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## **A population pharmacokinetic model for escitalopram and its major metabolite in depressive patients during the perinatal period: Prediction of infant drug exposure through breast milk**

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1 **A population pharmacokinetic model for escitalopram and its major metabolite in**  
2 **depressive patients during the perinatal period: prediction of infant drug exposure**  
3 **through breast milk**

4  
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37 **Conflict of interest:** The authors declare no relevant conflict of interest with the content of this  
38 manuscript.

39 **Abstract**

40 **Background and objectives:** Escitalopram figures among the most frequently prescribed  
41 drugs for the treatment of depression in pregnant and breastfeeding women. Available  
42 information on exposure to escitalopram during the perinatal period and its excretion into breast  
43 milk is however based on heterogeneous and incomplete data. A population pharmacokinetic  
44 model was therefore developed using prospectively collected samples and clinical information to  
45 better characterize maternal and infant exposure to escitalopram and its metabolite, and predict  
46 the exposure variability under various conditions.

47 **Methods:** The study population was composed of women taking escitalopram or racemic  
48 citalopram included in a multicenter prospective cohort study enrolling pregnant women taking  
49 selective serotonin reuptake inhibitors (SSRI) and willing to breastfeed. A joined structural  
50 model was first built for escitalopram (SCIT) and S-desmethylcitalopram (SDCIT) in plasma  
51 using NONMEM<sup>®</sup>. Then, drug breast milk concentrations were added to the basic model and  
52 described by estimating milk-to-plasma ratios (MPR). The effect of different influential covariates  
53 such as age, bodyweight, CYP2C19, 2D6 and 3A4/5 genotypes or milk fat content on drug and  
54 metabolite pharmacokinetics was tested. Finally, drug exposure of a suckling child through  
55 breast milk was predicted under various conditions by simulation.

56 **Results:** The study enrolled 33 patients treated with escitalopram or racemic citalopram who  
57 provided 80 blood and 104 milk samples. Mean SCIT clearance was 32.3 L/h with a between-  
58 subject variability of 31% (CV%) and apparent volume of distribution was 1590 L. Poor  
59 metabolizers of CYP2C19 showed a significant 51% decrease in SCIT clearance compared to  
60 other phenotypes. Both parent drug and metabolite were characterized by a MPR of 1.9, while  
61 an increased milk fat content was significantly associated with an increased drug transfer into  
62 breast milk (+28% for SCIT and +18% for SDCIT when fat amount passes from 3.1 to 6.2 g/100  
63 ml). Simulations suggested that an exclusively breastfed infant would ingest daily through breast  
64 milk 3.3% of the weight-adjusted maternal SCIT dose on average.

65 **Conclusion:** Escitalopram and its metabolite showed moderate between-subject variability in  
66 blood concentrations, partially explained by genetic polymorphisms in CYP2C19. Milk  
67 concentrations were similarly variable and mainly influenced by the milk fat content. The limited  
68 exposure to escitalopram through breast milk, as expected based on previous incomplete data,  
69 was confirmed by this population pharmacokinetic model approach. These findings provide  
70 reassurance with a good level of certainty for clinicians and patients successfully treated with  
71 escitalopram or racemic citalopram in the perinatal period.

72

73 **Keywords:** escitalopram, breastfeeding, exposure, population pharmacokinetics

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75

## 76 1. Introduction

77 Worldwide about 10% of pregnant women and 13% of women who have just given birth  
78 experience a mental disorder, primarily depression ([http://www.who.int/mental\\_health/maternal-](http://www.who.int/mental_health/maternal-child/en/)  
79 [child/en/](http://www.who.int/mental_health/maternal-child/en/)). If left untreated, depression has been associated with adverse outcomes for the  
80 mother, the infant and their family environment, such as reduced maternal sensitivity and  
81 involvement in caregiving, and child emotional or behavioral difficulties [3-5]. Antidepressants,  
82 mainly selective serotonin reuptake inhibitors (SSRI), are therefore commonly prescribed for  
83 depression in pregnant and breastfeeding women, when a pharmacological treatment is  
84 indicated.

85 Escitalopram (SCIT) belongs to the SSRI class and figures among the most frequently reported  
86 maternal treatments for chronic conditions in pregnancy [6]. SCIT represents the  
87 pharmacologically active S-(+) enantiomer of the racemic citalopram and is also marketed as  
88 the pure enantiomer escitalopram. After oral administration of doses of 10-20 mg of  
89 escitalopram per day, SCIT is rapidly absorbed ( $T_{max}$  of 3-4 h) and characterized by a volume of  
90 distribution (V), oral clearance (CL) and elimination half-life ( $t_{1/2}$ ) of 18.3 L/kg, 0.48 L/h/kg and  
91 about 30 h, respectively [7, 8]. SCIT is primarily metabolized in the liver by cytochrome P450  
92 (CYP) enzymes into S-(+)-desmethylcitalopram (SDCIT), which shows a prolonged elimination  
93 half-life of 50 h [7, 8]. CYP2C19, CYP3A4 and to a lesser extent CYP2D6 have been reported  
94 as the main metabolic pathways [9], and genetic polymorphisms in the enzyme-coding genes  
95 may be responsible for interpatient variations in drug plasma concentrations [10].

96 Escitalopram doses ingested by a breastfed infant through milk have been reported to be low  
97 (3-6% of the weight-adjusted maternal dose) and result very often in negligible drug  
98 concentrations in infant plasma [11]. However, the extent of drug transfer into breast milk varies  
99 widely between individuals in terms of milk-to-plasma concentration ratio (MPR, 1.7-2.7 for SCIT  
100 and 1.8-3.1 for SDCIT) [12, 13]. Sampling procedure (e.g. single vs. several time points), milk

101 composition (foremilk vs. hindmilk, colostrum vs. mature milk), factors influencing maternal drug  
102 disposition and sample size are possible sources of the observed variability. Based on these  
103 heterogeneous data, health care professionals may in some cases advice mothers taking  
104 escitalopram to discontinue breastfeeding due to the potential risk of adverse effects in the  
105 suckling child, despite the numerous proven health benefits of breastfeeding [14].

106 The aim of this study was to describe for the first time the pharmacokinetics of escitalopram and  
107 its major metabolite in depressive women during the perinatal period using a population  
108 pharmacokinetic (popPK) modeling approach. The influence of genetic and environmental  
109 factors on drug concentrations and transfer into breast milk was also assessed. Finally, drug  
110 exposure of a suckling child was predicted under various conditions by simulation.

111

## 112 **2. Methods**

### 113 *2.1. Study population*

114 All relevant samples and data were collected from women included in the “SSRI-Breast Milk”  
115 study (NCT01796132, more information on [clinicaltrials.gov](http://clinicaltrials.gov)). This multicenter prospective  
116 cohort study enrolls pregnant women willing to breastfeed and treated with a SSRI  
117 antidepressant or a serotonin noradrenalin reuptake inhibitor (SNRI) in one of the maternity  
118 wards collaborating to the study (i.e. the maternities of the Lausanne University Hospital,  
119 Geneva University Hospital, Ensemble hospitalier de la Côte in Morges, University Hospital of  
120 Nancy and the Hospices Civils in Lyon). Study protocol was approved in 2012-2013 by local  
121 Ethics Committees and health authorities in Switzerland and France.

