et al., 1993), neuroleptics (Syvalahti et al., 1997), and tranquilizers, relevant pharmacokinetic drug interactions are rather unlikely. Citalopram is, therefore, the most safe SSRI with respect to pharmacokinetic drug interactions.

#### 7. Synopsis

The various TCAs, the first generation of drugs that produce their antidepressant actions by inhibiting monoamine uptake, differ in their pharmacodynamic properties, especially with regard to side effects related to interactions with neurotransmitter receptors. The five SSRIs that are now available to treat depression or other disorders with a suggested dysfunctional serotonergic system exhibit similar therapeutic efficacies and similar adverse reaction profiles, in spite of a relatively wide range of affinities to serotonin uptake sites (Fig. 1). There are just a few differences in the incidence and extent of rare effects, such as hyponatremia (Wilkinson et al., 1999), extrapyramidal symptoms (Leo, 1996), or withdrawal symptoms after drug discontinuation (Price et al., 1996; Haddad, 1997), probably due to interactions with other target structures besides uptake sites (Goodnick & Goldstein, 1998). As explained in this review and summarized in Table 1, SSRIs primarily differ in their pharmacokinetic properties. To select a distinct SSRI, its  $t_{1/2}$ , linearity of kinetics, and interaction potential should be considered. The long  $t_{1/2}$  of fluoxetine may be both advantageous and disadvantageous. It is advantageous for a patient with poor compliance, since drug concentrations decrease only slightly when the patient omits a dose. On the other hand, at least 4 weeks of constant medication are necessary to reach steady-state levels of fluoxetine. Moreover, in the case of fluoxetine nonresponse long wash-out periods are necessary before switching the patient to a TCA or a monoamine oxidase inhibitor to avoid drug interactions or the development of a serotonin syndrome.

Nonlinear kinetics of fluvoxamine, fluoxetine, and paroxetine complicate dosing. Dose escalation leads to disproportionate increases in drug concentrations, which may be critical to the proposal that there might be an upper-threshold concentration in blood that determines nonresponse. TDM may be useful to attain optimal drug concentrations in an individual patient. Therapeutically effective blood concentrations of SSRIs, however, still need to be established. The statement that dose titration guided by TDM is necessary for TCAs, but not for SSRIs, is sometimes given in drug information brochures on SSRIs. However, this has neither been verified nor falsified in the literature. The suggested lack of data on a “therapeutic window” for SSRIs, therefore, cannot be considered as an advantage of SSRIs over TCAs, as long as valid studies on therapeutic serum concentrations are missing for SSRIs.

Table 1  
Pharmacokinetic parameters of SSRIs and clinically relevant interactions with CYP isoenzymes

SSRI	Daily dose (mg)	$t_{1/2}$	Time to reach steady state	$V_d$ (L/kg)	Linear kinetics	CYP inhibition
Fluoxetine	20–80	1–4 days	>4 weeks	20–45	No	2D6
Norfluoxetine		7–15 days				2D6, 3A4
Fluvoxamine	50–300	15 hr	10 days	5	No	1A2, 2C19
Paroxetine	20–50	20 hr	7–14 days	3–12	No	2D6
Sertraline	50–150	26 hr	5–7 days	20	Yes	Minimal
Citalopram	10–60	36 hr	6–10 days	14–16	Yes	Not relevant

Table 2  
Inhibitor constants ( $K_i$ ,  $\mu\text{mol/L}$ ) of SSRIs for CYP isoenzymes

SSRI	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
Fluoxetine	4–>100		5.2	0.07–3.5	60–83
Norfluoxetine	6–>100		1.1	0.19–3.5	11–19
Fluvoxamine	0.2	+	+	0.15–8.2	10–60
Paroxetine	5.5		7.5	0.15–2.0	39–>100
Setraline	8.8–70		2.0	0.7–22.7	23–>100
Citalopram	>100		87	5.1–19	>100

+, suggested inhibitor;  $K_i$  not determined.

Data from Brøsen et al. (1993), Lane (1996), and von Moltke et al. (1995, 1997).

The most serious difference between the five SSRIs is their potential for drug–drug interactions. Paroxetine, fluoxetine, and norfluoxetine are potent inhibitors of CYP2D6, and fluvoxamine of CYP1A2 and CYP2C19 (possibly also CYP3A4 and CYP2D6). Combining these SSRIs with drugs that are substrates of the inhibited enzymes has the potential for great harm, unless they are recognized and properly managed. Alternatively, drug interactions can also be used constructively to improve treatment effectiveness and reduce side effects (Silver & Nassar, 1992; Szegedi et al., 1995; Shen, 1997; Jefferson, 1998). Considering both risks and benefits of SSRI–drug interactions, the contention that “a noninteracting SSRI is advantageous to an interacting one” is premature. We need much more systematic clinical studies on drug–drug interactions for SSRIs.

With an expanding knowledge base, it will be possible to understand and predict drug interactions with SSRIs. Most drug interactions of SSRIs have been detected by chance, since there was no knowledge of CYP inhibitory properties when the drugs were introduced on the market. After having introduced SSRIs, we learned that systematic investigations on substrate and inhibitor properties of drugs must be conducted in the early phases of drug development. For SSRIs, even now our knowledge on substrate and inhibitor specificities of drug-metabolizing enzymes is incomplete.

Moreover, studies that have characterized substrate and inhibitor properties of SSRIs in vitro produced highly variable data between different studies (Table 2). Therefore, the test systems need to be optimized to raise data that are valid for clinical use of the drugs. In vitro cell systems that express distinct human metabolizing enzymes are now available to study substrate and inhibitor properties of new drugs. Such preclinical approaches will gain increasing importance in the future. Current drug development aims to identify drugs that act with high selectivity. This will increase the use of multiple drugs therapeutically instead of a single drug and thus, increase the likelihood of drug–drug interactions.

Looking back on the last 10 years of intensive SSRI use, we have learned that the introduction of SSRIs has not only brought a new class of drugs, but also refocused our attention on the importance of pharmacokinetic properties to the action of drugs in general. Pharmacokinetic properties of a drug must not be regarded as the basic properties of a chem-

ical substance. They may differ between and within individuals. Clinicians have to be aware of this to provide safe and efficacious care to their patients.

