Published in final edited form as:
*J Clin Psychopharmacol*. 2010 August ; 30(4): 381–386. doi:10.1097/JCP.0b013e3181e7be23.

# Disposition of Chiral and Racemic Fluoxetine and Norfluoxetine Across Childbearing

**Dorothy Sit, MD**, **James M. Perel, PhD**, **James F. Luther, MA**, **Stephen R. Wisniewski, PhD**, **Joseph C. Helsel, BS**, and **Katherine L. Wisner, MD, MS**
Women's Behavioral HealthCARE, Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA.

## Abstract

**Objective—**To add to the limited data on the clinical pharmacology of antidepressants during pregnancy, we examined the dose-corrected chiral and racemic levels (level/dose) of fluoxetine (FLX) and norfluoxetine (NorFLX) during pregnancy and early postpartum.

**Methods—**The authors evaluated 17 pregnant women who received fluoxetine therapy. Doses were recorded weekly across gestation and postpartum. At 20, 30, and 36 weeks of gestation, during delivery, and 12 weeks after delivery, the depression level was assessed with the Hamilton Rating Scale for Depression (HRS-D), and plasma samples were analyzed for levels of *S*- and *R*-FLX and *S*- and *R*-NorFLX.

**Results—**The mean ratios of the chiral parent drug (*S*-FLX + *R*-FLX) to metabolite levels (*S*-NorFLX + *R*-NorFLX) decreased across pregnancy. The differences were significant between 20–36 weeks and 30–36 weeks. After delivery, the mean dose–corrected level of the active moiety *S*-FLX and the mean ratio of the chiral parent drug (*S*-FLX + *R*-FLX) to metabolite level (*S*-NorFLX + *R*-NorFLX) significantly increased between delivery and 12 weeks postpartum. Most of the fluoxetine-treated subjects experienced remitted depressive episodes and euthymic mood levels during pregnancy and postpartum.

**Conclusions—**The findings extend earlier reports of increased antidepressant metabolism during pregnancy and refractory metabolism after delivery. These data may inform treatment decisions related to dosing in patients who receive fluoxetine during pregnancy.



Reprints: Dorothy Sit, MD, Women's Behavioral HealthCARE, Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine, 3811 O'Hara St, Oxford 410, Pittsburgh, PA 15213 (sitdk@upmc.edu).

The data were presented at the 47th NCDEU Annual Meeting, Boca Raton, June 2007; 31st Annual Meeting of the Teratology Society, Pittsburgh, June 2007; International Marce Society, Sydney, September 2008; and the 11th International Congress of Therapeutic Drug Monitoring and Clinical Toxicology, Montreal, October 2009.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal's Web site (www.psychopharmacology.com).

**AUTHOR DISCLOSURE INFORMATION**

Dr Sit and J Helsel report no competing interests.

J.M. Perel is a consultant and expert witness on atomoxetine and other nonpsychostimulants in the treatment of attention deficit hyperactivity disorder for a consortium of ten pharmaceutical companies. He also is a consultant on selective serotonin reuptake inhibitors metabolism and pharmacokinetics/pharmacodynamics in "The Effect of Gastric Bypass on Selective Serotonin Reuptake Inhibitor Pharmacokinetics/Pharmacodynamics," award by the American Society of Bariatric Surgery (G Hamad, PI).

S. Wisniewski has been a consultant of Cyberonic Inc (2005–2009), ImaRx Therapeutics, Inc (2006), Bristol-Myers Squibb Company (2007–2008), Organon (2007), and Case Western Reserve University (2007).

J. Luther has been a consultant of ImaRx Therapeutics, Inc (2006).

K. Wisner has received a donation of active and placebo transdermal estradiol patches from Novogyne (Novartis) Pharmaceuticals for a National Institute of Mental Health-funded study (R01 MH057102). She participated in an advisory group for Eli Lilly Co.