122 Maternal blood samples and breast milk samples were obtained from pregnant and  
123 breastfeeding women treated either with SCIT (n=21) or racemic citalopram (n=12). Maternal  
124 blood samples collected around the moment of delivery were available for 28 patients (1 sample

125 per patient; 14 during labor, 14 right after delivery). Paired blood and breast milk samples during  
126 the first week postpartum and at 1 month after delivery were collected in 29 and 23 patients,  
127 respectively (1 blood and 2 milk samples (fore- and hindmilk) per patient at each occasion). The  
128 analysis included therefore drug concentrations from a total of 80 blood samples and 104 breast  
129 milk samples. Median SCIT and citalopram doses were 10 mg/day (range 5-20 mg/day) and 15  
130 mg/day (range 5-60 mg/day), respectively. Sampling occurred under steady-state conditions at  
131 a median time-lapse of 11.17 h (range 0.02-34.00 h) and 10.25 h (range 0.25-52.25 h) after the  
132 last SCIT or citalopram dose intake, respectively.

### 133 *2.2. Analytical methods*

134 Venous blood samples (5 ml) were drawn on potassium-EDTA tubes and stored after  
135 centrifugation as plasma samples in polypropylene tubes at -20°C. Breast milk was collected in  
136 lactating mothers using an automatic or manual pump, and stored at -20°C or -80°C in  
137 polystyrene tubes until analysis. Subsequent quantification of SCIT and SDCIT in plasma and  
138 breast milk was performed using a validated stereoselective HPLC-MS/MS method (Acquity®  
139 UPLC I-Class, Waters, Milford, USA) described in details previously [15]. Composition of breast  
140 milk was determined using the Human Milk Analyzer® (Miris, Uppsala, Sweden) which provided  
141 information on fat, protein, carbohydrate and calorie content. Plasma concentrations of alpha-1-  
142 acid-glycoprotein (AAG) were measured by immunoturbidimetry using the Cobas Integra® 400  
143 plus analyzer (Roche Diagnostics, Rotkreuz, Switzerland).

### 144 *2.3. Genotyping*

145 Genomic DNA was first extracted from potassium-EDTA blood samples collected at delivery or  
146 later. Most single nucleotide polymorphisms (SNP) were analyzed by TaqMan®-Assay based  
147 real-time polymerase chain reaction (Applied Biosystems, Rotkreuz, Switzerland): *CYP2C19\*2*,  
148 *CYP2C19\*3*, *CYP219\*17*, *CYP2D6\*3*, *CYP2D6\*4*, *CYP2D6\*6*, *CYP3A4\*22*, *CYP3A5\*3* and



149 *POR*\*28. Duplication/multiplication of *CYP2D6*\**xN* and *CYP2D6*\*5 gene deletion were detected  
150 by TaqMan<sup>®</sup> copy number assay. Regarding *CYP2C19*, patients were classified into 4 predicted  
151 phenotypes: poor metabolizer (PM) if they were homozygous for the \*2/\*2 allele, intermediate  
152 metabolizer (IM) if they carried any of \*1/\*2 or \*17/\*2 allele, extensive metabolizer (EM) if they  
153 were homozygous for the wild-type allele \*1/\*1 and ultrarapid metabolizer (UM) if they carried  
154 either \*1/\*17 or \*17/\*17 genotype. Patients were also divided in 4 different predicted phenotypes  
155 according to *CYP2D6* genotype: poor metabolizer (PM; carriers of 2 non-functional alleles, e.g.  
156 \*4/\*4, \*4/\*5, \*4/\*6), intermediate metabolizer (IM; carriers of 1 functional and 1 non-functional  
157 allele, e.g. \*1/\*3, \*1/\*4, \*1/\*5), extensive metabolizer (EM; carriers of two functional alleles,  
158 \*1/\*1) and ultrarapid metabolizer (UM; carriers of 1 functional allele and an increased number of  
159 gene copies, \*1/\**xN*, or carriers of an increased number of gene copies, \**xN*/\**xN*). For control  
160 purposes, each analyzed batch of samples contained also DNAs with known genotypes.

#### 161 *2.4. Population pharmacokinetic analysis*

162 All popPK analyses were conducted using the non-linear mixed effects modeling tool  
163 NONMEM<sup>®</sup> (version 7.3.0, ICON Development Solutions, Ellicott City, USA), which enables the  
164 estimation of average population parameters as well as between-subject and residual variability.  
165 Due to the use of a stereoselective analytical method (see section 2.2), concentration data from  
166 both racemic citalopram and pure escitalopram could be pooled assuming a negligible effect of  
167 the R-(-) enantiomer on the SCIT pharmacokinetic profile. This assumption was confirmed by  
168 testing the influence of maternal treatment on SCIT profile (citalopram vs. pure escitalopram as  
169 a dichotomous variable), which demonstrated to be non-significant.

#### 170 *2.4.1 Structural and statistical models*

171 A stepwise approach was chosen in order to obtain a combined model with the best fit for both  
172 parent compound and its metabolite. First, one and two compartment models with linear drug

173 elimination were evaluated for SCIT plasma concentrations alone. Then, one additional  
 174 compartment was used to describe SDCIT plasma concentrations assuming linear metabolism.  
 175 Finally, parent drug and metabolite transfers into breast milk were characterized by MPR as a  
 176 scaling factor between concentration profiles in plasma and milk, as previously described [16].  
 177 The final structural model is illustrated in Figure 1 and described by the following differential  
 178 equations:

$$\frac{dSCIT_{dose}}{dt} = -k_{12} \times SCIT_{dose} \quad (1)$$

$$\frac{d(SCIT_{plasma} \times V_{SCIT})}{dt} = k_{12} \times SCIT_{dose} - k_{20} \times SCIT_{plasma} - k_{23} \times SCIT_{plasma} \quad (2)$$

$$\frac{d(SDCIT_{plasma} \times V_{SDCIT})}{dt} = k_{23} \times SCIT_{plasma} - k_{30} \times SDCIT_{plasma} \quad (3)$$

$$SCIT_{milk} = MPRD \times SCIT_{plasma} \quad (4)$$

$$SDCIT_{milk} = MPRM \times SDCIT_{plasma} \quad (5)$$

179 where  $SCIT_{dose}$  is the SCIT amount in the dose compartment,  $k_{12}$  the absorption rate constant,  
 180  $k_{20}$  the elimination rate constant from the parent drug compartment,  $k_{23}$  the metabolic rate  
 181 constant from SCIT to SDCIT,  $k_{30}$  the elimination rate constant from the metabolite  
 182 compartment,  $V_{SCIT}$  the volume of distribution of SCIT,  $SCIT_{plasma}$  and  $SDCIT_{plasma}$  the parent  
 183 drug and metabolite concentrations in plasma, respectively,  $SCIT_{milk}$  and  $SDCIT_{milk}$  the parent  
 184 drug and metabolite concentration in breast milk, MPRD and MPRM the milk-to-plasma ratio for  
 185 the parent drug and the metabolite, respectively. Due to identifiability issues, the volume of  
 186 distribution of SDCIT ( $V_{SDCIT}$ ) could not be estimated. We assumed that  $k_{23} = k_{30}$  and estimated  
 187  $V_{SDCIT}$  through the ratio of metabolite to parent drug volume of distribution (with VMR being the  
 188 volume metabolite ratio,  $V_{SDCIT} = V_{SCIT} \times VMR$ ).

189 Between-subject variability (BSV) of each pharmacokinetic parameter was described using an  
 190 exponential error model. A combined proportional and additive error model was first tested to

191 describe residual variations in plasma for SCIT and then simplified to a proportional error model,  
192 which was retained for both drug and metabolite.