## References

- Albers, L. A., Reist, C., Helmeke, D., Vu, R., & Tang, S. W. (1996). Paroxetine shifts imipramine metabolism. *Psychiatry Res* 59, 189–196.
- Alderman, J., Preskorn, S. H., Greenblatt, D. J., Harrison, W., Penenberg, D., Allison, J., & Chung, M. (1997). Desipramine pharmacokinetics when coadministered with paroxetine or sertraline in extensive metabolizers. *J Clin Psychopharmacol* 17, 284–291.
- Amsterdam, J. D., Fawcett, J., Quitkin, F. M., Reimherr, F. W., Rosenbaum, J. F., Michelson, D., Hornig-Rohan, M., & Beasley, C. M. (1997). Fluoxetine and norfluoxetine plasma concentrations in major depression: a multicenter study. *Am J Psychiatry* 154, 963–969.
- Apsehoff, G., Wilner, K. D., Gerber, N., & Tremaine, L. M. (1997). Effect of sertraline on protein binding of warfarin. *Clin Pharmacokinet* 32(suppl. 1), 37–42.
- Aranow, R. B., Hudson, J. I., Pope, H. G., Jr., Grady, T. A., Laage, T. A., Bell, I. R., & Cole, J. O. (1989). Elevated antidepressant plasma levels after addition of fluoxetine. *Am J Psychiatry* 146, 911–913.
- Avenoso, A., Spina, E., Campo, G., Facciola, G., Ferlito, M., Zuccaro, P., Perucca, E., & Caputi, A. P. (1997). Interaction between fluoxetine and haloperidol: pharmacokinetic and clinical implications. *Pharmacol Res* 35, 335–339.
- Baettig, D., Bondolfi, G., Montaldi, S., Amey, M., & Baumann, P. (1993). Tricyclic antidepressant plasma levels after augmentation with citalopram: a case study. *Eur J Clin Pharmacol* 44, 403–405.
- Barr, L. C., Goodman, W. K., & Price, L. H. (1994). Physical symptoms associated with paroxetine discontinuation. *Am J Psychiatry* 151, 289.
- Baumann, P. (1996a). Pharmacology and pharmacokinetics of citalopram and other SSRIs. *Int Clin Psychopharmacol* 11(suppl. 1), 5–11.
- Baumann, P. (1996b). Pharmacokinetic-pharmacodynamic relationship of the selective serotonin reuptake inhibitors. *Clin Pharmacokinet* 31, 444–469.
- Baumann, P., & Larsen, F. (1995). The pharmacokinetics of citalopram. *Rev Contemp Pharmacother* 6, 287–295.
- Baumann, P., & Rochat, B. (1995). Comparative pharmacokinetics of selective serotonin reuptake inhibitors: a look behind the mirror. *Int Clin Psychopharmacol* 10(suppl. 1), 15–21.
- Bayer, A. J., Roberts, N. A., Allen, E. A., Horan, M., Routledge, P. A., Swift, C. G., Byrne, M. M., Clarkson, A., & Zussman, B. D. (1989). The pharmacokinetics of paroxetine in the elderly. *Acta Psychiatr Scand* 80(suppl. 350), 85–86.
- Beasley, C. M., Jr., Bosomworth, J. C., & Wernicke, J. F. (1990). Fluoxetine: relationships among dose, response adverse events, and plasma concentrations in the treatment of depression. *Psychopharmacology* 26, 18–24.
- Bech, P. (1988). A review of the antidepressant properties of serotonin reuptake inhibitors. *Adv Biol Psychiatry* 17, 58–69.

