Impact of *CYP2C19* genetics on pharmacokinetic variability of escitalopram and sertraline - a study based on therapeutic drug monitoring data

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LIST OF PAPERS

Paper I

Heterozygous mutation in CYP2C19 significantly increases the concentration/dose ratio of racemic citalopram and escitalopram (S-citalopram). Rudberg I, Hendset M, Uthus LH, Molden E, Refsum H. Therapeutic Drug Monitoring. 2006;28:102-105.

Paper II

*Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients.* Rudberg I, Mohebi B, Hermann M, Refsum H, Molden E. Clininical Pharmacology and Therapeutics. 2008;83:322-327.

Paper III

Serum concentrations of sertraline and N-desmethyl sertraline in relation to CYP2C19 genotype in psychiatric patients. Rudberg I, Hermann M, Refsum H, Molden E. European Journal of Clinical Pharmacology. 2008;64:1181-1188.

Paper IV

Identification of a novel CYP2C19-mediated metabolic pathway of S-citalopram in vitro. Rudberg I, Reubsaet JL, Hermann M, Refsum H, Molden E. Drug Metabolism and Disposition. 2009;37:2340-2348.

ABBREVIATIONS

AUC	area under the plasma/serum concentration versus time curve
C_{ss}	mean dose-adjusted steady state serum concentration
CYP	cytochrome P450
def	defective allele
EM	extensive metaboliser
5-HTTLPR	serotonin transporter (5-HTT) gene-linked polymorphic region
PM	poor metaboliser
S-citalopram	escitalopram
SCIT PROP	propionic acid escitalopram
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant
TDM	therapeutic drug monitoring
UM	ultrarapid metaboliser

ABSTRACT

Escitalopram and sertraline are among the most widely used drugs in the treatment of depression in Norway. Both drugs show substantial pharmacokinetic variability. Previous studies have indicated that the drug metabolising enzyme cytochrome P450 2C19 (CYP2C19), which exhibits extensive variability in activity due to genetic polymorphism, is involved in the metabolism of escitalopram and sertraline. The aim of this thesis was therefore to investigate the impact of *CYP2C19* genetics on the pharmacokinetic variability of escitalopram and sertraline in psychiatric patients.

By use of data from therapeutic drug monitoring, *CYP2C19* genotype was shown to be a major determinant of the pharmacokinetics of escitalopram. On average, dose-adjusted serum concentration of escitalopram differed 9.7-fold between CYP2C19 poor metabolisers (PMs) and CYP2C19 ultrarapid metabolisers (UMs). Compared to CYP2C19 extensive metabolisers (EMs), the effect was more pronounced for CYP2C19 PMs than for UMs (5.7-fold higher vs. 42% lower mean dose-adjusted serum concentration, respectively). It was further identified that CYP2C19, besides catalysing the well known N-desmethylation of escitalopram, was able to catalyse formation of the propionic acid metabolite. The differences in serum concentration of escitalopram between *CYP2C19* genotypes were most likely caused by a combined effect on the two metabolic pathways. Genetic variability in *CYP2C19* was an important determinant of the pharmacokinetics of sertraline as well. Dose-adjusted serum concentration of sertraline was on average 3.2-fold higher in CYP2C19 PMs compared to EMs, but did not differ between CYP2C19 UMs and EMs.

The substantial differences in pharmacokinetics of escitalopram and sertraline between *CYP2C19* genotypes are of potential importance for the clinical response during treatment with these drugs. CYP2C19 UMs might constitute a subgroup of patients at increased risk of therapeutic failure, whereas CYP2C19 PMs are possibly at higher risk of dose-dependent side effects. Although further studies are needed to investigate the value of *CYP2C19* genotyping in the prevention of therapeutic failure and side effects during treatment with escitalopram and sertraline, the findings of the present thesis may provide a fundament for individual dosing to limit variability in exposure of these drugs.

1 INTRODUCTION

Individual variability in drug response is a major challenge in modern medicine.[1] Treating patients with a given drug generally implies lack of effect in some patients while others experience side effects. The reason for this is multifactorial, and the drug response is determined by both the drug concentration at its site of action (pharmacokinetics) and the interaction of the drug with its target protein, i.e. receptor, transporter or enzyme (pharmacodynamics) (**Figure 1**).

Besides being dependent of the drug dose, concentration of a drug at its site of action is determined by pharmacokinetic processes, i.e. absorption, distribution, metabolism and excretion of the drug. For a specific drug, variability in pharmacokinetic processes could be due to patient specific factors (e.g. genetics, co-morbidity and age), and/or environmental factors (e.g. smoking, diet and drug-drug interactions), and implies that administration of the same drug dose to different patients results in several-fold difference in drug concentrations.[1-4] It is generally difficult to measure the concentration of a drug at its site of action, for instance in the brain. Thus, as most drugs are distributed to their site of action via the systemic circulation, drug concentration in plasma/serum ('systemic exposure') is used as a surrogate measurement reflecting the drug concentration at its site of action.

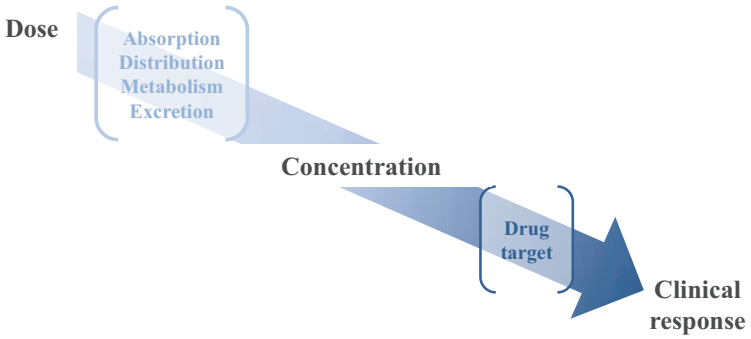

Figure 1 Clinical response during drug treatment depends on pharmacokinetics (light blue) and pharmacodynamics (dark blue).

1.1 Drug metabolism

The majority of drugs are foreign substances to the body. Natural defense mechanisms, which have evolved to avoid foreign substances in the environment causing harm to the body, will seek to limit drug exposure. Most drugs are lipophilic compounds, and elimination of many drugs therefore involves biotransformation (metabolism) into more hydrophilic compounds (metabolites) to enable excretion in urine and bile. Metabolic reactions are classified as either phase I or phase II reactions. Whereas phase I reactions introduce or expose a functional group on the drug, for example a hydroxyl or amino group, phase II reactions generate highly polar compounds by conjugation of the drug or phase I metabolite with endogenous compounds, for example glucuronic acid or sulphate. Multiple competitive reactions and sequential steps may take place and metabolism of a drug often leads to the formation of a number of different metabolites. Many metabolites are without therapeutic impact due to low concentrations or lack of affinity for targets molecules, whereas other metabolites are of importance for the therapeutic effect and/or toxicity of the drug treatment. As the formation of metabolites shows considerable variability, individual differences in metabolite pharmacokinetics could be even greater than for the parent drug.[5;6]

Metabolic reactions are usually enzyme-catalysed. The cytochrome P450 (CYP) enzymes is a superfamily comprising 57 related enzymes (isoenzymes).[7] Some of these are importantly involved in the phase I metabolism of a large number of drugs.[6;8] The superfamily of CYP enzymes is categorised into families and subfamilies based on similarity in amino acid sequence. These are named by the root symbol CYP (cytochrome P450), followed by a number designating the family, e.g. CYP2 (>40% similarity in amino acid sequence), a letter denoting the subfamily, e.g. CYP2C (> 55% similarity in amino acid sequence), and a final number indicating the specific isoenzyme, e.g. CYP2C19. The gene encoding the enzyme is referred to by placing the enzyme name in italics, i.e. *CYP2C19*.[9;10]

CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 play a prominent role in drug metabolism.[6;8] These isoenzymes have distinct, but overlapping, substrate specificity and catalyse a diversity of reactions, including dealkylation, hydroxylation, oxidation and deamination.[6] The CYP enzymes are located in the endoplasmatic reticulum, and are abundantly expressed in cells in the liver and intestine.[11] The activity (phenotype) of the CYP enzymes is influenced by patient specific factors (e.g. genetics, hormone status and

co-morbidity) and environmental factors (e.g. smoking, diet and drug-drug-interactions). Variable phenotype of CYP enzymes is a source of individual differences in the pharmacokinetics of many drugs.[1-4] For CYP2C9, CYP2C19 and CYP2D6, phenotype is distinctly correlated with the genotype, whereas this is not the case for CYP3A4 and CYP1A2.[4]