#### 193 *2.4.2 Covariate models*

194 The effect of genetic and environmental covariates on the final structural model was assessed  
195 by a forward insertion/backward deletion approach. Maternal age (AGE), bodyweight (BW),  
196 alpha-1-acid-glycoprotein concentration (AAG) and important CYP polymorphisms (CYP2C19,  
197 CYP2D6, CYP3A4, CYP3A5) were tested as covariates. Genotypes for both CYP2C19 and 2D6  
198 isoenzymes were classified into 4 distinct groups according to their predicted phenotype, while  
199 the actual genotype was used for CYP3A4 (\*1/\*1, \*1/\*22, \*22/\*22), 3A5 (\*1/\*1, \*1/\*3, \*3/\*3) and  
200 POR (\*1/\*1, 1/\*28, \*28/\*28). Regarding drug transfer into breast milk, feeding occasion (FEED;  
201 fore- versus hindmilk), fat (FAT), protein (PROT), carbohydrate (CARBO) and calorie content  
202 (ENERGY) were evaluated as potentially important covariates. The moment of blood or milk  
203 sampling (MOM; 4 categories: during labor, after delivery, 1<sup>st</sup> week postpartum or 1 month after  
204 delivery) was also tested on various parameter estimates as drug concentrations during the  
205 perinatal period may vary significantly due to physiological changes.

206 Continuous covariates (normalized and centered on their median population value, missing data  
207 were replaced by the median value) and dichotomous covariates (coded as 0/1) were tested  
208 using a linear function. Discrete variables including more than 2 groups were described as  
209 categorical covariates assigning a fixed effect to each category and reduced models combining  
210 different groups were tested as well for statistical significance.

211

#### 212 *2.4.3 Parameter estimation and model selection*

213 Data were fitted using the first-order conditional estimation method with interaction (FOCE-I) in  
214 NONMEM® (reference for NONMEM: Beal SL SL, Boeckmann A, Bauer RJ. NONMEM user's  
215 guide (1989–2009) Ellicott City: Icon Development Solutions. 2009). The log-likelihood ratio test  
216 was used to discriminate between two nested models (difference in the objective function value  
217 ( $\Delta\text{OFV}$ ) approximates a  $\chi^2$  distribution). A  $\Delta\text{OFV} < -3.84$  ( $\chi^2$ ,  $p < 0.05$ ,  $df = 1$ ) and  $> 6.63$   
218 ( $\chi^2$ ,  $p < 0.01$ ,  $df = 1$ ) were considered statistically significant for one additional parameter during  
219 forward insertion and backward deletion steps, respectively. Goodness-of-fit plots,  
220 pharmacokinetic parameter precision and decrease in between-subject variability were also  
221 considered for model quality assessment.

#### 222 *2.4.4 Model validation*

223 The precision of parameter estimates and stability of the final model were assessed using the  
224 non-parametric bootstrap method. Briefly, two thousand datasets were created through random  
225 resampling of original data (1000 stratified on CYP2C19 and 1000 on CYP2D6 genotypes,  
226 respectively). Median parameter values and percentile intervals (90% PI) were generated for  
227 each pharmacokinetic parameter based on all replicated datasets and compared to estimations  
228 from the original model. Prediction-corrected visual predictive checks (pcVPC) were also carried  
229 out by simulating 1000 individuals based on the final covariate model estimates using the PsN  
230 toolkit [17].

231

#### 232 *2.4.5 Simulation of drug concentrations and prediction of infant drug exposure*

233 Plasma and breast milk concentrations of SCIT and SDCIT at steady-state were simulated  
234 according to different dose regimens in 5'000 mothers based on the final structural model  
235 (without any covariates) as well as according to relevant covariates in 10'000 mothers based on  
236 intermediate covariate models (one single covariate added alternatively to the final structural

237 model). For this purpose, virtual datasets of breastfeeding women were generated with R<sup>®</sup> (R  
238 Development Core Team, Foundation for Statistical Computing, Vienna, Austria) by assigning  
239 random breastfeeding frequencies and intervals to each woman after the last dose intake. In  
240 order to best reflect usual breastfeeding frequencies, the mean frequency was set to 11±3  
241 feedings per day with a range between 6 and 18 times a day [18]. Finally, the daily infant  
242 dosage that is equivalent to the drug dose ingested by an exclusively breastfed infant through  
243 breast milk was calculated for each mother-infant pair and expressed in mg/kg/day, using the  
244 following equation:

$$Daily\ infant\ dosage = \sum_{i=1}^n C_{milk}^i * V_{milk}$$

245 where  $C_{milk}^i$  is the simulated drug concentration in milk at the  $i^{th}$  feeding time,  $n$  is the daily  
246 feeding frequency and  $V_{milk}$  is the ingested milk volume by a suckling child during a feeding  
247 occasion. For simplicity, typical  $V_{milk}$  was derived from literature by dividing the usual weight-  
248 adjusted daily milk intake of 150 ml/kg/day by the feeding frequency [19].

249  
250 In order to better evaluate the clinical relevance of the daily infant dosage, two additional  
251 exposure estimates were determined, namely the relative infant dose (RID) and the adult dose  
252 equivalent (ADE). RID represents the ratio between the daily infant dosage and the weight-  
253 adjusted maternal dose (based on a standard adult weight of 70 kg) and is expressed as a  
254 percentage [19]. For example, a RID of 10% indicates that a suckling child would daily ingest via  
255 breast milk 10% of the weight-adjusted maternal SCIT dose.

256 The ADE quantifies the virtual number of tablets that would be ingested by the infant over 6  
257 months of exclusive breastfeeding. This number was obtained by dividing the cumulated daily  
258 infant dosage over 6 months by a standard adult daily dose (i.e. 10 mg for escitalopram),  
259 assuming a mean child weight of 6 kg.

260

## 261 **3. Results**

262 Demographic and clinical characteristics of patients included in the popPk analysis are  
263 presented in Table 1.

### 264 *3.1. Structural models*

265 Regarding SCIT, data were best described by a one compartment model with first-order  
266 absorption and elimination. The two compartment model did not show any significant  
267 improvement of the fit ( $\Delta\text{OFV} = -1.0$ ,  $p > 0.05$ ). The addition of a BSV on CL, but not on V or  $k_a$   
268 ( $\Delta\text{OFV} = 0.0$ ,  $p > 0.05$ ), yielded a significantly better fit ( $\Delta\text{OFV} = -40.9$ ,  $p < 0.001$ ) and was  
269 therefore retained (40.1%, CV%).

270 In the next step, metabolite plasma concentrations (SDCIT) were added to the dataset. Due to  
271 identifiability issues, the metabolite's apparent volume of distribution was estimated using a  
272 scaling factor VMR (volume metabolite ratio), and resulted in acceptable parameter precision.  
273 The assignment of a BSV to VMR slightly improved the fit ( $\Delta\text{OFV} = -5.2$ ,  $p = 0.02$ ; 20.0%, CV%),  
274 while a variability on  $k_{23}$  did not ( $\Delta\text{OFV} = -2.9$ ,  $p > 0.05$ ).

275 Finally, SCIT and SDCIT milk concentrations were integrated into the model using the milk-to-  
276 plasma ratios (MPRD and MPRM, respectively). No changes in the model fit were observed  
277 assigning a BSV to MPRD or MPRM ( $\Delta\text{OFV} > -0.2$ ,  $p > 0.05$ ). Some individual covariates such as  
278 milk fat content were nevertheless tested on these parameters due to a priori knowledge.  
279 Pharmacokinetic parameters of the structural model are presented in Table 2.