- Becquemont, L., Le Bot, M. A., Riche, C., & Beaune, P. (1996). Influence of fluvoxamine on tacrine metabolism in vitro: potential implication for the hepatotoxicity in vivo. *Fundam Clin Pharmacol* 10, 156–157.
- Bender, S., & Eap, C. B. (1998). Very high cytochrome P4501A2 activity and nonresponse to clozapine. *Arch Gen Psychiatry* 55, 1048–1050.
- Benfield, P., & Ward, A. (1986). Fluvoxamine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. *Drugs* 32, 313–334.
- Benfield, P., Heel, R. C., & Lewis, S. P. (1986). Fluoxetine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in depressive illness. *Drugs* 32, 481–508.
- Bengtsson, F., Lundmark, J., Nordin, C., Reis, M., & Wålinder, J. (1997). TDM of selective serotonin reuptake inhibitors treating depression in the elderly reduces drug doses and costs. *Ther Drug Monit* 19, 579.
- Benkert, O., Szegedi, A., Wetzel, H., Staab, H. J., Meister, W., & Philipp, M. (1997). Dose escalation vs. continued doses of paroxetine and maprotiline: a prospective study in depressed out-patients with inadequate treatment response. *Acta Psychiatr Scand* 95, 288–296.
- Bergstrom, R. F., Peyton, A. L., & Lemberger, L. (1992). Quantification and mechanism of the fluoxetine and tricyclic antidepressant interaction. *Clin Pharmacol Ther* 51, 239–248.
- Bertschy, G., Vandel, S., Vandel, B., Allers, G., & Volmat, R. (1991). Fluvoxamine-tricyclic antidepressant interaction. *Eur J Clin Pharmacol* 40, 119–120.
- Bertschy, G., Baumann, P., Eap, C. B., & Baettig, D. (1994). Probable metabolic interaction between methadone and fluvoxamine in addict patients. *Ther Drug Monit* 16, 42–45.
- Bjerkenstedt, L., Flyckt, L., Fredricson-Overø, K., & Lingjærde, O. (1985). Relationship between clinical effects, serum drug concentration and serotonin uptake inhibition in depressed patients treated with citalopram. *Eur J Clin Pharmacol* 28, 553–557.
- Bloomer, J. D. C., Woods, F. R., Haddock, R. E., Lennard, M. S., & Tucker, G. T. (1992). The role of cytochrome P4502D6 in the metabolism of paroxetine by human liver microsomes. *Br J Clin Pharmacol* 33, 521–523.
- Breyer-Pfaff, U., Pfandl, B., Nill, K., Nusser, E., Monney, C., Jonzier-Perey, M., Baettig, D., & Baumann, P. (1992). Enantioselective amitriptyline metabolism in patients phenotyped for two cytochrome P450 isozymes. *Clin Pharmacol Ther* 52, 350–358.
- Brøsen, K. (1996). Are pharmacokinetic drug interactions with the SSRIs an issue? *Int Clin Psychopharmacol* 11(suppl. 1), 23–27.
- Brøsen, K., & Gram, L. F. (1988). First-pass metabolism of imipramine and desipramine: impact of the sparteine oxidation phenotype. *Clin Pharmacol Ther* 43, 400–406.
- Brøsen, K., & Skjelbo, E. (1991). Fluoxetine and norfluoxetine are potent inhibitors of P450IID6—the source of the sparteine/debrisoquine oxidation polymorphism. *Br J Clin Pharmacol* 32, 136–137.
- Brøsen, K., Skjelbo, E., Rasmussen, B. B., Poulsen, H. E., & Loft, S. (1993). Fluvoxamine is a potent inhibitor of cytochrome P4501A2. *Biochem Pharmacol* 45, 1211–1214.
- Caccia, S., Cappi, M., Fracasso, C., & Garattini, S. (1990). Influence of dose and route of administration on the kinetics of fluoxetine and its metabolite norfluoxetine in the rat. *Psychopharmacology* 100, 509–514.
- Carrillo, J. A., Dahl, M. L., Svensson, J. O., Alm, C., Rodriguez, I., & Bertilsson, L. (1996). Disposition of fluvoxamine in humans is determined by the polymorphic CYP2D6 and also by the CYP1A2 activity. *Clin Pharmacol Ther* 60, 183–190.
- Catterson, M. L., & Preskorn, S. H. (1996). Pharmacokinetics of selective serotonin reuptake inhibitors: clinical relevance. *Pharmacol Toxicol* 78, 203–208.
- Centorrino, F., Baldessarini, R. J., Frankenburg, F. R., Kando, J., Volpicelli, S. A., & Flood, J. G. (1996). Serum levels of clozapine and norclozapine in patients treated with selective serotonin reuptake inhibitors. *Am J Psychiatry* 153, 820–822.
- Ching, M. S., Blake, C. L., Ghabrial, H., Ellis, S. W., Lennard, M. S., Tucker, G. T., & Smallwood, R. A. (1995). Potent inhibition of yeast-expressed CYP2D6 by dihydroquinidine, quinidine, and its metabolites. *Biochem Pharmacol* 50, 833–837.
- Chong, S. A., Tan, C. H., & Lee, H. S. (1997). Worsening of psychosis with clozapine and selective serotonin reuptake inhibitor combination: two case reports. *J Clin Psychopharmacol* 17, 68–69.
- Claassen, V. (1983). Review of the animal pharmacology and pharmacokinetics of fluvoxamine. *Br J Clin Pharmacol* 15, 349S–355S.
- Cole, J. O. (1992). New directions in antidepressant therapy: a review of sertraline, a unique serotonin reuptake inhibitor. *J Clin Psychiatry* 53, 333–340.
- Crewe, H. K., Lennard, M. S., Tucker, G. T., Woods, F. R., & Haddock, R. E. (1992). The effect of selective serotonin re-uptake inhibitors on cytochrome P4502D6 (CYP2D6) activity in human liver microsomes. *Br J Clin Pharmacol* 34, 262–265.
- Cusack, B., Nelson, A., & Richelson, E. (1994). Binding of antidepressants to human brain receptors: focus on never generation compounds. *Psychopharmacology* 114, 559–565.
- Dalhoff, K., Almdal, T. P., Bjerrum, K., Keiding, S., Mengel, H., & Lund, J. (1991). Pharmacokinetics of paroxetine in patients with cirrhosis. *Eur J Clin Pharmacol* 41, 351–354.
- Daniel, D. G., Randolph, C., Jaskiw, G., Handel, S., Williams, T., Abi-Dargham, A., Shoaf, S., Egan, M., Elkashef, A., Liboff, S., & Linnoila, M. (1994). Coadministration of fluvoxamine increases serum concentrations of haloperidol. *J Clin Psychopharmacol* 14, 340–343.
- Daniel, W. A., & Wójcikowski, J. (1997a). Contribution of lysosomal trapping to the total tissue uptake of psychotropic drugs. *Pharmacol Toxicol* 80, 62–68.
- Daniel, W. A., & Wójcikowski, J. (1997b). Interactions between promazine and antidepressants at the level of cellular distribution. *Pharmacol Toxicol* 81, 259–264.
- Danish University Antidepressant Group (1990). Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. *J Affect Disord* 18, 289–299.
- Darley, J. (1994). Interaction between phenytoin and fluoxetine. *Seizure* 3, 151–152.
- De Bree, H., van der Schoot, J. B., & Post, L. C. (1983). Fluvoxamine maleate; disposition in man. *Eur J Drug Metab Pharmacokinet* 3, 175–179.
- Dechant, K. (1991). Paroxetine: a review. *Drugs* 41, 226–253.
- De Jonghe, F., & Swinkels, J. A. (1992). The safety of antidepressants. *Drugs* 43(suppl. 2), 40–47.
- den Boer, J. A., Westenbergh, H. G., De Leeuw, A. S., & van Vliet, I. M. (1995). Biological dissection of anxiety disorders: the clinical role of selective serotonin reuptake inhibitors with particular reference to fluvoxamine. *Int Clin Psychopharmacol* 9(suppl. 4), 47–52.
- DeVane, C. L., & Gill, H. S. (1997). Clinical pharmacokinetics of fluvoxamine: applications to dosage regimen design. *J Clin Psychiatry* 58(suppl. 5), 7–14.
- de Vries, M. H., Raghoebar, M., Mathlener, I. S., & van Harten, J. (1992). Single and multiple oral dose fluvoxamine kinetics in young and elderly subjects. *Ther Drug Monit* 14, 493–498.
- de Vries, M. H., van Harten, J., van Bommel, P., & Raghoebar, M. (1993). Pharmacokinetics of fluvoxamine maleate after increasing single oral doses in healthy subjects. *Biopharm Drug Dispos* 14, 291–296.
- De Wilde, J. E. M., & Doogan, D. P. (1982). Fluvoxamine and chlorimipramine in endogenous depression. *J Affect Disord* 4, 249–259.
- Dominguez, R. A., Kumar, A. M., & Cua, W. (1996). Lack of change in fluoxetine and norfluoxetine kinetics when switching from fluoxetine to paroxetine. *J Clin Psychopharmacol* 16, 320–323.
- Doyle, G. D., Laher, M., Kelly, J. G., Byrne, M. M., Clarkson, A., & Zussman, B. D. (1989). The pharmacokinetics of paroxetine in renal impairment. *Acta Psychiatr Scand* 80(suppl. 350), 89–90.
- Ereshfsky, L., Riesenman, C. L., Lam, Y. W. F., & Simpson, J. (1996). CYP2D6 drug interaction potential of four SSRI's using in vivo dextromethorphan. *Eur Neuropsychopharmacol* 6(suppl. 3), 42.
- Fjordside, L., Jeppesen, U., Eap, C. B., Powell, K., Baumann, P., &