1.2 Genetic polymorphism in cytochrome P450

The existence of genetic polymorphism affecting CYP enzymes was first recognised for CYP2D6 and CYP2C19 in the 1970s.[12-14] It was observed that a subgroup of individuals exhibited impaired metabolism of certain drugs, i.e. debrisoquine and sparteine (CYP2D6) and S-mephenytoin (CYP2C19). The bimodality was later shown to be caused by alleles encoding defective enzyme activity ('defective alleles'), which in its homozygous presence gave rise to the poor metaboliser (PM) phenotype, i.e. individuals totally deficient of enzyme activity.[15] Later, genetic variability that affects enzyme activity has been identified for several CYP enzymes,[16] but the association between genotype and phenotype is greatest for CYP2D6 and CYP2C19.[4]

1.2.1 CYP2D6

About 80 *CYP2D6* variant alleles, indicated by an asterisk and an Arabic numeral (e.g. *CYP2D6*4),* have so far been described.[16] Estimated frequencies of the most common *CYP2D6* variant alleles in different ethnic groups are presented in **Table 1**. Defective CYP2D6 alleles are most common in Caucasian populations, where 5-10% express the PM phenotype.[17] Amplification of functional *CYP2D6* alleles (*CYP2D6*1xN*, **2xN*, *N*=2-13)[16] gives rise to an ultrarapid CYP2D6 phenotype (CYP2D6 UMs)[18] which is common in Hispanic (~7%) and certain African populations whereas the incidence is less than 2% in northern Europe.[17;19] Most remaining Caucasians carry one or two functional gene copies (**1* or **2*), being heterozygous or homozygous extensive metabolisers (CYP2D6 EMs).[17;19] The frequencies of defective *CYP2D6* alleles, and hence the PM phenotype, are low in African and East Asian populations.[17] However, high occurrence of alleles encoding decreased ('intermediate') enzyme activity (**10* and **17*), implies an overall lower CYP2D6 activity in these populations than in Caucasians.[15;17]

A number of clinically important drugs, including antidepressants, antipsychotics, beta blockers, and antiarrhythmics, are metabolised by CYP2D6.[20;21] Examples where

clinical response is associated with *CYP2D6* genotype are haloperidol, [22] risperidone,[23] metoprolol,[24;25] and codeine.[26]

Table 1 Estimated frequencies of common *CYP2D6* variant alleles in different ethnic groups.

***CYP2D6* allele**	**Activity**	**Population, estimated allele frequencies (%)**			
		African	African American	Caucasian[b]	East Asian
**3*	None	0.1	0.4	1.8	
**4*	None	3.0	7.5	19.9	1.0
**5*	None	2.9	6.4	4.5	5.5
**6*	None			1.0	
**9*	Decreased	0		2.0	
**10*	Decreased	5.0	5.1	2.3	46.9
**17*	Decreased	22.3	21.6	0.1	
**41*	Decreased			7.9[a]	
**1xN /*2xN*	Increased	1.6-28.3[a, c]		1.2	1.0

Estimates are weighted for population size in studies reviewed by Bradford et al.,[17] [a]supplemented with data from Sistonen et al.[19] and/or Raimundo et al.[27] [b]German and US populations. [c]Range presented due to considerable differences between populations. Estimates are based on data from >350 subjects.

1.2.2 CYP2C19

For *CYP2C19*, seven defective alleles have so far been identified, i.e. *CYP2C19*2-*8*.[28-34] *CYP2C19*2* and **3,* characterised by single nucleotide polymorphisms in coding regions, account for a majority of the defective *CYP2C19* alleles.[33;34] Their distribution in different ethnic groups is summarized in **Table 2**. Both **2* and **3* are common in eastern Asia and give rise to an incidence of CYP2C19 PMs of 13-23% in these populations.[15] The **2* allele is the most frequent defective *CYP2C19* allele in Caucasian populations, where approximately 3% are CYP2C19 PMs.[15;35] Noteworthy, about 80% of the people living on the islands of Vanuatu are reported to be CYP2C19 PMs.[36]

Table 2 Estimated frequencies of common *CYP2C19* variant alleles in different ethnic groups.

***CYP2C19* allele**	**Activity**	**Population, estimated allele frequencies (%)**				
		African	African American	Caucasian	Chinese	Japanese
**2*	None	15.9	18.6	14.7	30.0	29.4
**3*	None	0.8	0.1	0.04	5.1	12.2
**17*	Increased	17.9[a]		22.8	0.6-4.4[b]	1.3

Estimates are weighted for population size in studies reviewed by Xie and co-workers[35;37;38] supplemented with studies in healthy subjects.[39-47] [a]Ethiopians. [b]Range presented due to discrepancies between the studies.[43;45;46] Estimates are based on data from ≥ 190 subjects.

Genetic variability has also been identified in the regulatory regions of *CYP2C19*,[46;48;49] and recently, a variant allele encoding increased CYP2C19 activity was identified (*CYP2C19*17*).[43] The higher enzyme activity was ascribed to a single nucleotide polymorphism (*-806C>T*) in the promoter region causing increased recruitment of transcription factor(s) and thereby higher levels of functional CYP2C19 enzyme.[43] The *CYP2C19*17/*17* genotype has been suggested to imply an ultrarapid CYP2C19 phenotype (CYP2C19 UM), but its impact on in vivo clearance of probe substrates seems to be variable.[43;50-52] A high frequency of the *CYP2C19*17* allele has been reported in Caucasian and African populations (**Table 2**),[43;47] indicating an incidence of CYP2C19 UMs of about 3-7% in these populations. In contrast, **17* seems to be rare in Asian populations.[43-46] Other *CYP2C19* variant alleles have been associated with reduced enzyme activity in vitro (**9*, **10* and **12*)[48] or a slower CYP2C19 phenotype in certain individuals *(*16*, **26*),[53;54] but their contribution to overall variability in CYP2C19 phenotype remains to be established.

CYP2C19 is involved in the metabolism of several drugs on the market, including proton pump inhibitors and antidepressants.[4;8;55] Selected drugs metabolised by CYP2C19 are listed in **Table 3**. Examples where *CYP2C19* genetics has been associated with clinical response are proton pump inhibitors[56] and the antiplatelet agent clopidogrel.[57-59]

Table 3 Selected drugs metabolised by CYP2C19.[4;8;55]

Antidepressants	Proton pump inhibitors	Others
amitriptyline	lanzoprazole	carisoprodol
citalopram	omeprazole	clopidogrel
clomipramine	pantoprazole	cyclophosphamide
escitalopram	rabeprazole	diazepam
imipramine		proguanil
moclobemide		phenobarbitone
sertraline		phenytoin
trimipramine		S-mephenytoin

1.3 *CYP* genotyping and therapeutic drug monitoring

Traditionally, physicians adjust drug therapy according to subjective or objective monitoring of clinical response. However, monitoring of clinical effect and possible side effects is a challenging task for many drugs. Suboptimal use of drugs is a common source of morbidity and mortality, and drug-related problems are estimated to account for 3-7% of all hospitalisations,[60] leading to increased burden of disease for the individual patient

and large costs to the society. *CYP* genotyping and therapeutic drug monitoring of serum concentration (TDM) are objective tools which could be used for individualisation and optimisation of drug therapy.[61] Based on the genotype-phenotype relationship for a given drug, the dose can be adjusted according to expected exposure in the individual patient.[62;63] However, besides genotype, the CYP phenotype is affected by physiological and environmental factors.[2;3] TDM captures the majority of this variability, and can be applied regardless of genotype-phenotype relationship for a given drug. In addition, TDM provides an objective assessment of patient compliance.