**Keywords**

fluoxetine; stereoisomers; metabolism; pregnancy; postpartum; depression level

In the United States, 14.5% of women develop a new episode of depression during pregnancy or the first 3 months after childbirth.[1] The prevalence increases across gestation with rates in the first, second, and third trimesters of 7.4% (95% confidence interval [CI], 2.2%–12.6%), 12.8% (10.7%–14.8%), and 12.0% (7.4%–16.7%), respectively.[2] The serotonin reuptake inhibitor (SRI) is the most commonly prescribed antidepressant class during pregnancy; each year, 92,000 (2.8%) pregnant women receive an SRI agent (Birth Defects Prevention Study, 1997–2002).[3] Of the SRI compounds, fluoxetine is a frequent choice for the management of major depression, obsessive compulsive disorder, panic disorder, bipolar depression, and bulimia nervosa. However, limited pharmacologic data are available for the disposition of fluoxetine across pregnancy and early postpartum.[4,5]

The dose requirement for antidepressant drugs taken during pregnancy may increase for several reasons. During pregnancy, hepatic enzyme induction accelerates drug metabolism to increase dose requirements.[4–7] Examples include nortriptyline,[6] which is a substrate of cytochrome (CYP) 2D6; citalopram, a substrate of 2C19, 3A4, and 2D6[7–10]; and sertraline, a substrate of CYP 2D6, 2C9, 2B6, 2C19, and 3A4.[10–14] High steroid hormone levels also induce CYP activity.[15] Other changes in pregnancy may increase drug clearance; the expanded plasma volume and total body water augment the volume of distribution of drugs. Altered hepatic perfusion (increased portal venous return and unchanged hepatic arterial blood flow),[16] reduced plasma protein (albumin) levels that lead to decreased drug binding, increased glomerular filtration and renal excretion[17,18] may give rise to increased dose requirements. These changes may explain the intraindividual variability in treatment response during the childbearing period.[19]

*N*-demethylation of the active parent compound fluoxetine (FLX) produces the active metabolite norfluoxetine (NorFLX), hepatic CYP 2D6, 2C9, 3A4, and, to a lesser degree, 2C19 demethylate fluoxetine.[20–23] The parent compound comprises a 50:50 (racemic) mixture of *S* and *R* isomers. The *S*-isomers are metabolized mainly by CYP 2D6,[21,24,25] and the *R*-isomers are metabolized mainly by 2D6 and 2C9.[20] *S*-NorFLX, *S*-FLX, and *R*-FLX are the moieties[26] that contribute to the potency of fluoxetine.[27,28]

The expected half-life of the parent compound FLX is 2 to 4 days, and that of the metabolite NorFLX is 7 to 15 days.[28–30] The parent compound FLX reaches steady-state concentration within 23 days.[21] In patients who are slow metabolizers or patients who receive doses higher than 40 mg daily, the half-lives of FLX and NorFLX are prolonged (*S*- and *R*-FLX, 6.1 and 9.5 days; *S*- and *R*-NorFLX, 17.4 and 6.9 days).[24,30] Correlations between the dose and steady-state concentrations indicate linear pharmacokinetics (PK) at doses less than 40 mg daily.[29] At doses of 40 to 60 mg daily, the PK is no longer linear,[29] although saturation kinetics at higher doses have not been detected.[31]

We explored the dose-corrected plasma chiral and racemic fluoxetine, norfluoxetine levels (level/dose [L/D]), and depression scores of women across gestation, delivery, and postpartum. We assessed changes in the chiral and racemic fluoxetine, norfluoxetine, and fluoxetine/norfluoxetine levels. Because the metabolite *R*-norfluoxetine is not active plus the parent compound comprises a 50:50 (racemic) mixture of *S*- and *R*-isomers, analysis of the parent drug–metabolite ratios is reasonable to estimate metabolic activity.[5,7] We hypothesized that: (1) dose-corrected fluoxetine/norfluoxetine levels would decrease during pregnancy with accelerated drug metabolism, and (2) dose-corrected fluoxetine/

norfluoxetine levels would increase after delivery during the brief refractory metabolic state. We explored the association between dose-corrected fluoxetine/norfluoxetine levels and depression scores across pregnancy and postpartum. To our knowledge, there are no previous studies of chiral and racemic fluoxetine/norfluoxetine levels and depression scores across multiple time points during the childbearing period.