- Brösen, K. (1999). The stereoselective metabolism of fluoxetine in poor and extensive metabolizers of sparteine. *Pharmacogenetics* 9, 55–60.
- Fleishaker, J. C., & Hulst, L. K. (1994). A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. *Eur J Clin Pharmacol* 46, 35–39.
- Foglia, J. P., Pollock, B. G., Kirshner, M. A., Rosen, J., Sweet, R., & Mulsant, B. (1997). Plasma levels of citalopram enantiomers and metabolites in elderly patients. *Psychopharmacol Bull* 33, 109–112.
- Frazer, A. (1997). Pharmacology of antidepressants. *J Clin Psychopharmacol* 17(suppl. 2), 2S–18S.
- Fredricson-Overø, K. (1982). Kinetics of citalopram in man; plasma levels in patients. *Prog Neuropsychopharmacol Biol Psychiatry* 6, 311–318.
- Fredricson-Overø, K. (1987). The role of pharmacokinetics in the development of new drugs: an illustration by studies on citalopram. Thesis, University of Copenhagen.
- Fredricson-Overø, K., Toft, B., Christophersen, L., & Gylding-Sabroe, J. P. (1985). Kinetics of citalopram in elderly patients. *Psychopharmacology* 86, 253–257.
- Fuller, R. W., Perry, K. W., & Molloy, B. B. (1975). Effect of 3-(*p*-trifluoromethylphenoxy)-*N*-methyl-3-phenylpropylamine on the depletion of brain serotonin by 4-chloroamphetamine. *J Pharmacol Exp Ther* 193, 796–803.
- Fuller, R. W., Snoddy, H. D., Krushinski, J. H., & Robertson, D. W. (1992). Comparison of norfluoxetine enantiomers as serotonin uptake inhibitors *in vivo*. *Neuropharmacology* 31, 997–1000.
- George, J., Byth, K., & Farrell, G. C. (1995). Age but not gender selective affects expression of individual cytochrome P450 proteins in human liver. *Biochem Pharmacol* 50, 727–730.
- Gonzales, F. J. (1992). Human cytochromes P450: problems and prospects. *Trends Pharmacol Sci* 13, 346–352.
- Goodnick, P. J., & Goldstein, B. J. (1998). Selective serotonin reuptake inhibitors in affective disorders—I. Basic pharmacology. *J Psychopharmacol* 12(3 suppl. B), S5–S20.
- Gram, L. F. (1994). Fluoxetine. *N Engl J Med* 331, 1354–1361.
- Gram, L. F., Hansen, M. G. J., Sindrup, S. H., Brösen, K., Poulsen, J. H., Aaes-Jørgensen, T., & Overø, K. F. (1993). Citalopram: interaction studies with levomepromazine, imipramine and lithium. *Ther Drug Monit* 15, 18–24.
- Greenblatt, D. J., Preskorn, S. H., Cotreau, M. M., Horst, W. D., & Harmatz, J. S. (1992). Fluoxetine impairs clearance of alprazolam but not of clonazepam. *Clin Pharmacol Ther* 52, 479–486.
- Greenblatt, D. J., von Moltke, L. L., Schmider, J., Harmatz, J. S., & Shader, R. I. (1996). Inhibition of human cytochrome P450-3A isoforms by fluoxetine and norfluoxetine: *in vitro* and *in vivo* studies. *J Clin Pharmacol* 36, 792–798.
- Gunasekara, N. S., Noble, S., & Benfield, P. (1998). Paroxetine. An update of its pharmacology and therapeutic use in depression and a review of its use in other disorders. *Drugs* 55, 85–120.
- Gupta, R. N., & Dziurdzy, S. A. (1994). Therapeutic monitoring of sertraline. *Clin Chem* 40, 498–499.
- Haddad, P. (1997). Newer antidepressants and the discontinuation syndrome. *J Clin Psychiatry* 58(suppl. 7), 17–21.
- Hamelin, B. A., Turgeon, J., Vallée, F., Bélanger, P. M., Paquet, F., & LeBel, M. (1996). The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. *Clin Pharmacol Ther* 60, 512–521.
- Härtter, S., Wetzel, H., Hammes, E., & Hiemke, C. (1993). Inhibition of antidepressant demethylation and hydroxylation by fluvoxamine in depressed patients. *Psychopharmacology* 110, 302–308.
- Härtter, S., Hermes, B., Szegedi, A., & Hiemke, C. (1994). Automated determination of paroxetine and its main metabolite by column switching and on-line high-performance liquid chromatography. *Ther Drug Monit* 16, 400–406.
- Härtter, S., Wetzel, H., Hammes, E., Torkzadeh, M., & Hiemke, C. (1998a). Non-linear pharmacokinetics of fluvoxamine and gender differences. *Ther Drug Monit* 20, 446–449.
- Härtter, S., Wetzel, H., Hammes, E., Torkzadeh, M., & Hiemke, C. (1998b). Serum concentrations of fluvoxamine and clinical effects. A prospective open clinical trial. *Pharmacopsychiatry* 31, 199–200.