280

### 281 *3.2. Covariate models*

282 Univariate analyses showed that MOM, BW and CYP2C19 were significantly associated with  
283  $\text{CL}_{\text{SCIT}}$  ( $\Delta\text{OFV} < -14.1$ ,  $p < 0.05$ ). No differences could be observed between concentrations

284 collected during labor, right after delivery and during the 1<sup>st</sup> week postpartum ( $\Delta\text{OFV} = 0$ ,  
285  $p > 0.05$ ), nor between CYP2C19 IM, EM and UM ( $\Delta\text{OFV} = 0$ ,  $p > 0.05$ ). These categorical  
286 covariates could therefore be reduced to dichotomous variables. Maternal age, CYP2D6, 3A4,  
287 3A5, POR or AAG did not show any significant effect on  $\text{CL}_{\text{SCIT}}$  ( $\Delta\text{OFV} > -3.8$ ,  $p > 0.05$ ). Only  
288 MOM importantly influenced  $V_{\text{SCIT}}$  ( $\Delta\text{OFV} = -46.4$ ,  $p = 0.05$ ) but not BW, AGE or AAG ( $\Delta\text{OFV} > -$   
289  $1.6$ ,  $p > 0.05$ ). VMR was affected by MOM, CYP2C19 and CYP2D6 ( $\Delta\text{OFV} < -6.9$ ,  $p < 0.05$ ) but  
290 not by BW, AGE, CYP3A4, 3A5, POR or AAG ( $\Delta\text{OFV} > -3.4$ ,  $p > 0.05$ ). No differences could be  
291 observed between CYP2D6 IM and EM ( $\Delta\text{OFV} = 0$ ,  $p > 0.05$ ). Regarding univariate analyses  
292 conducted on MPRD and MPRM, the covariates MOM, FAT, ENERGY and FEED all  
293 significantly influenced the model ( $\Delta\text{OFV} < -4.0$ ,  $p = 0.05$ ).

294 In multivariate analyses, MOM and CYP2C19 showed an independent impact on  $\text{CL}_{\text{SCIT}}$  but not  
295 BW ( $\Delta\text{OFV} = -3.8$ ,  $p = 0.05$ ). SCIT clearance was reduced by 51% in CYP2C19 PM compared to  
296 the other genetic polymorphisms. A 10% decrease in  $\text{CL}_{\text{SCIT}}$  at 1 month after delivery was  
297 observed compared to the perinatal period. The influence of both CYP2D6 and CYP2C19 on  
298 VMR remained significant in multivariate analysis ( $\Delta\text{OFV} < -12.8$ ,  $p < 0.05$ ). These results  
299 suggest lower plasma concentrations of the active metabolite SDCIT in CYP2C19 PM (-72%)  
300 and higher concentrations in UM (+22%) in comparison to IM/EM. In addition, patients carrying  
301 CYP2D6 PM genotype had also reduced SDCIT concentrations (-104%) compared to IM/EM.

302 The combined addition of MOM and FAT to MPRD improved the description of the data, but  
303 ENERGY and FEED did not remain significant in multivariate analyses ( $\Delta\text{OFV} > -3.4$ ,  $p > 0.05$ ).  
304 Only FAT remained statistically significant on MPRM, since it was correlated with ENERGY and  
305 FEED ( $\Delta\text{OFV} > -3.8$ ,  $p > 0.05$ ). The transfer of SCIT and SDCIT into breast milk increased by  
306 28% and 18%, respectively, with a doubling of fat content from 3.1 to 6.2 g/100 ml. The final  
307 parameter estimates, influencing covariates and variabilities together with their bootstrap  
308 estimations are presented in Table 3 and diagnostic plots are shown in Figure 2 and 3.

309

### 310 3.3. Model validation

311 The pcVPCs shown in Figure 4 supported the good predictive performance of the model. All  
312 parameter estimates from the final covariate model lied within the 90% percentile interval (90%  
313 PI) calculated from the bootstrap method and were close to the median values (<11%),  
314 indicating a reasonably robust model.

315

### 316 3.4. Prediction of infant drug exposure by simulation

317 Based on the final structural model without any covariates, simulation of 5'000 mothers treated  
318 with 10 mg escitalopram daily revealed that the daily infant dosage would lie between 0.001 and  
319 0.016 mg/kg/day (median: 0.005 mg/kg/day). Expressed as the ratio to the weight-adjusted  
320 maternal dose, RID values for escitalopram ranged from 0.8% to 11.3% (median: 3.3%; Figure  
321 5), which is in line with previously reported values [11, 20]. In terms of ADE, an exclusively  
322 breastfed infant would ingest over 6 months a cumulated dose of 1.2-17.4 mg (median: 5.0 mg)  
323 equivalent to 0.1-1.7 tablets of escitalopram (median: 0.5; Figure 5). RID and ADE would be  
324 slightly higher in mothers who are PM for CYP2C19, while the influence of other covariates on  
325 these exposure estimates remained negligible. Simulations performed on the active metabolite  
326 SDCIT showed only a minor impact on overall infant drug exposure (data not shown).

327

## 328 4. Discussion

329 This study described for the first time the population pharmacokinetics of SCIT and its major  
330 metabolite SDCIT in depressive patients during the perinatal period, while taking into account  
331 genetic, demographic and environmental factors. Estimated pharmacokinetic parameters and



332 mean MPR of both parent drug and metabolite are in line with available data [7, 8, 21, 22] [12,  
333 13]. These results suggest that this antidepressant drug has a higher affinity for breast milk than  
334 for plasma (MPR>1.0), but infant exposure through breast milk remains limited as illustrated by  
335 a median RID of 3.3% and an ADE of 0.5 tablets.

336 Model results showed a slight decrease of 10% in clearance of SCIT one month after delivery  
337 compared to the perinatal period. A similar finding has been reported previously for racemic  
338 citalopram, where concentrations measured at delivery and corrected to a daily dose of 20 mg  
339 were 20-30% lower than at 2-4 months postpartum. These small studies observed even higher  
340 differences when comparing to the 2<sup>nd</sup> and 3<sup>rd</sup> trimester and attributed them to physiological  
341 changes in pregnancy affecting renal and hepatic functions (e.g. increased glomerular filtration  
342 rate, induced CYP2D6 and 3A4 activity) [23, 24]. This effect could not be investigated in our  
343 population due to the lack of drug measurements earlier in pregnancy, but may potentially  
344 suggest the need for dose adjustment in pregnant women in order to prevent relapse of  
345 depressive symptoms. Yet, the clinical relevance of such a measure still requires confirmation  
346 from larger studies.

347 The significant influence of CYP2C19 predicted phenotype on SCIT clearance and SDCIT  
348 volume metabolite ratio is in agreement with numerous other publications reporting similar  
349 effects in the psychiatric population. According to a recent meta-analysis, CYP2C19 PM show a  
350 mean increase in (es)citalopram concentrations of 95% compared to EM [25]. In these patients,  
351 enhanced drug exposure could potentially lead to a lower drug tolerance or even to toxicity (e.g.  
352 QT prolongation), reason why authorities and consensus guidelines recommend dose  
353 adjustments in these situations [26]. Similar considerations are of particular interest for  
354 depressive women during the perinatal period as higher maternal drug concentrations will lead  
355 to higher exposure of the suckling child through breastmilk. In addition to CYP2C19,  
356 polymorphisms in genes coding for CYP2D6 had also a significant effect on metabolite plasma  
357 concentrations. However, this finding was based on only two CYP2D6 PM patients (and no

358 UM), thus no specific conclusions on the real effect size can be drawn. Polymorphisms in  
359 CYP3A4, 3A5 or POR did not show any effect on SCIT elimination in exploratory analyses, but  
360 study population included only one CYP3A5 \*1/\*1 carrier and no CYP3A4 \*22/\*22 carrier.