## MATERIALS AND METHODS

The University of Pittsburgh Institutional Review Board approved and annually reviewed the protocol. All subjects provided written informed consent.

### Subjects

Seventeen women enrolled in a study of Antidepressant Drug Use in Pregnancy (R01 MH60335; PI: Wisner) received fluoxetine therapy. The patients were white; they ranged in age from 25 to 43 years (mean, 34.5 years). The authors used the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*; SCID)[32] to confirm the diagnosis of major depressive disorder. Patients with alcohol or substance abuse or dependence (based on the SCID and/or urine drug screen) or medical conditions that could affect outcomes (such as twin gestation, pre-existing type I diabetes) were excluded. To assess depression levels, the 17-item Hamilton Rating Scale for Depression (HRS-D)[33] was administered at each study visit.

### Procedure

Psychiatric episodes, depression level on the HRS-D, exposure to fluoxetine and other drugs, and smoking were tracked with the Timeline technique.[34] Measures were obtained at study visits at 20, 30, and 36 weeks of gestation, during delivery, and 12 weeks postpartum. Dose information was corroborated with the treating physician and/or pharmacy records for accuracy. The subjects received fluoxetine mono-antidepressant therapy. Three women received concurrent drugs that have not been reported to impact fluoxetine metabolism. The concurrent drugs included trazodone intermittently for insomnia (CYP 3A4), montelukast for seasonal allergies and mild asthma (CYP 3A4 and 2C9), levoxyl for hypothyroidism (deiodination and conjugation), and labetolol for hypertension in pregnancy (glucuronidation).

### Laboratory Methodology

The subjects were taking stable doses of fluoxetine for 4 weeks or more before the serum level measurements. The serum measurements were obtained 15 to 23 hours postdose to assess steady-state concentrations. Plasma samples were analyzed in the Clinical Pharmacology Program Laboratories (Director: JM Perel, PhD) at Western Psychiatric Institute and Clinic, University of Pittsburgh Medical Center.

For the analysis of racemic drug, 0.5 to 1.0 mL of plasma was added to a polypropylene tube with 10 µL of 10-µg/mL chloroimipramine (internal standard). To each sample, 0.5 mL of 0.06-mol/L carbonate, pH 10.4 buffer, and 4 mL of 1.5% isobutanol in *n*-heptane were added. At this pH, the various types of drug plasma protein bindings (solubility, covalent and ionic bonds) are broken so that the total (bound plus unbound) drug is analyzed. After shaking and centrifugation at 3000×*g*, at 4°C, the organic layer is transferred to another polypropylene tube containing 100 µL of 0.025-mol/L $KH_2PO_4$ at a pH of 2.5. After removal of residual organic solvent, 80 µL of each sample is injected via Kontron Autosampler (Kontron USA, Poway, Calif). The analyses were performed on a Beckman gradient liquid chromatograph (Beckman Coulter, Inc, Brea, Calif) with an SSI 500 variable wavelength photometric detector at a wavelength of 205 nm. The column was a stainless

steel, 120 × 4.6 mm I.D. packed with 5-µm C-18, Knauer-Nucleosil I-100 (MACHEREY-NAGEL Inc, Bethlehem, Pa). The mobile phase was 64.3/35.7, with a 0.02-mol/L phosphate buffer with pH 2.5/acetonitrile (vol/vol) plus 100 µL of *N*-octyl-dimethylamine. Retention times were 6.0 minutes for norfluoxetine, 7.0 minutes for fluoxetine, and 8.4 minutes for the internal standard. The day-to-day coefficients of variation ranged from 2.5% to 6.8%. The limit of quantitative detection was 2.0 ng/mL.