- Harvey, A., & Lane, R. (1996). SSRIs and inhibition of the cytochrome P4502D6 isoenzyme. *Eur Neuropsychopharmacol* 6(suppl. 3), 42.
- Harvey, A. T., & Preskorn, S. H. (1995). Interactions of serotonin reuptake inhibitors with tricyclic antidepressants. *Arch Gen Psychiatry* 52, 783–784.
- Harvey, A. T., & Preskorn, S. H. (1996). Cytochrome P450 enzymes: Interpretation of their interactions with selective serotonin reuptake inhibitors. Part I. *J Clin Psychopharmacol* 16, 273–285.
- Harvey, A., Preskorn, S., Lane, R., & Wilner, K. (1996). Sertraline and P4503A/4. *Eur Neuropsychopharmacol* 6(suppl. 3), 40.
- Hiemke, C., Weigmann, H., Härtter, S., Dahmen, N., Wetzel, H., & Müller, H. (1994). Elevated levels of clozapine in serum after addition of fluvoxamine. *J Clin Psychopharmacol* 14, 279–281.
- Hotopf, M., Lewis, G., & Normand, C. (1996). Are SSRIs a cost-effective alternative to tricyclics? *Br J Psychiatry* 168, 404–409.
- Hyttel, J. (1993). Comparative pharmacology of selective serotonin reuptake inhibitors (SSRIs). *Nord J Psychiatry* 47(suppl. 30), 5–12.
- Hyttel, J., Bøgesø, K. P., Perregaard, J., & Sánchez, C. (1992). The pharmacological effect of citalopram resides in the (*S*)-(+)-enantiomer. *J Neural Transm (Gen Sect)* 88, 157–160.
- Hyttel, J., Arnt, J., & Sánchez, C. (1995). The pharmacology of citalopram. *Rev Comtemp Pharmacother* 6, 271–285.
- Jalil, P. (1992). Toxic reaction following the combined administration of fluoxetine and phenytoin: two case reports. *J Neurol Neurosurg Psychiatry* 55, 412–413.
- Jefferson, J. W. (1998). Drug interactions—friend or foe? *J Clin Psychiatry* 59(suppl. 4), 37–47.
- Jeppesen, U., Gram, L. F., Vistisen, K., Loft, S., Poulsen, H. E., & Brösen, K. (1996). Dose-dependent inhibition of CYP1A2, CYP2C19 and CYP2D6 by citalopram, fluoxetine, fluvoxamine and paroxetine. *Eur J Clin Pharmacol* 51, 73–78.
- Jerling, M., Lindstrom, L., Bondesson, U., & Bertilsson, L. (1994). Fluvoxamine inhibition and carbamazepine induction of the metabolism of clozapine: evidence from a therapeutic drug monitoring service. *Ther Drug Monit* 16, 368–374.
- Karlson, C. N., Newton, J. E., Livingstone, R., Jolly, J. B., Cooper, T. B., Sprigg, J., & Komorski, R. A. (1993). Human brain fluoxetine concentrations. *J Neuropsychiatry Clin Neurosci* 5, 322–329.
- Kashuba, A. D. M., Nafziger, A. N., Kearns, G. L., Leeder, S., Gotschall, R., Rocci, M. L., Kulawy, R. W., Beck, D. J., & Bertino, J. S. (1998). Effect of fluvoxamine therapy on the activities of CYP1A2, CYP2D6, and CYP3A as determined by phenotyping. *Clin Pharmacol Ther* 64, 257–268.
- Kasper, S., Dötsch, M., Kick, H., Vieira, A., & Möller, H. J. (1993). Plasma concentrations of fluvoxamine and maprotiline in major depression—implications on therapeutic efficacy and side effects. *Eur Neuropsychopharmacol* 3, 13–21.
- Kaye, C. M., Haddock, R. E., Langley, P. F., Mellows, G., Taker, T. C. G., Zussman, B. D., & Greb, W. H. (1989). A review of the metabolism and pharmacokinetics of paroxetine in man. *Acta Psychiatr Scand* 80(suppl. 350), 60–75.
- Kerr, B. M., Thummel, K. E., Wurden, C. J., Klein, S. M., Kroetz, D. L., Gonzalez, F. J., & Levy, R. H. (1994). Human liver carbamazepine metabolism. Role of CYP3A4 and CYP2C8 in 10,11-epoxide formation. *Biochem Pharmacol* 47, 1969–1979.
- Ketter, T. A., Post, R. M., & Worthington, K. (1991). Principles of clinically important drug interactions with carbamazepine. Part I. *J Clin Psychopharmacol* 11, 198–203.
- Kobayashi, K., Yamamoto, T., Chiba, K., Tani, M., Ishizaki, T., & Kuroiwa, Y. (1995). The effects of selective serotonin reuptake inhibitors and their metabolites on *S*-mephenytoin 4'-hydroxylase activity in human liver microsomes. *Br J Clin Pharmacol* 40, 481–485.
- Kobayashi, K., Chiba, K., Yagi, T., Shimada, N., Taniguchi, T., Horie, T., Tani, M., Yamamoto, T., Shizaki, T., & Kuroiwa, Y. (1997). Identification of cytochrome P450 isoforms involved in citalopram N-demethylation by human liver microsomes. *J Pharmacol Exp Ther* 280, 927–933.