361 SCIT and its major metabolite are excreted into breast milk with a MPR of 1.9. Breast milk fat  
362 content, which varies during a feed (i.e. hind milk vs fore milk) and breastfeeding periods (i.e.  
363 colostrum vs mature milk), mainly influenced this passage. Similar findings showing a higher  
364 affinity of lipophilic drugs for milk richer in lipids have been published previously (Berle et al.  
365 2004, PMID: 15367050). In fact, simulations performed in 10'000 mother-infant pairs showed  
366 that a doubling of fat content from 2.1 g to 4.3 g/100 ml increased median RID from 2.8% to  
367 3.5%. Despite this increase, the RID can still be considered as reassuringly low. This clearly  
368 outweighs the possible effect of a small additional drug transfer.

369 Regarding prediction of infant drug exposure, maternal CYP2C19 phenotype was identified as  
370 the most influential covariate in our population. Breastfed infants of poor metabolizing mothers  
371 would ingest via milk 5.7% of the weight-adjusted maternal dose in average compared to 3.0%  
372 in other phenotypes. Based on average multiethnic frequencies, 2-15% of individuals may be  
373 CYP2C19 PM and therefore concerned by elevated drug concentrations [26=Hicks]. However,  
374 95% of their suckling children would not exceed a RID value of 10% and would receive in total  
375 after 6 months of exclusive breastfeeding an ADE of 0.3-2.3 tablets, indicating a low absolute  
376 exposure to the drug. Clinical implications of even very low drug exposure for the long term  
377 development of a breastfed infant remain however largely uncertain. Simulations performed on  
378 the active metabolite SDCIT showed only a minor impact on overall infant drug exposure,  
379 probably due to its low plasma and milk concentrations. The lower potency of SDCIT as an  
380 antidepressant compared to SCIT would further limit its potential impact on the suckling child.

381 One limitation of the present study was the limited sample size of 33 patients for the PK  
382 analysis. Large clinical trials are particularly difficult to conduct in pregnant and nursing women

383 as they are considered a vulnerable population. Observed frequencies of CYP2C19 phenotypes  
384 were however representative of the general population [26=Hicks] and thereby reinforcing  
385 representativeness of the study sample and thus the validity of the model-based simulations.  
386 The remaining unexplained between-subject variability observed suggests that information on  
387 potentially influencing covariates were not available for analysis as not captured by the study  
388 protocol (e.g. compliance, unknown genetic factors). A limited compliance in our study sample  
389 would be linked to an underestimated RID. However, the level of compliance is not expected to  
390 be below average in our sample of patient with a high level of education (data not shown).

## 391 **5. Conclusions**

392 Escitalopram and its metabolite showed moderate between-subject variability in blood  
393 concentrations, partially explained by genetic polymorphisms in CYP2C19. Milk concentrations  
394 were similarly variable and mainly influenced by the milk fat content. The limited exposure to  
395 escitalopram through breast milk, as expected based on previous incomplete data, was  
396 confirmed by this population pharmacokinetic model approach. These findings provide  
397 reassurance with a good level of certainty for clinicians and patients successfully treated with  
398 escitalopram or racemic citalopram in the perinatal period.

399

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406 Clinical Investigation Center (Hospices Civils de Lyon).

407

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471 Serotonin Reuptake Inhibitors. *Clin Pharmacol Ther* 2015;98:127-34

472

473

474 **Table 1:** Demographic and clinical characteristics of the study population

	Study population (n=33)
Age (years), median (range)	34.0 (21.0-43.0)
Bodyweight (kg), median (range)	
Term pregnancy (n=27)	76.0 (60.8-120.0)
1 <sup>st</sup> week postpartum (n=23)	68.0 (53.0-114.0)
1 <sup>st</sup> month postpartum (n=19)	68.0 (50.0-87.6)
Alpha-1-acid-glycoprotein (g/L), median (range)	
Term pregnancy (n=28)	0.42 (0.23-1.16)
1 <sup>st</sup> week postpartum (n=27)	0.80 (0.25-1.47)
1 <sup>st</sup> month postpartum (n=23)	0.75 (0.48-1.24)
CYP2C19 predicted phenotype, n (%)	
Poor metabolizer	4 (12%)
Intermediate metabolizer	5 (15%)
Extensive metabolizer	12 (36%)
Ultrarapid metabolizer	12 (36%)
CYP2D6 predicted phenotype, n (%)	
Poor metabolizer	2 (6%)
Intermediate metabolizer	8 (24%)
Extensive metabolizer	23 (70%)
Ultrarapid metabolizer	0 (0%)
CYP3A4 genotype, n (%)	
*1/*1	30 (91%)
*1/*22	3 (9%)
*22/*22	0 (0%)
CYP3A5 genotype, n (%)	
*1/*1	1 (3%)
*1/*3	6 (18%)
*3/*3	26 (79%)
POR genotype, n (%)	
*1/*1	18 (55%)
*1/*28	10 (30%)

\*28/\*28 5 (15%)

Breast milk\*, median (range)

Fat content (g/100 ml; n=29) 3.1 (0.2-9.3)

Protein content (g/100 ml; n=29) 1.4 (0.0-4.3)

Carbohydrate content (g/100 ml; n=29) 6.2 (1.0-7.8)

Calorie content (kcal/100 ml; n=29) 57.0 (18.7-112.0)

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475 \* mixed fore- and hindmilk

476

477 **Table 2:** Parameter estimates of intermediate and final structural pharmacokinetic models for  
 478 escitalopram (SCIT) alone or combined with S-desmethylescitalopram (SDCIT) in plasma and/or  
 479 breast milk

	Model for SCIT alone plasma		Model for SCIT+SDCIT plasma		Model for SCIT+SDCIT plasma + breast milk	
	estimate	RSE (%)	estimate	RSE (%)	estimate	RSE (%)
<b>Structural model</b>						
CL <sub>SCIT</sub> (L/h)	29.6	8	27.7	9	28.7	8
V <sub>SCIT</sub> (L)	900	19	1440	9	1310	24
k <sub>a</sub> / k <sub>12</sub> (h <sup>-1</sup> )	0.57	34	0.99	37	0.73	60
k <sub>30</sub> (h <sup>-1</sup> )			0.74	42	0.54	162
VMR			2.6	8	2.5	8
MPRD					2.1	4
MPRM					1.9	4
<b>Statistical model</b>						
ω <sub>CL</sub> (%)	40.1	16	26.2	24	35.4	18
ω <sub>VMR</sub> (%)			20.0	33	33.9	24
σ SCIT <sub>plasma</sub> (%)	33.8	9	41.6	11	35.3	10
σ SDCIT <sub>plasma</sub> (%)			20.3	10	21.0	10
σ SCIT <sub>milk</sub> (%)					31.5	12
σ SDCIT <sub>milk</sub> (%)					22.8	9