Optimisation of drug treatment for psychiatric disorders is particularly complicated due to lack of objective measurement of response, slow onset of effects, high degree of placebo- and non-response, and occurrence of side effects which mimic symptoms of the underlying diseases.[64;65] Furthermore, many psychoactive drugs show extensive pharmacokinetic variability, partly because they are metabolised by polymorphic CYP enzymes.[8] Prolonged hospitalisation and higher treatment costs are reported for psychiatric patients with a PM/UM phenotype compared to EMs,[66;67] probably due to increased incidence of side effects and therapeutic failure in these patients.[22;23;66;68;69] The potential benefit of TDM and *CYP* genotyping for antidepressive treatment was illustrated in a study by Kootstra-Ros et al.[70] TDM showed that more than half of the patients possessed serum concentrations outside the therapeutic ranges, and the *CYP* genotyping was reported to clarify medication-related problems in individual patients, e.g. occurrence of side effects and low serum concentrations despite use of standard drug doses. For more than 60% of the patients advices were provided to the general practitioner regarding current and/or future medication regimens.[70] Thus, within the psychiatric field, TDM and *CYP* genotyping appear to be valuable tools to aid individualisation, optimisation and evaluation of drug therapy.[61;68;71-74]

1.4 Selective serotonin reuptake inhibitors

Depression is characterised by persistent low mood, loss of interest and pleasure, and symptoms like decreased appetite, insomnia and fatigue.[75] An association between depressive symptoms and the ability of certain drugs to affect monoaminergic transmission was observed during the 1950s and 60s. This led to the monoamine theory, which hypothesised that depression was caused by functional deficit of certain monoamine neurotransmitters (serotonin and noradrenalin) in the brain.[76;77] The tricyclic antidepressants (TCAs), which increase noradrenergic and serotonergic transmission by

inhibition of transporters in the nerve terminals, were the primary drugs for treatment of depression throughout the 1960s and 70s.[78] However, troublesome side effects and toxicity due to their affinity for ion channels and neurotransmitter receptors prompted the search for antidepressants targeting the neurotransmitter transporters more specifically. This led to the introduction of the selective serotonin reuptake inhibitors (SSRIs) in the 1980s.[64;78] They are effective in the treatment of depression, but without the serious cardiac side effects, seizures and risk of death from overdose associated with the TCAs.[64;65]

Today the SSRIs, comprising fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram and escitalopram, are the first line treatment of depression, and are also widely used in the treatment of other psychiatric disorders, for example anxiety and eating disorders.[64;65] The SSRIs selectively inhibit the serotonin transporter and produce an immediate increase in serotonergic transmission.[64] However, their effect on depression takes several weeks to develop, and it is therefore believed that long-term effects secondary to the increased serotonergic transmission are of importance for the antidepressive effect of the SSRIs, for example downregulation of serotonin receptors.[64] The substantial increase in the use of antidepressants during the last 20 years is primarily due to increased use of the SSRIs, and according to the Norwegian Prescription Database about 4% of the Norwegian population had a SSRI prescription dispensed in 2008.[79] Based on efficacy, tolerability, drug-drug interaction profile and cost, citalopram, escitalopram and sertraline are often recommended when starting treatment of depression.[80] In line with this, these agents accounted for well over 80% of the daily doses of SSRIs sold in Norway in 2008.[81]

1.4.1 Pharmacology of citalopram, escitalopram and sertraline

Citalopram (1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile), which was introduced to the marked in 1989, is a racemic compound. The pharmacological activity as serotonin reuptake inhibitor resides in the S-enantiomer (escitalopram, S-citalopram)[82] whereas the R-enantiomer is actually reported to inhibit the effect of the S-enantiomer.[83] Thus, escitalopram (S-citalopram) was introduced as an individual drug in 2001.

Escitalopram allosterically inhibits the serotonin transporter[84] and is the most selective reuptake inhibitor among the SSRIs, exhibiting low inhibition of both noradrenalin and dopamine transporters.[85] Escitalopram undergoes phase I metabolism to

N-desmethyl, N-didesmethyl, N-oxide, and propionic acid escitalopram (**Figure 2**).[86;87] The N-oxide and N-desmethylated metabolites exhibit weaker inhibition of serotonin reuptake in vitro[88] and are present at lower plasma concentrations than the parent compound at steady state.[86;89] Thus, the therapeutic effect of escitalopram treatment is mainly ascribed to the parent compound. In vitro studies have shown that CYP3A4, CYP2C19 and CYP2D6 are able to catalyse formation of N-desmethyl escitalopram, whereas formation of the N-didesmethyl and N-oxide metabolites seems to be catalysed primarily by CYP2D6.[90;91] In vivo studies have indicated that CYP2C19 is involved in the metabolic clearance of escitalopram, whereas CYP2D6 and CYP3A4 seem to play a minor role.[92-99] The metabolites, as well as unmetabolised escitalopram, are recovered in urine, partly as glucuronide conjugates.[86;100;101]

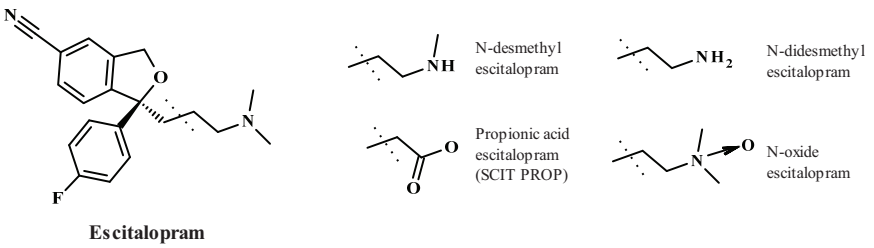

Figure 2 Phase 1 metabolites of escitalopram.[86;87]

Sertraline ((1S,4S)-4-(3,4-dichlorophenyl)-N-methyl-1,2,3,4-tetrahydronaphthalen-1-amine) was introduced to the market in 1990, and next to citalopram/escitalopram, it shows the lowest inhibition of noradrenalin uptake among the SSRIs.[85] Its dopamine uptake blocking effects is however marked compared to other SSRIs,[85] and dopaminergic effects are reported in patients treated with sertraline.[65;102;103] The primary metabolic pathway of sertraline is suggested to be N-desmethylation followed by deamination to the sertraline ketone, which is hydroxylated prior to elimination in urine (conjugated to glucuronic acid) and in faeces **(Figure 3)**.[104-107] However, direct deamination of sertraline to sertraline ketone and formation of a carbamic acid and a N-hydroxy metabolite have also been reported.[105;108] Plasma concentration of N-desmethyl sertraline is higher than that of sertraline at steady state,[104;109] and comparable brain/plasma ratios have been reported for the N-desmethylated metabolite and the parent drug in rats.[105] However, the

potency of N-desmethyl sertraline to inhibit serotonin uptake is less than 15% compared to that of sertraline,[110-113] and the antidepressive effect is therefore assumed to be mainly attributable to the parent compound. However, regarding inhibition of noradrenalin and dopamine uptake, N-desmethyl sertraline shows potency up to 100% compared to the parent drug.[110-113] Multiple CYP enzymes are able to catalyse the N-desmethylation of sertraline in vitro, including CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4.[108;114-116] In vivo studies have indicated that CYP2C19[117] and CYP3A4[118;119] are both involved in the metabolism of sertraline, but not CYP2D6.[120]

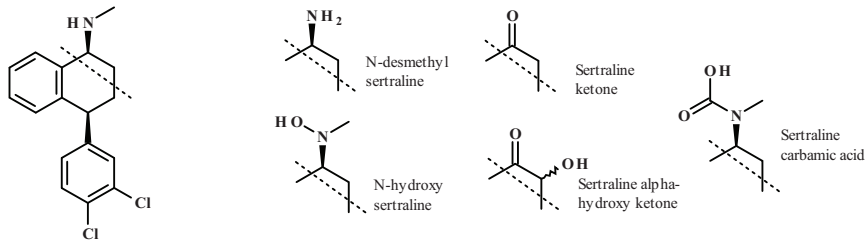

Figure 3 Phase I metabolites of sertraline.[104-107]

1.4.2 Dose-effect relationship

In registration studies with SSRIs, response rates are reported not to increase with dose.[121;122] One possible explanation for this apparently flat dose-response curve could be the use of fixed doses and the last observation carried forward approach in these studies. As described by Preskorn et al. this may mask a better effect of the higher drug doses.[123] Noteworthy, Bech et al.[124] revealed a clear dose-response relationship in the subpopulation of severely depressed patients in a fixed dose study with escitalopram,[122] possibly due to lower rates of placebo response compared to less severely depressed patients.[125] Furthermore, flexible dosing studies have been reported to show advantage of higher doses of SSRIs.[64] Regarding side effects of SSRIs, it seems to be a more consistent dose-dependency, and nausea, insomnia, and sexual dysfunction are common side effects reported to attenuate with dose reduction.[64;121;122] Thus, despite some uncertainty regarding the dose-effect relationship, individual dose titration is recommended to optimise clinical effect and limit side effects of SSRIs.[64;65]

Serum concentrations of escitalopram and sertraline are reported to vary up to 40-fold among patients treated with the same dose,[109;126] but little is known about the relationship between serum concentration and therapeutic outcome of treatment with these drugs.[74] However, the fact that drug dosage is recognised as a variable of importance for the therapeutic outcome of SSRIs, implies that drug concentration is also a relevant outcome variable. Thus, the extensive variability in the pharmacokinetics of escitalopram and sertraline is likely to be a reason for differences in clinical response among patients treated with these drugs. To enable better individualisation of treatment with escitalopram and sertraline, it is therefore important to identify the factors contributing to their extensive pharmacokinetic variability.