The analytical method of the chiral moieties was adapted from that described by Piperaki and colleagues.[35] The authors used a high-performance liquid chromatography (Astec, Inc, Whippany, NJ) Chirobiotic V (vancomycin stationary phase), 5-µm, 25-cm, 4.6-mm (catalog # 11024) column with UV absorbance detection (229 nm). Ethanol solutions of FLX and Nor-FLX stored at −75°C were used to prepare standard curves per enantiomer. The internal standard working solution was 10 µg/mL nefazodone in ethanol to which 20 µL (200 ng) were added to each assay tube for optimal precision and accuracy. The extraction was shortened by re-extracting from the isobutanol/heptane layer into a small volume of 0.1-mol/L HCl, which was dried in a centrifuge evaporator and reconstituted in the mobile phase of 35/55/10 vol/vol ethanol/methanol/0.1% aqueous triethylamine, adjusted to pH 4.1 with glacial acetic acid (buffer was filtered through a 0.2-µm nylon-66 filter). The retention times were 22.1 minutes for the internal standard, 34.3 minutes for *S*-FLX, 30.1 minutes for *S*-Nor-FLX, 41.3 minutes for *R*-FLX, and 36.1 minutes for *R*-Nor-FLX. The day-to-day coefficients of variation were 5.8%–8.5% for the medium and high control and 8.9%–10.6% for the low control. The limit of quantitative detection was 5.0 ng/mL.

Treatment adherence is a critical component of L/D measures, depression level, and response. One reliable method to detect adherence is by examining the standard deviation (SD) of repeated drug levels. Higher SD values (SD >3) suggested larger variations among the drug levels for the subject and possible inconsistent drug intake. This method accurately predicted outcome measures that vary with nonadherence.[36] To assess adherence, we examined the SD of the repeated dose-corrected chiral and racemic levels.

Within each subject, there is a low variation in dose-corrected FLX and Nor-FLX levels (high intraindividual correlations = 0.66–0.80; $P \leq 0.001$).[29] Researchers noted no significant effect of body weight on antidepressant levels[10,13,37] or only small correlations between increased body weight or body mass index and reduced dose-corrected levels of FLX plus Nor-FLX (Spearman rank correlation coefficient = −0.23, $P < 0.05$ and −0.27, $P < 0.01$, respectively).[29] Thus, we reported the unadjusted L/D values.

## Statistical Analysis

The authors analyzed the repeated dose-corrected chiral and racemic fluoxetine/norfluoxetine levels and HRS-D depression scores with general linear mixed (GLM) models to determine the effect of timing during pregnancy or postpartum on fluoxetine/norfluoxetine concentration and depression levels. The GLM models were estimated using SAS/STAT software, version 9.2 (SAS Institute Inc, Cary, NC). Subjects were incorporated into the model as random effects; the structure of the covariance matrix was assumed to be first-order autoregressive. The authors used logarithmic transformations of the non–randomly distributed dose-corrected levels and HRS-D scores (dependent measures) to analyze the data. We used the 12-week postpartum time point to approximate the nongravid time point in the GLM models. If the GLM models indicated a significant effect of time, then post hoc Tukey tests with pairwise comparisons were used to find the specific times with significant difference.

# RESULTS

The subjects received fluoxetine at doses of 10 to 80 mg daily (Supplemental Table A, Supplemental Digital Content 1, which shows drug dose, chiral and racemic fluoxetine levels, http://links.lww.com/JCP/A24). One patient (subject 11) smoked cigarettes throughout pregnancy and postpartum. Four women reported levels of alcohol consumption that were unlikely to interfere with hepatic metabolism (≤1 drink weekly; subjects 2, 9, 6, and 15). The mean HRS-D scores at 20, 30, and 36 weeks of gestation, during delivery, and 12 weeks postpartum measured 7.3 ± 3.3, 8.7 ± 5.6, 7.1 ± 3.2, 8.3 ± 5.9, and 7.6 ± 6.5, respectively. Among the 16 subjects with 2 or more repeated depression scores, 13 subjects had remitted depression (HRS-D ≤8) and 3 subjects had mild to moderate depression levels (subjects 1, 2, and 6; HRS-D 12–22).

Chiral levels were available for 9 subjects, and racemic levels were available for 8 subjects. The drug dose, chiral and racemic FLX and NorFLX levels are reported in Supplemental Table A (Supplemental Digital Content 1, http://links.lww.com/JCP/A24). The mean and total dose-corrected drug levels are reported in Table 1.