480 RSE, relative standard error defined as SE/estimate; CL<sub>SCIT</sub>, apparent clearance of SCIT; V<sub>SCIT</sub>, apparent volume of  
 481 distribution of SCIT; k<sub>a</sub> / k<sub>12</sub>, apparent absorption rate constant from dose compartment; k<sub>30</sub>, apparent metabolic and  
 482 elimination rate constant of SDCIT; VMR, scaling factor of V<sub>SDCIT</sub>; MPRD, milk-to-plasma ratio of SCIT; MPRM, milk-  
 483 to-plasma ratio of SDCIT; ω, between-subject variability estimate; σ, residual variability expressed as coefficient of  
 484 variation

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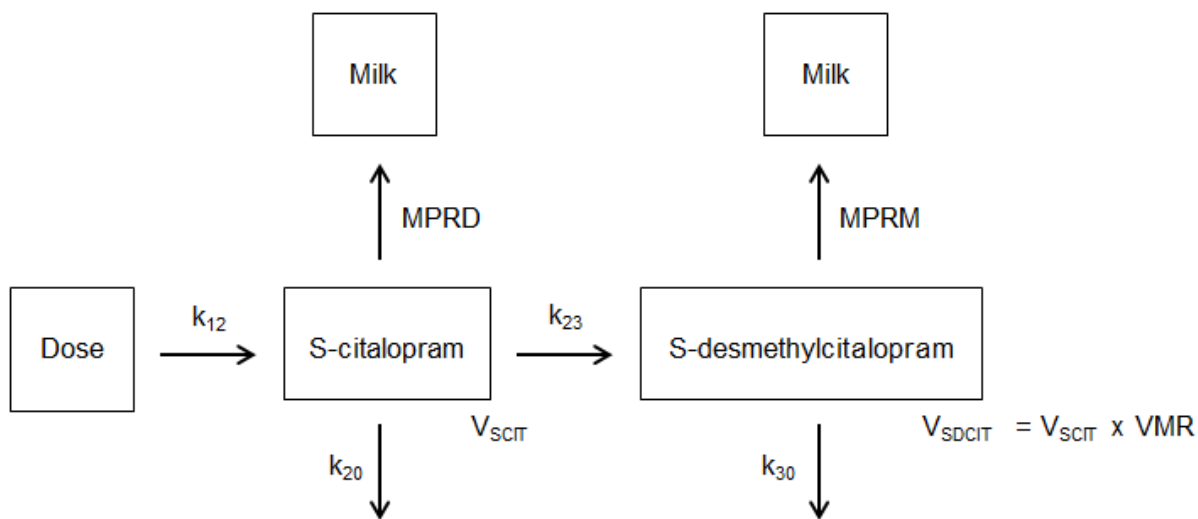


487 **Table 3:** Final covariate population model and bootstrap results for escitalopram and its major  
 488 metabolite

	Final covariate model		Bootstrap (n=2000)	
	estimate	RSE (%)	median	90% PI
CL <sub>SCIT</sub> (L/h)	32.3	8	32.0	28.4 – 36.1
CYP2C19	-0.51	17	-0.50	-0.64 to -0.34
MOM	-0.10	54	-0.10	-0.17 to -0.01
V <sub>SCIT</sub> (L)	1590	14	1474	811 – 1856
k <sub>a</sub> / k <sub>12</sub> (h <sup>-1</sup> )	0.87	36	0.83	0.20 – 1.73
k <sub>30</sub> (h <sup>-1</sup> )	0.67	53	0.59	0.05 – 1.28
VMR for CYP2C19 PM	4.1	22	4.1	3.0 – 6.3
VMR for CYP2C19 IM/EM	2.4	7	2.4	2.2 – 2.8
VMR for CYP2C19 UM	1.9	7	1.9	1.7 – 2.1
CYP2D6	1.04	11	1.04	0.82 – 1.26
MPRD	1.9	4	1.9	1.8 – 2.1
MOM	0.16	53	0.16	0.03 – 0.30
FAT	0.28	20	0.28	0.20 – 0.39
MPRM	1.9	3	1.9	1.8 – 2.0
FAT	0.18	20	0.17	0.11 – 0.23
ω <sub>CL</sub> (%)	31.2	12	30.5	23.8 – 36.8
ω <sub>VMR</sub> (%)	21.0	19	18.9	9.3 – 24.7
σ SCIT <sub>plasma</sub> (%)	33.5	8	33.0	28.7 – 37.4
σ SDCIT <sub>plasma</sub> (%)	20.8	9	20.0	16.7 – 23.2
σ SCIT <sub>milk</sub> (%)	24.0	11	23.1	18.7 – 27.7
σ SDCIT <sub>milk</sub> (%)	19.4	9	18.4	14.9 – 21.6

489 RSE, relative standard error defined as SE/estimate; 90% PI, percentile interval between 5 and 95%; CL<sub>SCIT</sub>,  
 490 apparent clearance of SCIT; CYP2C19, relative deviation of CL<sub>SCIT</sub> if PM compared to IM/EM/UM; MOM, relative  
 491 deviation of CL<sub>SCIT</sub> or MPRD if moment of sampling at 1 month after delivery compared to labor/early postpartum;  
 492 V<sub>SCIT</sub>, apparent volume of distribution of SCIT; k<sub>a</sub> / k<sub>12</sub>, apparent absorption rate constant from dose compartment;  
 493 k<sub>30</sub>, apparent metabolic and elimination rate constant of SDCIT; VMR, scaling factor of V<sub>SDCIT</sub>; CYP2D6, relative  
 494 deviation of VMR if PM compared to IM/EM; MPRD, milk-to-plasma ratio of SCIT; FAT, relative deviation of MPRD or  
 495 MPRM depending on fat content of breast milk; MPRM, milk-to-plasma ratio of SDCIT; ω, between-subject variability  
 496 estimate; σ, residual variability expressed as coefficient of variation