2 AIM OF THESIS

Based on the substantial variability in the pharmacokinetics of escitalopram and sertraline, two of the most frequently used antidepressants in Norway, the overall objective of this thesis was to investigate the impact of *CYP2C19* genetics on the pharmacokinetic variability of these drugs in psychiatric patients.

3 SUMMARY OF RESULTS

Paper I

'Heterozygous mutation in CYP2C19 significantly increases the concentration/dose ratio of racemic citalopram and escitalopram (S-citalopram)'

In this study, the impact of heterozygosity for defective *CYP2C19* alleles on serum concentration of racemic citalopram and escitalopram was investigated based on TDM data and *CYP* genotype in 83 patients. For both racemic citalopram and escitalopram, median dose-adjusted serum concentration and parent drug/metabolite ratio were from 1.6- to 2.0-fold higher in the subgroups of patients heterozygous for defective *CYP2C19* alleles compared to the subgroups homozygous for *CYP2C19*1* (CYP2C19 EMs) ($p<0.01$). The observed differences were somewhat larger for escitalopram than for racemic citalopram. Higher median non-dose-corrected serum concentration was observed in the subgroups of patients heterozygous for defective alleles than in CYP2C19 EMs for both racemic citalopram and escitalopram (2.2-fold; $p=0.066$, and 2.5-fold; $p<0.01$, respectively), indicating that the impaired metabolic clearance in this patient subgroup was not compensated for by dose reductions in clinical practice.

The observed differences in median dose-adjusted serum concentration and parent drug/metabolite ratio of citalopram and escitalopram between heterozygous carriers of defective *CYP2C19* alleles and EMs showed that considerable pharmacokinetic variability within patients expressing functional CYP2C19 enzyme was due to heterozygosity for defective *CYP2C19* alleles.

Paper II

*'Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients'*

In this study, the impact of the *CYP2C19*17* allele on serum concentration of escitalopram and N-desmethyl escitalopram was quantified, and compared with defective *CYP2C19* alleles. The study included TDM data and *CYP* genotype from 166 patients. When available, multiple serum concentration measurements from the same individual were included. Homozygous carriers of the *CYP2C19*17* allele (CYP2C19 UMs) (n=7 patients) obtained significantly lower mean dose-adjusted steady state serum concentration (C_{ss}) of escitalopram (42%) compared to the subgroup of CYP2C19 EMs

($p<0.01$). The *CYP2C19*17* allele had a less pronounced effect than the defective *CYP2C19* alleles, which in homozygous carriers (CYP2C19 PMs) (n=6 patients) resulted in a 5.7-fold higher C_{ss} of escitalopram compared to CYP2C19 EMs ($p<0.001$). Overall, C_{ss} of escitalopram differed 9.7-fold between the outmost *CYP2C19* genotypes. There were no consistent differences in C_{ss} of N-desmethyl escitalopram among the *CYP2C19* genotype subgroups. The study also revealed a gender difference and an effect of *CYP2D6* genetics, with higher C_{ss} of both escitalopram and N-desmethyl escitalopram in females (26% and 40%, respectively, $p<0.01$) and in carriers of defective *CYP2D6* alleles (28% and 12%, respectively, $p<0.05$).

The observed 9.7-fold range in C_{ss} of escitalopram across different genotypes shows that CYP2C19 is a major determinant of the pharmacokinetics of escitalopram. The substantial differences in C_{ss} are of potential importance for the clinical response to treatment with escitalopram. CYP2C19 UMs might constitute a subgroup of patients at increased risk of therapeutic failure, whereas CYP2C19 PMs might be at higher risk of dose-dependent side effects, or potentially improved antidepressive effect.

Paper III

'Serum concentrations of sertraline and N-desmethyl sertraline in relation to CYP2C19 genotype in psychiatric patients'

In this study, the impact of genetic variability in *CYP2C19* on serum concentration of sertraline and N-desmethyl sertraline was investigated based on TDM data and *CYP* genotype from 121 patients. Multiple serum concentration measurements from the same individual were included when available. Carriers of defective *CYP2C19* alleles obtained significantly higher C_{ss} of both sertraline and N-desmethyl sertraline compared to CYP2C19 EMs. In CYP2C19 PMs (n=5 patients), the effect was expressed as a 3.2- and 4.5-fold higher C_{ss} of sertraline ($p<0.01$) and N-desmethyl sertraline ($p<0.001$), respectively. There was no detectable effect of the *CYP2C19*17* allele on C_{ss} of sertraline or N-desmethyl sertraline. Patients aged ≥ 70 years on average obtained 1.8- and 2.0-fold higher C_{ss} of sertraline and N-desmethyl sertraline, respectively ($p<0.001$).

The differences in C_{ss} between CYP2C19 EMs and PMs show that CYP2C19 metabolism is an important determinant of the pharmacokinetics of both sertraline and N-desmethyl sertraline. The differences in C_{ss} are of possible relevance for the clinical response to sertraline.

Paper IV

'Identification of a novel CYP2C19-mediated metabolic pathway of S-citalopram in vitro'

This combined in vitro/in vivo study aimed to investigate to what extent CYP2C19-catalysed clearance of escitalopram (S-citalopram) was due to a metabolic pathway different from N-desmethylation, and to identify the product(s) of this possible alternative pathway. Metabolism of escitalopram was investigated in vitro by the use of recombinant microsomes expressing CYP2C19. It was identified that CYP2C19, besides catalysing the well known N-desmethylation, was able to catalyse formation of the propionic acid metabolite of escitalopram (SCIT PROP). Formation of SCIT PROP accounted for 35% of total CYP2C19-mediated clearance of escitalopram in vitro, whereas 51% was due to N-desmethyl escitalopram formation.

Analysis of six serum samples from patients treated with escitalopram showed that, relative to CYP2C19 EMs, C_{ss} of SCIT PROP and mean SCIT PROP/escitalopram ratio was lower in the two PMs (0.48 and 0.32, respectively) and higher in the two UMs (1.42 and 2.69, respectively). Thus, CYP2C19 seemed to be importantly involved in the in vivo formation of this metabolite. This indicates that the differences in C_{ss} of escitalopram between *CYP2C19* genotypes (Paper I, II and IV) were caused by a combined effect on formation of N-desemethyl escitalopram and SCIT PROP.

4 DISCUSSION

In the present work, genetic variability in *CYP2C19* was shown to be an important determinant of the pharmacokinetics of escitalopram and sertraline (Paper I-IV), two of the most widely used antidepressants in Norway. The several-fold differences in mean dose-adjusted serum concentrations between various *CYP2C19* genotypes are of potential importance for the clinical response during treatment with these drugs.

4.1 Impact of *CYP2C19* genetics on the pharmacokinetic variability of escitalopram

Mean dose-adjusted steady state serum concentration (C_{ss}) of escitalopram differed 9.7-fold between patients carrying different *CYP2C19* genotypes, showing that genetic variability in *CYP2C19* is a major determinant of C_{ss} of escitalopram (Paper II). Sorted from the lowest to the highest C_{ss}, the *CYP2C19* genotypes arranged as follows: *CYP2C19*17/*17<CYP2C19*1/*17<CYP2C19*1/*1<CYP2C19*17/def<CYP2C19*1/def <CYP2C19def/def* (*def* = defective allele). Patients homozygous for defective *CYP2C19* alleles (CYP2C19 PMs) obtained 5.7-fold higher C_{ss} of escitalopram compared to patients carrying the *CYP2C19*1/*1* genotype (CYP2C19 EMs). Impaired elimination of escitalopram in CYP2C19 PMs is consistent with other studies,[92;93;96;97] but the nearly 6-fold higher C_{ss} in PMs was a considerably larger effect than the 1.7- to 1.9-fold higher area under the plasma concentration versus time curve (AUC) reported by Noehr-Jensen et al. and Herrlin et al.[92;93] In the study by Noehr-Jensen et al.[92] the participants were classified based on phenotyping with omeprazole, and confirmative genotyping showed that both the CYP2C19 EM and PM subgroup included carriers of the *CYP2C19*1/*2* genotype. This is possibly a reason for the less pronounced difference in that study compared to the study presented in Paper II. See section 4.6 Methodological considerations, for further discussion.