## Dose-Corrected Fluoxetine Levels Across Pregnancy and Postpartum

Mean dose-corrected racemic NorFLX levels changed significantly across pregnancy and postpartum (degrees of freedom of the numerator = 4, degrees of freedom of the denominator = 15, F = 3.07, $P = 0.049$; Table 1); the decrease in the racemic NorFLX levels was significant between 30 weeks of gestation and delivery (df = 15, t = 3.27, $P = 0.036$). The mean dose-corrected *S*-FLX levels (active moiety; num df = 3, den df = 20, F = 4.38, $P = 0.016$) and the total chiral FLX (*S*-FLX + *R*-FLX) levels (num df = 3, den df = 20, F = 3.84, $P = 0.026$) changed significantly across antenatal and postnatal times (Table 1); increases in the *S*-FLX and the total chiral FLX levels were significant between 36 weeks of gestation and 12 weeks postpartum (*S*-FLX: df = 20, t = −3.46, $P = 0.012$; total chiral FLX: df = 20, t = −3.09, $P = 0.027$). Analyses indicated no significant differences in the dose-corrected levels of *S*-NorFLX, *R*-NorFLX and the FLX racemate in follow-up (Table 1).

## Parent Drug Versus Metabolite Levels

Ratios of the dose-corrected chiral parent drug (*S*-FLX + *R*-FLX) to metabolite levels (*S*-NorFLX + *R*-NorFLX) changed significantly across pregnancy and postpartum (num df = 3, den df = 20, F = 8.12, $P = 0.001$; Table 1). The mean ratio of the dose-corrected chiral parent drug to metabolite levels significantly decreased between 20–36 weeks of gestation (df = 20, t = 3.84; adjusted Tukey, $P = 0.005$) and 30–36 weeks of gestation (df = 20, t = 3.11; adjusted Tukey, $P = 0.026$). After delivery, the mean ratio of the chiral parent drug to metabolite levels increased significantly between 36 weeks of gestation and 12 weeks postpartum (df = 20, t = −4.54; adjusted Tukey, $P = 0.001$). Analyses of the ratios of racemic FLX to Nor-FLX levels across times did not change significantly (Table 1).

## Stereoselective Disposition

The dose-corrected levels of the *S*-isomers (*S*-FLX + *S*-NorFLX; potent moieties) exceeded those of the *R*-isomers (*R*-FLX + *R*-NorFLX; less potent moieties) by 2 to 3 times in the antenatal and postnatal weeks (Table 1).

## Relationship Between Depression Scores and Dose-Corrected Drug Levels

Using GLM models, the exploratory analyses suggested a significant negative relationship between depression scores and dose-corrected *S*-FLX levels (num df = 1, den df = 19, F = 8.69, $P = 0.008$) or chiral parent drug levels (*S*-FLX + *R*-FLX; num df = 1, den df = 19, F = 6.39, $P = 0.021$), independent of the pregnancy or postpartum study visit. The Bonferroni

correction is used for testing multiple main effects. With these exploratory analyses, the type I error levels were not modified after correcting for the multiple comparisons.

### Adherence

The subjects provided chiral samples for 3.6 ± 0.5 mean visits (range, 3–4) and racemic samples for 3.4 ± 0.9 mean visits (range, 2–5). The mean SD of the dose-corrected chiral levels was 3.0 ± 3.1 (range, 0.4–10.4), and that of the racemic levels was 1.7 ± 1.2 (range, 0.4–4.2). These values were within the range of SD values that suggest sufficient treatment adherence and adequate data for analysis from Shemesh and colleagues.[36]

## DISCUSSION

The main finding was that the mean ratios of the chiral parent drug to metabolite levels significantly decreased between 20–36 weeks of gestation and 30–36 weeks of gestation. Reduced dose-corrected levels of chiral parent drug compared with the metabolite levels suggested that drug clearance increased during pregnancy (Table 1). This finding is similar to earlier reports of lowered drug concentrations and accelerated drug clearance in pregnant women[4] who received fluoxetine[4,5] or short-acting antidepressants.[6–10,13,37] In contrast, the ratios of racemic FLX to Nor-FLX levels across pregnancy did not change significantly. Because the laboratory methods to analyze the chiral and racemic samples were reliable, the different methods do not explain why we observed changes in the chiral ratios only. The chiral analysis is a more refined methodology, which may be more sensitive to detect changes in drug levels across time; additional research is needed to replicate the findings.