- Koran, L. M., Cain, J. W., Dominguez, R. A., Rush, J. A., & Thiemann, S. (1996). Are fluoxetine plasma levels related to outcome in obsessive-compulsive disorder? *Am J Psychiatry* 153, 1450–1454.
- Kragh-Sørensen, P., Fredricson-Overø, K., Petersen, O. L., Jensen, K., & Parnas, W. (1981). The kinetics of citalopram: single and multiple dose studies in man. *Acta Pharmacol Toxicol* 48, 53–60.
- Kuhs, H., Schlake, H. P., Rolf, L. H., & Rudolf, G. A. E. (1992). Relationship between parameters of serotonin transport and antidepressant plasma levels or therapeutic response in depressive patients treated with paroxetine and amitriptyline. *Acta Psychiatr Scand* 85, 364–369.
- Kurz, D. L., Bergstrom, R. F., Goldberg, M. J., & Cerimele, B. J. (1997). The effect of sertraline on the pharmacokinetics of desipramine and imipramine. *Clin Pharmacol Ther* 62, 145–156.
- Kuss, H.-J., & Hegerl, U. (1998). Serum concentrations of paroxetine are influenced by CYP3A. *Naunyn Schmiedebergs Arch Pharmacol* 358, R782.
- Lane, R. M. (1996). Pharmacokinetic drug interaction potential of selective serotonin reuptake inhibitors. *Int Clin Psychopharmacol* 11(suppl. 5), 31–61.
- Lasher, T. A., Fleishaker, J. C., Steenwyk, R. C., & Antal, E. J. (1991). Pharmacokinetic pharmacodynamic evaluation of the combined administration of alprazolam and fluoxetine. *Psychopharmacology* 104, 323–327.
- Leclercq, Y. (1992). The place of the SSRIs and fluvoxamine in the treatment of patients with depression. *Drugs* 43(suppl. 2), 1–2.
- Leinonen, E., Koponen, H. J., & Lepola, U. (1995). Paroxetine increases serum trimipramine concentration. A report of two cases. *Hum Psychopharmacol* 10, 345–347.
- Leinonen, E., Lepola, U., & Koponen, H. (1996). Substituting carbamazepine with oxacabazepine increases citalopram levels. A report on two cases. *Pharmacopsychiatry* 29, 156–158.
- Leo, R. J. (1996). Movement disorders associated with the selective serotonin reuptake inhibitors. *J Clin Psychiatry* 57, 449–454.
- Leonard, B., & Tollefson, G. (1994). Focus on SSRIs: broadening the spectrum of clinical use. *J Clin Psychiatry* 55, 459–466.
- Leonard, H. L. (1997). New developments in the treatment of obsessive-compulsive disorder. *J Clin Psychiat* 58(suppl. 14), 39–45.
- Levine, B., Jenkins, A. J., & Smialek, J. E. (1994). Distribution of sertraline in postmortem cases. *J Anal Toxicol* 18, 272–274.
- Levine, M., & Bellward, G. D. (1995). Effect of cimetidine on hepatic cytochrome P450: evidence for formation of a metabolite-intermediate complex. *Drug Metab Dispos* 23, 1407–1411.
- Levy, R. H. (1995). Cytochrome P450 isoenzyme and antiepileptic drug interactions. *Epilepsia* 36(suppl. 5), S8–S13.
- Lund, J., Lomholt, B., Fabricius, J., Christensen, J. A., & Bechgaard, E. (1979). Paroxetine: pharmacokinetics, tolerance and depletion of blood 5-HT in man. *Acta Pharmacol Toxicol* 44, 289–295.
- Lundmark, J., Thomsen, J. S., Fjord-Larsen, T., Manniche, P. M., Mengel, H., Møller-Nielsen, E. M., Pauser, H., & Walinder, J. (1989). Paroxetine: pharmacokinetic and antidepressant effect in the elderly. *Acta Psychiatr Scand* 80(suppl. 350), 76–80.
- Milne, R. J., & Goa, K. L. (1991). Citalopram. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in depressive illness. *Drugs* 41, 450–477.
- Murdoch, D., & McTavish, D. (1992). Sertraline. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in depression and obsessive-compulsive disorder. *Drugs* 44, 604–624.
- Nelson, D. R., Koymans, L., Kamataki, T., Stegeman, J. J., Feyereisen, R., Waxman, D. J., Waterman, M. R., Gotoh, O., Coon, M. J., Estabrook, R. W., Gunsalus, I. C., & Nebert, D. W. (1996). P450 superfamily: update on new sequences, gene mapping, accession numbers and nomenclature. *Pharmacogenetics* 6, 1–2.
- Nemeroff, C. B., DeVane, C. L., & Pollock, B. G. (1996). Newer antidepressants and the cytochrome P450 system. *Am J Psychiatry* 153, 311–320.
- Otton, S. V., Wu, D., Joffe, R. T., Cheung, S. W., & Sellers, E. M. (1993). Inhibition of fluoxetine of cytochrome P450 2D6 activity. *Clin Pharmacol Ther* 53, 401–409.
- Overmars, H., Scherpenisse, P. M., & Post, L. C. (1983). Fluvoxamine maleate: metabolism in man. *Eur J Drug Metab Pharmacokin* 8, 269–280.
- Owens, M. J., Morgan, W. N., Plott, S. J., & Nemeroff, C. B. (1997). Neurotransmitter receptor and transporter binding profile of antidepressants and their metabolites. *J Pharmacol Exp Ther* 283, 1305–1322.
- Øyehaug, E., & Østensen, E. T. (1984). High-performance liquid chromatographic determination of citalopram and four of its metabolites in plasma and urine samples from psychiatric patients. *J Chromatogr B* 308, 199–208.
- Piccinelli, M., Pini, S., Bellantuono, C., & Wilkinson, G. (1995). Efficacy of drug treatment in obsessive-compulsive disorder. A meta-analytic review. *Br J Psychiatry* 166, 424–43.
- Pinninti, N. R., & de Leon, J. (1997). Interaction of sertraline with clozapine. *J Clin Psychopharmacol* 17, 119–120.
- Preskorn, S. H. (1993). Pharmacokinetics of antidepressants: why and how they are relevant to treatment. *J Clin Psychiatry* 54(suppl.), 14–34.
- Preskorn, S. H. (1996a). *Clinical Pharmacology of Selective Serotonin Reuptake Inhibitors*. Caddo: Professionals Communications, Inc.
- Preskorn, S. H. (1996b). Reducing the risk of drug-drug interactions: a goal of rational drug development. *J Clin Psychiatry* 57(suppl. 1), 3–6.
- Preskorn, S. H. (1997). Clinically relevant pharmacology of selective serotonin reuptake inhibitors. *Clin Pharmacokin* 32(suppl. 1), 1–21.
- Preskorn, S. H., & Baker, B. (1997). Fatality associated with combined fluoxetine-amitriptyline therapy. *JAMA* 277, 1682.
- Preskorn, S. H., & Lane, R. M. (1995). Sertraline 50 mg daily: the optimal dose in the treatment of depression. *Int J Clin Psychopharmacol* 10, 129–141.
- Preskorn, S. H., & Magnus, R. (1994). Inhibition of hepatic P-450 isoenzymes by serotonin selective reuptake inhibitors: *in vitro* and *in vivo* findings and their implications for patient care. *Psychopharmacol Bull* 30, 251–259.
- Preskorn, S. H., Alderman, J., Chung, M., Harrison, W., Messig, M., & Harris, S. (1994). Pharmacokinetics of desipramine coadministered with sertraline or fluoxetine. *J Clin Psychopharmacol* 14, 90–98.
- Preskorn, S. H., Alderman, J. A., Greenblatt, D. J., & Horst, D. (1997). Sertraline does not inhibit cytochrome P450 (CYP) 3A-mediated drug metabolism *in vivo*. *Biol Psychiatry* 42, 45S.
- Price, J. S., Waller, P. C., Wood, S. M., & McKay, A. V. (1996). A comparison of the post-marketing safety of four selective serotonin re-uptake inhibitors including the investigation of symptoms occurring on withdrawal. *Br J Clin Pharmacol* 42, 757–763.
- Priskorn, M., Larsen, F., Segonzac, A., & Moulin, M. (1997). Pharmacokinetic interaction study of citalopram and cimetidine in healthy subjects. *Eur J Clin Pharmacol* 52, 241–242.
- Rapeport, W. G., Muirhead, D. C., Williams, S. A., Cross, M., & Wesnes, K. (1996a). Absence of effect of sertraline on the pharmacokinetics and pharmacodynamics of phenytoin. *J Clin Psychiatry* 57(suppl. 1), 24–28.
- Rapeport, W. G., Williams, S. A., Muirhead, D. C., Dewland, P. M., Tanner, T., & Wesnes, K. (1996b). Absence of a sertraline-mediated effect of the pharmacokinetics and pharmacodynamics of carbamazepine. *J Clin Psychiatry* 57(suppl. 1), 20–23.
- Rasmussen, B. B., Mäenpää, J., Pelkonen, O., Loft, S., Poulsen, H. E., Lykkesfeldt, J., & Brøsen, K. (1995). Selective serotonin reuptake inhibitor and theophylline metabolism in human liver microsomes: potent inhibition by fluvoxamine. *Br J Clin Pharmacol* 39, 151–159.
- Redmond, A. M., Harkin, A., Kelly, J. P., & Leonard, B. E. (1999). Effects of acute and chronic antidepressant administration on phencyclidine (PCP) induced locomotor hyperactivity. *Eur Neuropsychopharmacol* 9, 165–170.
- Redmond, G. (1997). Mood disorders in the female patient. *Int J Fertil Womens Med* 42, 67–72.
- Renshaw, P. F., Guimaraes, A. R., Fava, M., Rosenbaum, J. F., Pearlman, J. D., Flood, J. G., Puopolo, P. R., Clancy, K., & Gonzalez, R. G. (1992). Accumulation of fluoxetine and norfluoxetine in human brain during therapeutic administration. *Am J Psychiatry* 149, 1592–1594.
- Richelson, E. (1994). Pharmacology of antidepressants—characteristics of the ideal drug. *Mayo Clin Proc* 69, 1069–1081.