Patients carrying the *CYP2C19*17/*17* genotype (CYP2C19 UMs) obtained 42% lower C_{ss} of escitalopram compared to CYP2C19 EMs. This was in accordance with the study by Sim et al. reporting that the *CYP2C19*17* allele encodes increased CYP2C19 activity,[43] but two other studies with escitalopram have not found a significant effect of *CYP2C19*17*.[96;127] Whereas Ohlsson Rosenborg et al. observed a non-significantly 21% lower AUC of escitalopram in CYP2C19 UMs compared to CYP2C19 EMs,[127] Jin et al. reported no differences in oral clearance between CYP2C19 UMs and a combined group

of *CYP2C19*1/*1* and **1/*17* carriers.[96] Again, different design of the studies and limited number of CYP2C19 UMs (n=5-7) are possible reasons for inter-study discrepancies regarding the effect on escitalopram pharmacokinetics. Thus, it is uncertain to which degree the CYP2C19 UM phenotype affects the systemic exposure of escitalopram. However, from the findings in Paper II, it could not be excluded that patients homozygous for *CYP2C19*17* are at higher risk of therapeutic failure.

In Paper I and Paper II it was shown that C_{ss} of escitalopram also differed between CYP2C19 EMs and patients heterozygous for *CYP2C19* variant alleles. The difference between the CYP2C19 EMs and carriers the *CYP2C19*1/def* genotype in Paper I was somewhat larger for escitalopram than for racemic citalopram (2.0- vs. 1.6-fold, respectively). Similarly, previous studies have reported that CYP2C19 is of greater importance for the metabolism of the S-enantiomer compared to the R-enantiomer.[90;93;95;128] Inclusion of genotyping of the *CYP2C19*17* allele in the study presented in Paper II resulted in three subgroups of patients carrying heterozygous mutations. Compared to CYP2C19 EMs, C_{ss} of escitalopram was higher in the *CYP2C19*1/def* subgroup (1.9-fold, $p<0.001$), whereas non-significantly lower C_{ss} was observed in the subgroup of patients carrying the *CYP2C19*1/*17* genotype (0.87-fold, $p=0.13$). Besides verifying the importance of heterozygosity for defective *CYP2C19* alleles revealed in the study presented in Paper I, this confirms that *CYP2C19*17* has a less pronounced impact on the C_{ss} of escitalopram compared to the defective *CYP2C19* alleles.

The bioavailability of escitalopram is reported to be about 80%,[97;129] implying that impaired metabolism potentially affects bioavailability only to a minor extent. Thus the higher C_{ss} associated with defective *CYP2C19* alleles (Paper II) is primarily due to reduced clearance. However, the increased CYP2C19 activity in UMs might imply higher first pass metabolism of CYP2C19 substrates in these patients.[130] Therefore, the lower C_{ss} of escitalopram observed in CYP2C19 UMs may be due to both higher clearance and lower bioavailability.

Despite previous in vitro studies reporting that CYP2C19 catalyses the N-desmethylation of escitalopram,[90;91;128] there were no consistent differences in C_{ss} of N-desmethyl escitalopram among the *CYP2C19* genotype subgroups in Paper II. This is in line with other pharmacogenetic[92;93;127] and drug-drug interaction studies[95;131] where systemic exposure of N-desmethyl escitalopram has been reported to be largely unaffected by differences in CYP2C19 activity. In Paper II, it was therefore stated that

CYP2C19 appears to be of minor importance for the formation of N-desmethyl escitalopram. However, from Figure 1 in Paper II it appears that the N-desmethyl escitalopram/escitalopram ratio was lower in CYP2C19 PMs compared to EMs. This reflects a lower formation rate of N-desmethyl escitalopram in CYP2C19 PMs. However, the further metabolism of N-desmethyl escitalopram to N-didesmethyl escitalopram is assumed to be independent of CYP2C19 (Paper IV).[90;91] The similar C_{ss} of N-desmethyl escitalopram in different *CYP2C19* genotype subgroups therefore indicates that a comparable amount of the administered dose is eliminated by N-desmethylation regardless of CYP2C19 activity. This is consistent with the study of Herrlin et al.[93] reporting only a slightly lower recovery of N-desmethylated metabolites of escitalopram in urine from CYP2C19 PMs compared to EMs. Thus, *CYP2C19* genotype affects the rate of N-desmethylation, whereas the amount of escitalopram finally eliminated as N-desmethylated metabolites appears to be unaltered.

Based on the low urinary recovery of escitalopram as N-desmethylated metabolites in CYP2C19 EMs[93] and the limited contribution from CYP2C19 to the N-desmethylation of escitalopram in vitro,[90;91;128] the lower rate of N-desmethylation in CYP2C19 PMs could not alone account for the nearly six-fold difference in C_{ss} of escitalopram between CYP2C19 EMs and PMs in Paper II. Thus, CYP2C19 appeared to be involved in metabolic pathways of escitalopram besides the N-desmethylation. This was investigated in the in vitro study presented in Paper IV, which identified that CYP2C19 is able to catalyse formation of the propionic acid metabolite of escitalopram (SCIT PROP). SCIT PROP accounted for one third of the substrate loss of escitalopram in recombinant CYP2C19 microsomes. In comparison, about one half of the substrate loss was due to formation of N-desmethyl escitalopram. Thus, more than 80% of the CYP2C19-mediated clearance of escitalopram in vitro was explained by formation of these two metabolites (**Figure 4**).

Although it is well known that escitalopram is deaminated to SCIT PROP in vivo,[87;95;132;133] the in vitro study presented in Paper IV appears to be the first to identify that CYP2C19 is able to catalyse the formation of this metabolite. Analysis of serum samples from a limited number of *CYP2C19*-genotyped patients treated with escitalopram showed that C_{ss} of SCIT PROP and mean SCIT PROP/escitalopram ratio was lower in two CYP2C19 PMs and higher in two UMs relative to two EMs (Paper IV). This appears to be consistent with data presented for racemic citalopram in a previous study,[134] and indicates a key role of CYP2C19 for the in vivo formation of SCIT PROP. Thus, it seems

that the difference in clearance of escitalopram between *CYP2C19* genotypes is caused by a combined effect on the formation of N-desmethyl escitalopram and SCIT PROP. Identification of this novel CYP2C19-mediated metabolic pathway of escitalopram may therefore explain the larger effect of defective CYP2C19 activity on systemic exposure of escitalopram than what is accounted for by the impaired N-desmethylation.

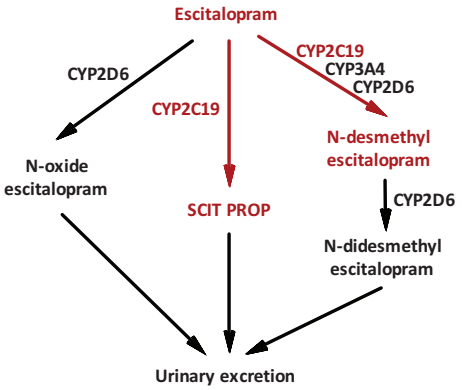

Figure 4 Suggested phase I metabolism of escitalopram. Metabolic pathways catalysed by CYP2C19 indicated in red. SCIT PROP; propionic acid escitalopram.

SCIT PROP was also detected in CYP2C19 PMs (Paper IV). This may be explained by previous studies reporting that monoamine oxidase is able to catalyse formation of this metabolite in vitro.[135-137] However, the lower C_{ss} of SCIT PROP, in contrast to the N-desmethylated metabolite, in CYP2C19 PMs compared to EMs (Paper II and Paper IV) indicates that formation of SCIT PROP is more specific for the CYP2C19 enzyme than formation of N-desmethyl escitalopram. Furthermore, previous in vivo studies with racemic citalopram have reported that the ratio between plasma concentrations of the S- and R-enantiomers was 3.5-5.0 for the propionic acid metabolite and 0.6-0.8 for N-desmethyl citalopram,[87;89;95;101;132;133] indicating that propionic acid formation is stereoselective for the S-enantiomer. Existence of a metabolic pathway specific for CYP2C19 with preference for the S-enantiomer is supported by previous pharmacogenetic[93] and drug-drug interaction[95;132] studies where impaired CYP2C19 activity has been associated with increased S/R ratios of the parent compound.