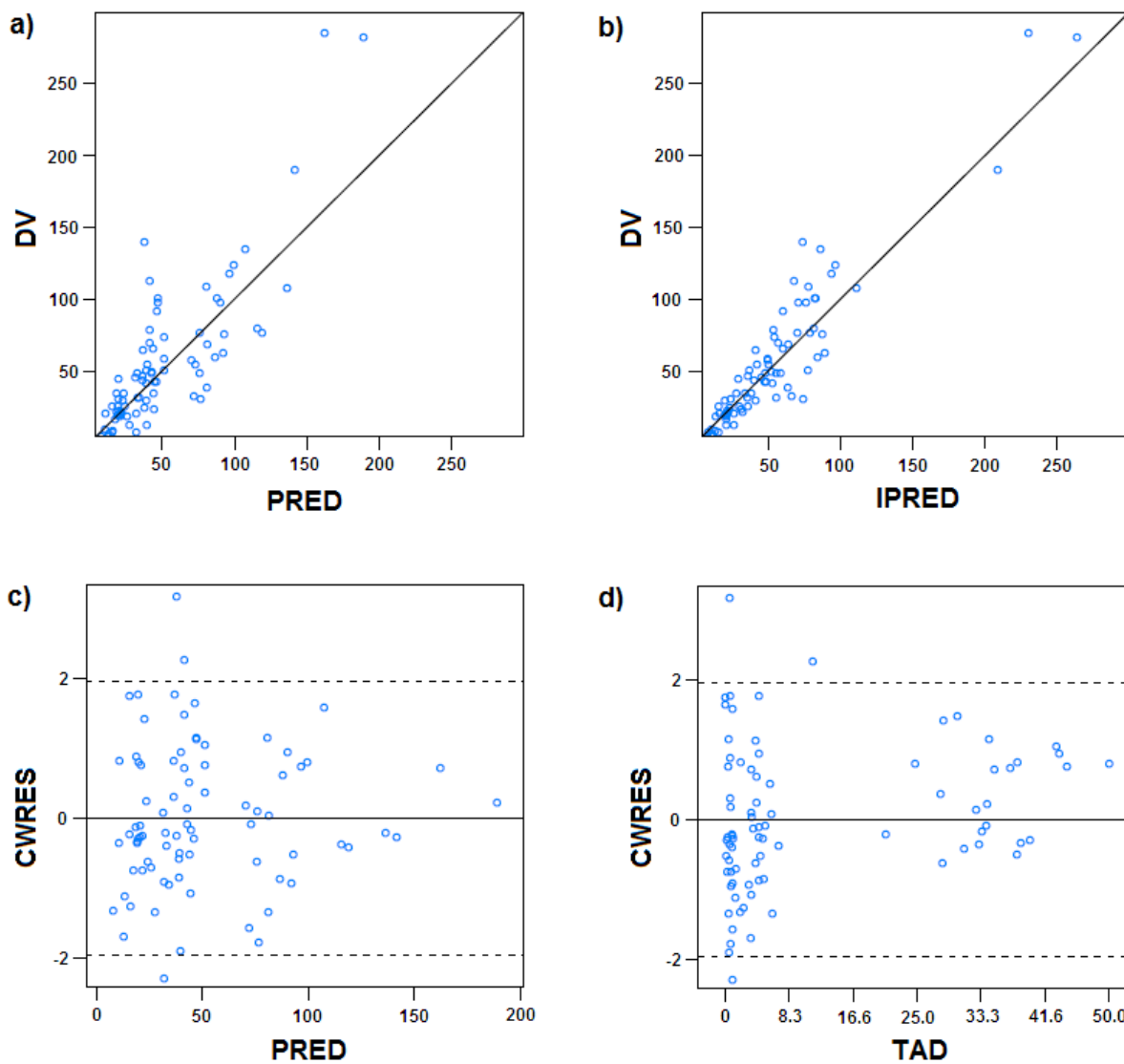
497 **Figure 1:** Compartmental structure of the final model and its main pharmacokinetic parameters  
498 ( $V_{SCT}$ : volume of distribution of escitalopram; VMR: volume metabolite ratio;  $k_{xy}$ :  
499 absorption/metabolic/elimination rate constant; MPRD: milk-to-plasma ratio of escitalopram;  
500 MPRM: milk-to-plasma ratio of S-desmethylescitalopram)



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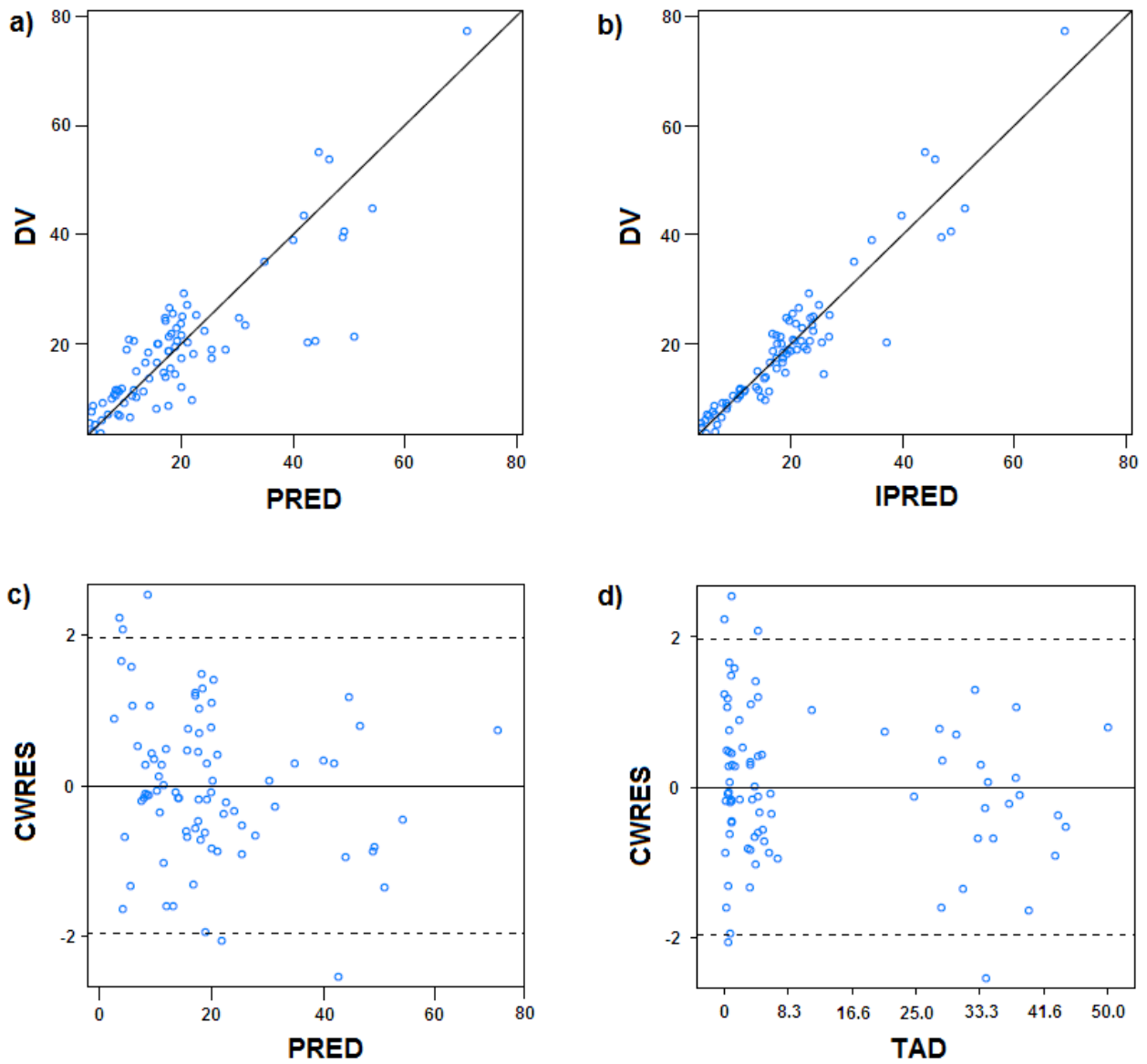
503 **Figure 2:** Goodness-of-fit plots of escitalopram with a) observed concentrations (DV) vs.  
504 population predictions (PRED), b) DV vs. individual predictions (IPRED), c) conditional weighted  
505 residuals (CWRES) vs. PRED and d) CWRES vs. time after dose (TAD) (solid line: unity line)