- Rickels, K., & Schweizer, E. (1990). Clinical overview of serotonin reuptake inhibitors. *J Clin Psychiatry* 51(suppl. B), 9–12.
- Ring, B. J., Binkley, S. N., Roskos, L., & Wrighton, S. A. (1995). Effect of fluoxetine, norfluoxetine, sertraline and desmethylsertraline on human CYP3A catalyzed 1' hydroxy midazolam formation in vitro. *J Pharmacol Exp Ther* 275, 1131–1135.
- Rochat, B., Amey, M., & Baumann, P. (1995a). Analysis of enantiomers of citalopram and its demethylated metabolites in plasma of depressive patients using chiral reverse-phase liquid chromatography. *Ther Drug Monit* 17, 273–279.
- Rochat, B., Amey, M., van Gelderen, H., Testa, B., & Baumann, P. (1995b). Determination of the enantiomers of citalopram, its demethylated and propionic acid metabolites in human plasma by chiral HPLC. *Chirality* 7, 389–395.
- Rochat, B., Amey, M., Gillet, M., Meyer, U. A., & Baumann, P. (1997). Identification of three cytochrome P450 isozymes involved in N-demethylation of citalopram enantiomers in human liver microsomes. *Pharmacogenetics* 7, 1–10.
- Ronfeld, R. A., Tremaine, L. M., & Wilner, K. D. (1997). Pharmacokinetics of sertraline and its N-demethyl metabolite in elderly and young male and female volunteers. *Clin Pharmacokinet* 32(suppl. 1), 22–30.
- Rosenstein, D. L., Takeshita, J., & Nelson J. C. (1991). Fluoxetine-induced elevation and prolongation of tricyclic levels in overdose. *Am J Psychiatry* 148, 807.
- Rudorfer, M. V., & Potter, W. Z. (1997). The role of metabolites of antidepressants in the treatment of depression. *CNS Drugs* 7, 273–312.
- Schmider, J., Greenblatt, D. J., von Moltke, L. L., Karsov, D., & Shader, R. I. (1997). Inhibition of CYP2C9 by selective serotonin reuptake inhibitors in vitro: studies of phenytoin p-hydroxylation. *Br J Clin Pharmacol* 44, 495–498.
- Seifritz, E., Holsboer-Trachsler, E., Hemmeter, U., Eap, C. B., & Baumann, P. (1994). Increased trimipramine plasma levels during fluvoxamine comedication. *Eur Neuropsychopharmacol* 4, 15–20.
- Shader, R. I., Greenblatt, D. J., & von Moltke, L. L. (1994). Fluoxetine inhibition of phenytoin metabolism. *J Clin Psychopharmacol* 14, 375–376.
- Shader, R. I., von Moltke, L. L., Schmider, J., Harmatz, J. S., & Greenblatt, D. J. (1996). The clinician and drug interactions—an update. *J Clin Psychopharmacol* 16, 197–201.
- Shen, W. W. (1997). The metabolism of psychoactive drugs: a review of enzymatic biotransformation and inhibition. *Biol Psychiatry* 41, 814–826.
- Silver, H., & Nassar, A. (1992). Fluvoxamine improves negative symptoms in treated chronic schizophrenia: an add-on double-blind, placebo-controlled study. *Biol Psychiatry* 31, 698–704.
- Silver, H., & Shmugliakov, N. (1998). Augmentation with fluvoxamine but not maprotiline improves negative symptoms in treated schizophrenia: evidence for a specific serotonergic effect from a double-blind study. *J Clin Psychopharmacol* 18, 208–211.
- Silver, H., Kaplan, A., & Jahjah, N. (1995). Fluvoxamine augmentation for clozapine-resistant schizophrenia. *Am J Psychiatry* 152, 1098.
- Sindrup, S. H., Brøsen, K., & Gram, L. F. (1992a). Pharmacokinetics of the selective serotonin reuptake inhibitor paroxetine: nonlinearity and relation to the sparteine oxidation polymorphism. *Clin Pharmacol Ther* 51, 288–295.
- Sindrup, S. H., Brøsen, K., Gram, L. F., Hallas, J., Skjelbo, E., Allen, A., Allen, G. D., Cooper, S. M., Mellows, G., Tasker, T. C. G., & Zussman, B. D. (1992b). The relationship between paroxetine and the sparteine oxidation polymorphism. *Clin Pharmacol Ther* 51, 278–287.
- Sindrup, S. H., Brøsen, K., Hansen, M. G., Aaes-Jørgensen, T., Overø, K. F., & Gram, L. F. (1993). Pharmacokinetics of citalopram in relation to the sparteine and the mephenytoin oxidation polymorphisms. *Ther Drug Monit* 15, 11–17.
- Solai, L. K., Mulsant, B. H., Pollock, B. G., Sweet, R. A., Rosen, J., Yu, K., & Reynolds, C. F. (1997). Effect of sertraline on plasma nortriptyline levels in depressed elderly. *J Clin Psychiatry* 58, 440–443.
- Spigset, O. (1999). Adverse reactions of selective serotonin reuptake inhibitors – Reports from a spontaneous reporting system. *Drug Saf* 20, 277–287.
- Spigset, O., Carleborg, L., Hedenmalm, K., & Dahlqvist, R. (1995). Effect of cigarette smoking on fluvoxamine pharmacokinetics in humans. *Clin Pharmacol Ther* 58, 399–403.
- Spigset, O., Granberg, K., Hägg, S., Norström, A., & Dahlqvist, R. (1997a). Relationship between fluvoxamine pharmacokinetics and CYP2D6/CP2C19 phenotype polymorphism. *Eur J Clin Pharmacol* 52, 129–133.
- Spigset, O. P., Granberg, K., Hägg, S., Söderström, E., Carleborg, I., & Dahlqvist, R. (1997b). Non-linear fluvoxamine disposition and relation to some CYP activities. *Eur J Clin Pharmacol* 52(suppl.), A172.
- Spigset, O., Granberg, K., Hägg, S., Söderström, E., & Dahlqvist, R. (1998). Non-linear fluvoxamine disposition. *Br J Clin Pharmacol* 45, 257–263.
- Spina, E., Avenoso, A., Facciola, G., Fabrazzo, M., Monteleone, P., Maj, M., Perucca, E., & Caputi, A. P. (1998). Effect of fluoxetine on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenia. *Int Clin Psychopharmacol* 13, 141–145.
- Sproule, B. A., Otton, S. V., Cheung, S. W., Zhong, X. H., Romach, M. K., & Sellers, E. M. (1997). CYP2D6 inhibition in patients treated with sertraline. *J Clin Psychopharmacol* 17, 102–106.
- Stanford, S. C. (1996). Prozac: panacea or puzzle? *Trends Pharmacol Sci* 17, 150–154.
- Stevens, J. C., & Wrighton, S. A. (1993). Interaction of the enantiomers of fluoxetine and norfluoxetine with human liver cytochromes P450. *J Pharmacol Exp Ther* 266, 964–971.
- Stock, A. J., & Kofoed, L. (1994). Therapeutic interchange of fluoxetine and sertraline: experience in the clinical setting. *Am J Hosp Pharm* 51, 2279–2281.
- Strauss, W. L., Layton, M. E., Hayes, C. E., & Dager, S. R. (1997). <sup>19</sup>F magnetic resonance spectroscopy investigation in vivo of acute and steady-state brain fluvoxamine levels in obsessive-compulsive disorder. *Am J Psychiatry* 154, 516–522.
- Suckow, R. F., Roose, S. P., & Cooper, T. B. (1992). Effect of fluoxetine on plasma desipramine and 2-hydroxydesipramine. *Biol Psychiatry* 31, 200–204.
- Syvalahti, E. K., Taiminen, T., Saarijarvi, S., Lehto, H., Niemi, H., Ahola, V., Dahl, M. D., & Salokangas, R. K. (1997). Citalopram causes no significant alterations in plasma neuroleptic levels in schizophrenic patients. *J Int Med Res* 25, 24–32.
- Szegedi, A., Wiesner, J., & Hiemke, C. (1995). Improved efficacy and fewer side effects under clozapine treatment after addition of fluvoxamine. *J Clin Psychopharmacol* 15, 141–143.
- Szegedi, A., Wetzel, H., Leal, M., Härtter, S., & Hiemke, C. (1996). Combination treatment with clomipramine and fluvoxamine: drug monitoring, safety and tolerability data. *J Clin Psychiatry* 57, 257–264.
- Szegedi, A., Wetzel, H., Angersbach, D., Philipp, M., & Benkert, O. (1997). Response to treatment in minor and major depression: results of a double-blind comparative study with paroxetine and maprotiline. *J Affect Disord* 45, 167–178.
- Tasker, T. C. G., Kaye, C. M., Zussman, B. D., & Link, C. G. G. (1989). Paroxetine plasma levels: lack of correlation with efficacy or adverse events. *Acta Psychiatr Scand* 80(suppl. 350), 152–155.
- Taylor, D. (1997). Pharmacokinetic interactions involving clozapine. *Br J Psychiatry* 171, 109–112.
- Vandel, S., Bertschy, G., Bonin, B., Nezelof, S., Francois, T. H., Vandel, B., Sechter, D., & Bouzard, P. (1992). Tricyclic antidepressant plasma levels after fluoxetine addition. *Neuropsychobiology* 22, 202–207.
- van den Berg, S. J. (1995). Comparing SSRIs: from chemistry to clinical choice. *Hum Psychopharmacol* 10, S199–S209.
- van Harten, J. (1993). Clinical pharmacokinetics of selective serotonin reuptake inhibitors. *Clin Pharmacokinet* 24, 203–220.
- van Harten, J. (1995). Overview of the pharmacokinetics of fluvoxamine. *Clin Pharmacokinet* 29(suppl. 1), 1–9.
- van Harten, J., Duchier, J., Devissaguet, J. P., van Bommel, P., de Vries, M. H., & Rghoebar, M. (1993). Pharmacokinetics of fluvoxamine