In **Figure 4**, a summary of the phase I metabolism of escitalopram is illustrated based on the present work (Paper I, II and IV) and previous in vivo studies.[92-99] CYP2C19-catalysed formation of N-desmethyl escitalopram and SCIT PROP appears to

be the primary elimination pathways of escitalopram in CYP2C19 EMs and UMs. Escitalopram is eliminated by N-desmethylation and SCIT PROP formation in CYP2C19 PMs as well, but alternative pathways are probably of greater importance in these subjects.

4.2 Impact of *CYP2C19* genetics on the pharmacokinetic variability of sertraline

CYP2C19 PMs obtained a 3.2-fold higher C_{ss} of sertraline compared to CYP2C19 EMs (Paper III). CYP2C19 catalyses both N-desmethylation and direct deamination of sertraline (**Figure 5**),[108] and impaired enzyme activity may affect both these metabolic pathways. As the bioavailability of sertraline is estimated to be about 45%,[106] the higher C_{ss} was possibly a result of both higher bioavailability and lower clearance in CYP2C19 PMs compared to EMs.[130]

Apart from a report on higher-than-average plasma concentrations in two CYP2C19 PMs,[138] the study presented in Paper III seems to be the first to investigate the pharmacokinetics of sertraline in relation to *CYP2C19* genotype at steady state. However, a single dose study in 12 healthy Chinese volunteers has previously been performed.[117] In this study, a 1.4-fold higher AUC of sertraline was observed in CYP2C19 PMs compared to CYP2C19 EMs ($p<0.05$). One possible reason for the different effect size in the study presented in Paper III and the study by Wang et al. may be differences in the pharmacokinetics of sertraline following single and multiple dosing. Furthermore, inclusion of subjects heterozygous for defective *CYP2C19* alleles in the reference group may also be a reason for the less pronounced difference between CYP2C19 EMs and PMs in the study by Wang et al. Based on the work by Wang et al. and in vitro data,[108;114;116;117] it has been assumed that genetic variability in *CYP2C19* is of minor importance for the systemic exposure of sertraline.[63;139] However, this should be reconsidered in light of the findings in the study presented in Paper III.

Compared to escitalopram, genetic variability in *CYP2C19* influenced C_{ss} of sertraline to a lesser extent. This was expressed both as a less pronounced difference in C_{ss} between CYP2C19 EMs and PMs and by the absence of effect of the *CYP2C19*17* allele. This possibly reflects that clearance of sertraline in CYP2C19 EMs to a lesser degree is mediated by CYP2C19. On the other hand, sertraline has a higher hepatic extraction ratio than escitalopram.[97;106;129] As clearance of drugs with a high hepatic extraction ratio is limited by hepatic blood flow rather than the intrinsic clearance, the

difference in extraction ratio might also be a reason for the different impact of genetic variability in *CYP2C19* on C_{ss} of the two drugs.

Like for the parent compound, C_{ss} of N-desmethyl sertraline was higher in the subgroups of patients carrying defective *CYP2C19* alleles (Paper III). The in vitro study by Obach et al. showed that CYP2C19 catalyses the deamination of N-desmethyl sertraline to sertraline ketone,[108] and the higher C_{ss} of N-desmethyl sertraline in CYP2C19 PMs was therefore likely due to lower clearance of this metabolite. Furthermore, the results of the in vitro study[108] indicated that direct deamination of sertraline to sertraline ketone is more specific for CYP2C19 than the N-desmethylation. Thus, higher C_{ss} of N-desmethyl sertraline in CYP2C19 PMs may also be due to a shift in sertraline metabolism from direct deamination to the N-desmethylation pathway (**Figure 5**).

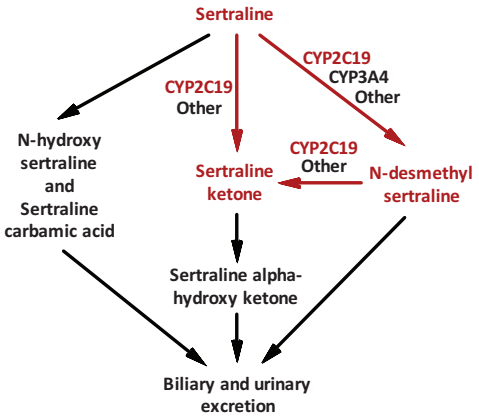

Figure 5 Suggested phase II metabolism of sertraline. Metabolic pathways catalysed by CYP2C19 indicated in red. Other; involvement of additional enzymes indicated in vitro.

The higher C_{ss} of N-desmethyl sertraline in CYP2C19 PMs was in contrast to the study by Wang et al., reporting 35% lower AUC of this metabolite in CYP2C19 PMs compared to EMs.[117] Like for the parent compound, the discrepancies between the two studies may be due to differences in composition of the EM groups as well as potential differences in the pharmacokinetics following single and multiple drug dosing. Furthermore, measuring N-desmethyl sertraline up to 144 hours post dose in the study by Wang et al. may be insufficient, as N-desmethyl sertraline is reported to have half-life up to 200 hours.[104]

4.3 Additional contributors to the pharmacokinetic variability of escitalopram and sertraline

4.3.1 CYP2D6 and CYP2C9

For both escitalopram and sertraline, there was a considerable variability in dose-adjusted serum concentrations within the same *CYP2C19* genotype. In Paper II and III additional factors contributing to pharmacokinetic variability of escitalopram and sertraline were identified by covariate analyses in the mixed model approach. For escitalopram, carriers of defective *CYP2D6* alleles obtained higher C_{ss} than patients homozygous for functional *CYP2D6* alleles (28%). This is consistent with *in vitro* studies showing that CYP2D6 catalyses the formation of the N-desmethyl and N-oxide metabolites of escitalopram.[90;91] However, pharmacogenetic studies have reported that impaired CYP2D6 activity is of minor importance for the systemic exposure of this drug in vivo.[93;97] Nevertheless, it is possible that CYP2D6-mediated metabolism of escitalopram is of importance primarily in subjects with impaired CYP2C19 activity. This hypothesis was investigated using the study population from Paper II supplemented with new data from the TDM database. Patients were separated by *CYP2C19* genotype (*CYP2C19*1/*1*, *CYP2C19*1/def* and *CYP2C19def/def*), and further subdivided according to *CYP2D6* genotype (*CYP2D6*1/*1*, *CYP2D6*1/def* and *CYP2D6def/def*). The effect of *CYP2D6* genotype on C_{ss} of escitalopram was assessed within each *CYP2C19* genotype subgroup (**Figure 6**).

Whereas C_{ss} of escitalopram was unaffected by *CYP2D6* genotype within the *CYP2C19*1/*1* subgroup (**Figure 6A**), a 1.4-fold higher C_{ss} was observed among carriers of the *CYP2D6*1/def* genotype within the *CYP2C19*1/def* subgroup (**Figure 6B**, p=0.041). Within the *CYP2C19def/def* group, similar C_{ss} of escitalopram was observed in carriers of *CYP2D6*1/*1* and *CYP2D6*1/def* genotypes (**Figure 6C**), but it should be noted that the number of observations were limited compared to the two other *CYP2C19* genotypes. Noteworthy, one of the highest dose-adjusted serum concentrations was observed in the single patient with a combined CYP2C19/CYP2D6 PM phenotype, and in line with a recent report on racemic citalopram,[140] *CYP2D6* genetics primarily appears to be of importance in patients with impaired CYP2C19 metabolism. Thus, the higher C_{ss} associated with defective *CYP2D6* alleles in the study presented in Paper II was likely due to an effect in patients carrying defective *CYP2C19* alleles.