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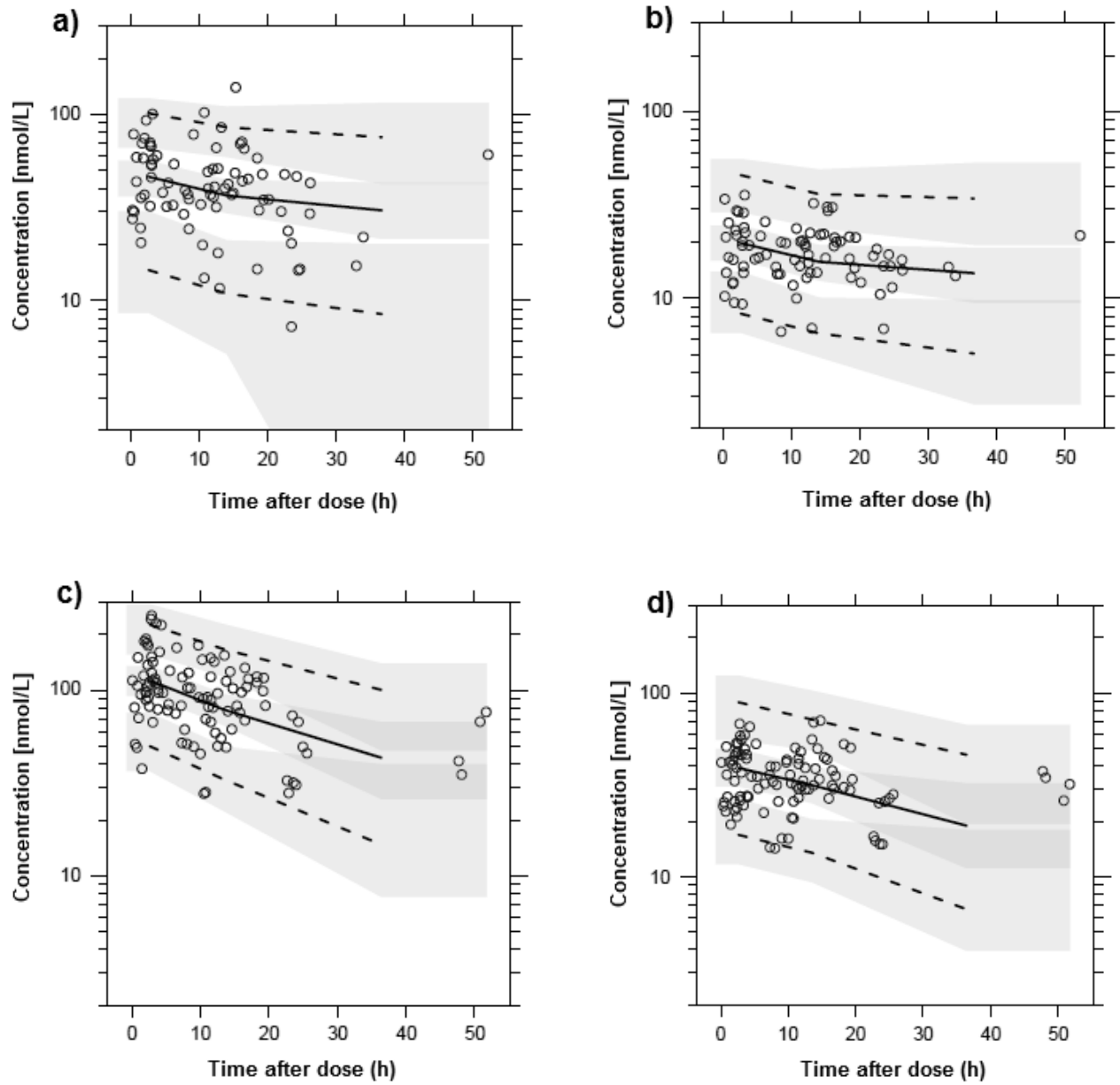
508 **Figure 3:** Goodness-of-fit plots of S-desmethylcitalopram with a) observed concentrations (DV)  
509 vs. population predictions (PRED), b) DV vs. individual predictions (IPRED), c) conditional  
510 weighted residuals (CWRES) vs. PRED and d) CWRES vs. time after dose (TAD) (solid line:  
511 unity line)



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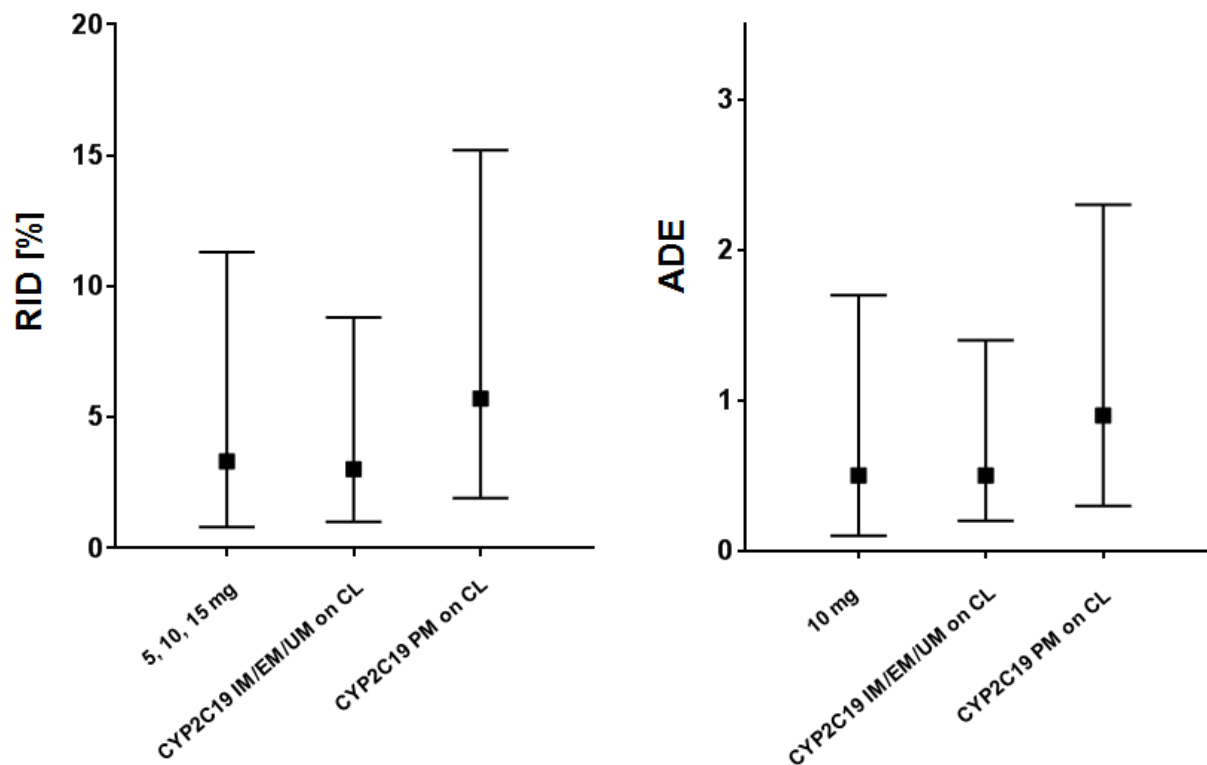
514 **Figure 4:** Prediction-corrected visual predictive checks (pcVPC) of the final covariate model for  
515 a) escitalopram in plasma, b) S-desmethylocitalopram in plasma, c) escitalopram in breast milk  
516 and d) S-desmethylocitalopram in breast milk. (circles: prediction-corrected drug concentrations;  
517 continuous line: population median prediction; dashed lines: 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles; semi-  
518 transparent grey fields: model-based percentile confidence interval).



519

520

521 **Figure 5:** Relative infant dose (RID) and adult dose equivalent (ADE) of escitalopram in 5'000-  
522 10'000 simulated mother-infant pairs under various conditions (median  $\pm$  range).



523

524