- maleate in patients with liver cirrhosis after single-dose oral administration. *Clin Pharmacokinet* 24, 177–182.
- van Harten, J., Lönnebo, A., & Grahnén, A. (1994). Pharmacokinetics of fluvoxamine after intravenous and oral administration. *Neuropsychopharmacology* 10, 104S.
- von Moltke, L. L., Greenblatt, D. J., Court, M. H., Duan, S. X., Harmatz, J. S., & Shader, R. I. (1995). Inhibition of alprazolam and desipramine hydroxylation in vitro by paroxetine and fluvoxamine: comparison with other selective serotonin reuptake inhibitor antidepressants. *J Clin Psychopharmacol* 15, 125–131.
- von Moltke, L. L., Greenblatt, D. J., Duan, S. X., Schmider, J., Wright, C. E., Harmatz, J. S., & Shader, R. I. (1997). Human cytochromes mediating N-demethylation of fluoxetine in vitro. *Psychopharmacology* 132, 402–407.
- Walczak, D. D., Apter, J. T., Halikas, J. A., Borison, R. L., Carman, J. S., Post, G. L., Patrick, R., Cohn, J. B., Cunningham, L. A., Rittberg, B., Preskorn, S. H., Kang, J. S., & Wilcox, C. S. (1996). The oral dose-effect relationship for fluvoxamine: a fixed-dose comparison against placebo in depressed outpatients. *Ann Clin Psychiatry* 8, 139–151.
- Warrington, S. J., Ronfeld, R. A., Wilner, K. D., & Lazar, J. D. (1992). Human pharmacokinetics of sertraline. *Clin Neuropharmacol* 15(suppl. 1), P-54.
- Wetzel, H., Angheliescu, I., Szegedi, A., Wiesner, J., Weigmann, H., Härtter, S., & Hiemke, C. (1998). Pharmacokinetic interactions of clozapine with selective serotonin reuptake inhibitors: differential effects of fluvoxamine and paroxetine in a prospective study. *J Clin Psychopharmacol* 18, 2–9.
- Wilkinson, T. J., Bgg, E. J., Winter, A. C., & Sainsbury, R. (1999). Incidence and risk factors for hyponatraemia following treatment with fluoxetine or paroxetine in elderly people. *Br J Clin Pharmacol* 47, 211–217.
- Wilner, K. D., Henry, E. B., Tremaine, L. M., Lazar, J. D., Gunn, K., McEwan, J., & Moreland, T. (1992). Effect of sertraline on the pharmacokinetics of oral hypoglycemic agents in healthy volunteers. *Clin Neuropharmacol* 15(suppl. 1), P-54.
- Wilner, K. D., Baris, B. A., Foulds, G. H., Anziano, R. J., Berl, T., & Ziegler, M. G. (1996a). Multiple dose pharmacokinetics of sertraline in subjects with varying degrees of renal impairment. *Eur Neuropsychopharmacol* 6(suppl. 3), 41.
- Wilner, K. D., Everson, G., Foulds, G. H., Hansen, R. A., Shrestha, R., McKinley, C., & McClain, C. J. (1996b). Multiple dose pharmacokinetics of sertraline in subjects with varying degrees of hepatic impairment. *Eur Neuropsychopharmacol* 6(suppl. 3), 40.
- Wong, D. T., Bymaster, F. P., Horng, J. S., & Molloy, B. B. (1975). A new selective inhibitor for uptake of serotonin into synaptosomes of rat brain: 3-(p-trifluoromethylphenoxy)-N-methyl-3-phenylpropylamine. *J Pharmacol Exp Ther* 193, 804–811.
- Xu, Z. H., Xie, H. G., & Zhou, H. H. (1996). In vivo inhibition of CYP2C19 but not CYP2D6 by fluvoxamine. *Br J Clin Pharmacol* 42, 518–521.
- Ziegler, M. G., & Wilner, K. D. (1996). Sertraline does not alter the  $\beta$ -adrenergic blocking activity of atenolol in healthy male volunteers. *J Clin Psychiatry* 57(suppl. 1), 12–15.