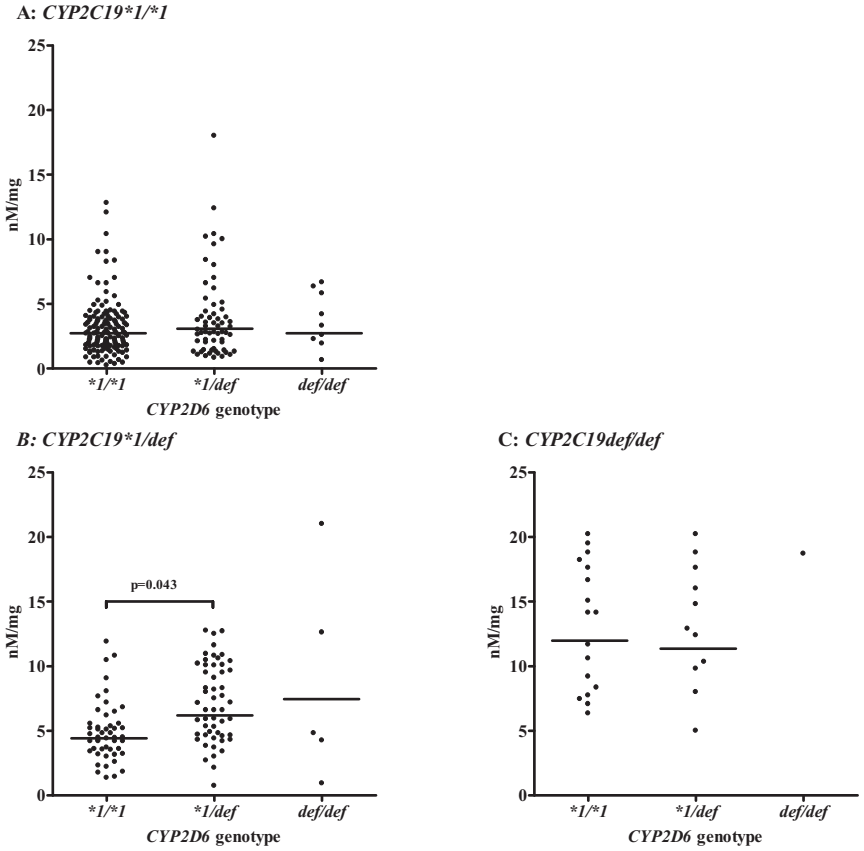

Figure 6 Dose-adjusted serum concentrations of escitalopram (n=353) in relation to *CYP2D6* genotype in patients (n=194) carrying the A: *CYP2C19*1/*1*, B: *CYP2C19*1/def*, and C: *CYP2C19def/def* genotype. Lines indicate geometric mean values estimated in mixed model analyses. *def* indicates defective allele.

CYP genotyping also included analyses of variant alleles encoding decreased activity of CYP2C9 (i.e. *CYP2C9*2*, **3* and **5*).[16] However, despite previous studies reporting that CYP2C9 catalyses N-desmethylation of sertraline in vitro,[108;114-116] presence of variant alleles encoding reduced CYP2C9 activity did not influence C_{ss} of sertraline or N-desmethyl sertraline in the study presented in Paper III. However, *CYP2C9* variant alleles were co-inherited with alleles encoding functional CYP2C19 activity (Paper II and Paper III).[141;142] Thus, it is possible that use of a CYP2C9 inhibitor influences metabolism of sertraline in subjects with impaired CYP2C19 activity, although this is not detected in pharmacogenetic studies due to the relative absence of subjects with genetically impaired activity in both enzymes.

4.3.2 Gender and age

In the study presented in Paper II females obtained higher C_{ss} of escitalopram than males. One possible explanation for this is concurrent use of oral contraceptives, which are reported to inhibit CYP2C19 activity.[143-145] Although the requisition forms were screened for potentially interacting drugs, it cannot be ruled out that non-reported use of oral contraceptives contributed to the higher C_{ss} of escitalopram in females. Alternatively, since clearance of escitalopram is reported to increase with increasing body weight,[96] it is possible that the observed gender difference was secondary to a most likely lower body weight in females than in males. A true gender difference in hepatic CYP2C19 activity is controversial, as studies addressing this topic have reported conflicting results.[12;143-148]

In the study presented in Paper III, patients aged ≥70 years obtained higher C_{ss} of sertraline and N-desmethyl sertraline than younger patients (<70 years). This was in accordance with previous reports,[104;107;109;149] and possibly reflects lower hepatic CYP2C19 activity or reduced hepatic blood flow with increasing age.[3;147;148;150;151] The potential effect of age on C_{ss} of escitalopram was not assessed, as the study population in Paper II included only a limited number of elderly patients. However, higher systemic exposure of escitalopram has been reported in elderly patients in previous studies.[96;126;152]

4.3.3 Factors not investigated

In the study presented in Paper II, dose-adjusted serum concentrations of escitalopram appeared to vary less within the subgroups of CYP2C19 UMs and PMs compared to CYP2C19 EMs (Figure 1a in Paper II). This was confirmed by assessing the coefficient of variation in CYP2C19 UMs, EMs and PMs, which was 36%, 78% and 21%, respectively. Likewise, the coefficient of variation for dose-adjusted serum concentrations of sertraline was lower within the CYP2C19 PM group compared to EMs (45% vs. 75%, respectively). A similar tendency was reported for AUC of escitalopram in the study by Ohlsson Rosenborg et al.[127] and is also evident from studies with other CYP2C19 substrates (omeprazole and S-mephenytoin).[43;50;52;153] The relative homogeneity in phenotype within CYP2C19 UMs and PMs suggests that genetic variability affected the allele classified as *CYP2C19*1* in these studies. Variant alleles encoding defective or reduced CYP2C19 activity other than those analysed have been identified,[31;32;48;53;54] as well as genetic variability in regulatory regions besides **17* possibly affecting the constitutive expression of the *CYP2C19* gene and/or its response to environmental factors.[46;48;49;154;155]

Sertraline and escitalopram are reported to be substrates for other CYP enzymes, for example CYP3A4 and CYP2B6 (only sertraline), and the efflux transporter P-glycoprotein.[90;91;108;114-116;128;156-158] The latter plays a protective role against potential toxic substances by limiting their absorption from the intestine, and may therefore affect bioavailability of certain drugs.[159] The activity of CYP3A4, CYP2B6 and P-glycoprotein shows extensive individual variability, due to genetic, physiological and environmental factors,[2;159;160] and have most likely contributed to the observed variability in serum concentrations of escitalopram and sertraline.[94;118;119;161-163] Nevertheless, the present work shows that genetic variability *CYP2C19* is an important pharmacokinetic determinant of both escitalopram and sertraline.

4.4 Impact of the *CYP2C19*17* allele on CYP2C19 phenotype

The *CYP2C19*17* allele had a less pronounced influence on C_{ss} of escitalopram and sertraline than the defective *CYP2C19* alleles (Paper II and III). This is consistent with previous studies with omeprazole and imipramine in Caucasians.[43;50;164] In contrast, the difference in S/R ratio of mephenytoin has been reported to be of similar magnitude for CYP2C19 UMs and PMs compared to CYP2C19 EMs.[43;51;52] However, the studies on mephenytoin were performed in African populations, where CYP2C19 EMs are reported to exhibit lower CYP2C19 activity than EMs of Caucasian origin.[50-52;165;166] Hence, the apparent difference in relative importance of the *CYP2C19* variant alleles between the mentioned CYP2C19 substrates might be due to inter-study differences in CYP2C19 enzyme activity in the EM subgroups. A true substrate difference in the relative importance of *CYP2C19*17* seems less probable, as the variant alleles encode altered amount of active enzyme rather than enzyme with qualitatively altered catalytic activity.[16;33;34;43]

The term 'ultrarapid' was introduced by Sim et al. to denote the phenotype of *CYP2C19*17/*17* carriers.[43] However, the effect of the *CYP2C19*17* allele on drug exposure might be characterised as moderate as the decrease in systemic exposure in homozygous carriers is reported to be less than 2-fold for most drugs investigated (Paper II, Paper III).[43;127;153;164] Furthermore, the *CYP2C19*17/*17* genotype does not seem to constitute a separate CYP2C19 phenotype, as there is almost an entire overlap with observations in CYP2C19 EMs in most studies (Paper II, Paper III).[43;127;153;164] Thus, although it seems evident that the *CYP2C19*17* allele is associated with a faster-than-

average metabolism of CYP2C19 substrates, the term 'ultrarapid' may overstate the phenotypic importance of the *CYP2C19*17* allele.

4.5 Clinical relevance of the findings

The impact of *CYP2C19* genotype was particularly pronounced for escitalopram, where CYP2C19 PMs displayed almost 10-fold higher C_{ss} than CYP2C19 UMs. In order to obtain a systemic exposure of escitalopram comparable to that of an average CYP2C19 EM patient, CYP2C19 UMs would need a 1.5- to 2-fold higher dose. On the other hand, CYP2C19 PMs require on average less than one fifth the dose of an average CYP2C19 EM patient. Thus, founded on the principle that drug dose is of importance for the therapeutic response, it seems reasonable to assume that *CYP2C19* genotype would affect the clinical response to escitalopram if patients from various subgroups are given equal doses. The present work suggests that CYP2C19 UMs might constitute a subgroup of patients at increased risk of therapeutic failure, whereas CYP2C19 PMs may be at higher risk of dose-dependent side effects, or potentially improved antidepressive effect.

The difference in C_{ss} between *CYP2C19* genotypes was less pronounced for sertraline than for escitalopram. Nevertheless, the more than 3-fold higher C_{ss} of sertraline in CYP2C19 PMs than in EMs might be of relevance for the clinical effect during sertraline treatment. Moreover, CYP2C19 PMs also obtained a 4.5-fold higher C_{ss} of N-desmethyl sertraline. The low inhibitory potency of N-desmethyl sertraline on serotonin reuptake[110-113] indicates a limited contribution from this metabolite to the serotonergic effects of sertraline treatment. However, N-desmethyl sertraline is reported to exhibit dopamine blocking effects up to 60% compared to the parent compound.[110;112;113] Thus it is possible that in particular the dopaminergic effects of sertraline treatment are more pronounced in CYP2C19 PMs than in EMs.[65;102;103]

Systematic studies investigating the impact of genetic variability in *CYP2C19* on therapeutic outcome of treatment with escitalopram or sertraline seem to be absent. However, three studies have investigated the association between *CYP2C19* genetics and response to racemic citalopram,[167-169] but none of these provided statistically significant relationships between *CYP2C19* genotype and clinical response. The studies may not have been optimally designed to detect potential differences in therapeutic effect or side effects, but the larger study by Peters et al.[167] indicates that genetic variability in *CYP2C19* is of limited importance for the clinical response to racemic citalopram. However, as the R-enantiomer of citalopram is reported to antagonise the effect of the S-

enantiomer during treatment with racemic citalopram,[83] it is possible that the higher systemic exposure of the S-enantiomer in CYP2C19 PMs during treatment with racemic citalopram is of less importance than an equally elevated systemic exposure of the S-enantiomer during treatment with escitalopram. Thus, further studies are needed to elucidate the value of *CYP2C19* genotyping in preventing side effects and therapeutic failure during treatment with escitalopram and sertraline.

Genetic factors besides those assessed in the present work are also likely to affect clinical response to escitalopram and sertraline. Variable phenotype of P-glycoprotein may, due to its expression in the blood-brain barrier,[159] influence distribution of these drugs into the brain.[156-158] Furthermore, genetic differences in molecular targets, i.e. pharmacodynamic variability, are possibly of importance for the therapeutic effect and side effects of escitalopram and sertraline.[170;171] Transcription of the gene encoding the serotonin transporter (*SLC6A4*) is affected by genetic polymorphism in its promoter region (5-HTT gene-linked polymorphic region, 5-HTTLPR), which produces a short and a long variant of the 5-HTTLPR.[172;173] Studies have provided contradictory results regarding the impact of the 5-HTTLPR polymorphism for the clinical effect of sertraline and escitalopram,[174-178] however a recent meta analysis reported that the long variant was associated with better response to SSRI treatment as well as lower risk of side effects.[179] Moreover, genetic polymorphism in genes encoding serotonin receptors have been linked to clinical response to various SSRIs,[171] including escitalopram.[180]

Therapeutic effect and side effects of antidepressants have been associated with genetic variability in several loci besides those mentioned here, as well as to clinical features, including course of illness, co-morbidity, age and gender.[170;181;182] In general, only small fractions of the overall variability in response have been explained by single variables.[180;181] In light of this complex nature of the therapeutic response to antidepressants, it is suboptimal to assess the impact of variability in isolated factors. The 'monogenetic' approach in most studies is likely to be a reason for the considerable inconsistency regarding the impact of pharmacogenetic variability on clinical outcome of treatment with SSRIs. Thus, a multivariate approach seems required in order to determine to what extent various factors, including genetic variability in *CYP2C19*, contribute to variability in clinical outcome of escitalopram and sertraline treatment.[1;182]

4.6 Methodological considerations

Genetic variability as a source to differences in drug exposure are increasingly recognised. However, as conventional pharmacogenetic studies often include a low number of healthy individuals receiving a single drug dosage, their applicability to assist dosing of drugs to individual patients is often limited. By use of TDM data it is possible to include larger amounts of data from real-world patients to assess the impact of genetic polymorphism on the overall pharmacokinetic variability of a drug in a clinical treatment setting. The results from such studies are therefore valuable in the translation of basic pharmacogenetic science into practical applications in the clinical everyday life. However, the use of TDM data is associated with some methodological weaknesses, such as lack of compliance control, variable sampling time, incomplete information on the requisition forms, different drug doses, and use of single point measurements. Hence, the extensive variability in dose-adjusted serum concentrations in the present work might to some degree be due to the naturalistic nature of the data material. This could increase the risk of type II errors, i.e. false negative results. However, it is less likely to provide false positive associations between *CYP2C19* genotype and pharmacokinetics of escitalopram and sertraline (type I errors).

The impact of *CYP2C19* genetics on C_{ss} of escitalopram was more pronounced in the study presented in Paper II than in other studies which have investigated steady state pharmacokinetics of escitalopram in relation to CYP2C19 activity (see section 4.1).[92;93;96;97;127] Some of these studies[92;93;127] assessed systemic exposure of escitalopram in terms of AUC. However inspection of the concentration versus time curves indicated that use of trough concentrations instead of AUC would provide similar differences between the studies. Another potential explanation for the reported discrepancies in the quantitative impact of *CYP2C19* genotype is differences in study populations. The other studies were controlled pharmacokinetic studies, whereas the study presented in Paper II was based on data from TDM. As TDM and *CYP* genotyping are not routinely carried out for all patients receiving treatment with SSRIs, it is possible that these analyses are performed more often in clinically problematic cases, i.e. patients experiencing therapeutic failure or side effects, than in other patients. As drug exposure is one of the factors assumed to be of importance for treatment outcome, one might speculate whether the TDM database comprises an overrepresentation of patients with serum concentrations at both extremes (very high PMs or very low UMs). If so, the use of TDM data might

result in an overestimation of the effect sizes in these outmost *CYP2C19* genotypes. Thus, further studies are necessary in order to investigate to which degree the effect sizes estimated from TDM data are representative for the differences in serum concentrations between *CYP2C19* genotypes in the general population of patients treated with escitalopram and sertraline. Nevertheless, the studies presented in Paper II and Paper III showed that, in a naturalistic treatment setting, substantial differences in serum concentrations of escitalopram and sertraline exist between subgroups of patients carrying different *CYP2C19* genotypes.

5 CONCLUSION

Genetic variability in *CYP2C19* is a major determinant of the pharmacokinetics of escitalopram in psychiatric patients, with an almost 10-fold difference in mean dose-adjusted serum concentration between CYP2C19 UMs and PMs. Besides the well known N-desmethylation of escitalopram, CYP2C19 is able to catalyse formation of the propionic acid metabolite, and it appears that the differences in serum concentration of escitalopram between *CYP2C19* genotypes are caused by a combined effect on the two metabolic pathways. *CYP2C19* genetics is an important determinant of the pharmacokinetics of sertraline as well, but the difference in mean dose-adjusted serum concentration between *CYP2C19* genotypes is less pronounced compared to escitalopram.

The substantial differences in pharmacokinetics of escitalopram and sertraline between *CYP2C19* genotypes might be related to the individual's risk of adverse effects and therapeutic failure during treatment with these drugs, and the findings in the present thesis may provide a fundament for individual dosing of these drugs.

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Paper I

Heterozygous mutation in CYP2C19 significantly increases the concentration/dose ratio of racemic citalopram and escitalopram (S-citalopram).

Therapeutic Drug Monitoring. 2006;28:102-105.

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Paper II

*Impact of the ultrarapid CYP2C19*17 allele on serum concentration of escitalopram in psychiatric patients.*

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Paper III

Serum concentrations of sertraline and N-desmethyl sertraline in relation to CYP2C19 genotype in psychiatric patients.

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Paper IV

Identification of a novel CYP2C19-mediated metabolic pathway of S-citalopram in vitro.

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