The dose-corrected levels of *S*-FLX and combined *S*-FLX + *R*-FLX increased significantly between 36 weeks of gestation and 12 weeks postpartum. The significant increase in the ratios of the chiral parent drug to the metabolite levels after delivery suggested that drug clearance decreased shortly after delivery (Table 1). This finding replicated the reports of refractory metabolism of antidepressants after delivery.[4,6,10,21]

Selective disposition of the fluoxetine moieties[5] may contribute to treatment response and adverse effects.[31] Concentrations of the bioactive *S*-isomers exceeded those of the *R*-isomers by 2- to 3-fold across time (Table 1). This stereoselective disposition was similar to that of nonpregnant control subjects.[5,21,31] Increased levels of the bioactive (*S*)-isomers compared with the less active (*R*)-isomers may explain the sustained (minimally variable) antidepressant response.

Most of the patients (13/17) were enrolled with remitted episodes, and the rest (14/17) remained euthymic. Even so, the data still produced a significant association between the decreased *S*-FLX levels ($F = 8.69$, $P = 0.008$) or *S*-FLX + R-FLX levels ($F = 6.39$, $P = 0.021$) and increased depression scores regardless of the time point. Relationships between the depression levels and the other chiral moieties and racemates were not significant. Others also were unable to detect an association between depressive symptoms and fluoxetine concentrations across gestation.[4] A potential limitation in the analyses is the missing data. We made reasonable assumptions that the data were missing at random and used appropriate statistical methods, which do not produce biased results. The loss of power (which can be regained only with a bigger sample size) to detect associations cannot be corrected through the statistical analyses. With inadequate power, associations that seem to be clinically significant are found to be not statistically significant, that is, analyses of the racemic data.

Cytochrome variants contribute to variable response and adverse effects.[31,37–39] Polymorphisms of CYP 2D6 result in slowed metabolism in 5% to 10% of white patients,

20% to 35% of black Africans, and up to 51% of Asians.[38,39] Fluoxetine prescribed at mid to high doses (40–80 mg daily) can inhibit 2D6 activity.[25,38,40] Future research is needed to improve our understanding of the relationship between CYP polymorphisms and treatment response or adverse effects during the peripartum period.[37]

These findings extend earlier reports of increased antidepressant metabolism during pregnancy and refractory metabolism after delivery. The data may inform treatment decisions related to the dosing of fluoxetine in pregnant or postpartum women. An increased dose is indicated if symptoms recur or worsen during pregnancy. After delivery, patients who report increased adverse effects may require a dose reduction to the nonpregnant dose of response or 2/3 of the final dose in pregnancy.[41]

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

The authors thank the staff at Women's Behavioral HealthCARE for their efforts to perform the research, support the subjects, and organize the extensive data collection.

Dr Sit's contributions were supported by the National Institute of Mental Health (NIMH) grant R01 MH60335 (K Wisner, PI), the Junior Faculty Scholar's Program NIMH R25 MH060473 (P Pilkonis, PI), and the Career Development Award NIMH 1K23 MH082114 (D Sit, PI).

Dr Wisniewski receives grant supports from the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Neurological Disorders and Stroke, and the National Institute of Mental Health, Bethesda, MD.

Dr Wisner's effort was supported primarily by the NIMH grants R01 MH60335 (Antidepressant Drug Use During Pregnancy), R01 MH071825 (Identification and Therapy of Postpartum Depression), R01 MH075921 (Antimanic Use During Pregnancy), and R01 MH057102 (Transdermal Estradiol for Postpartum Depression).

## REFERENCES

1. Gaynes BN, Gavin N, Meltzer-Brody S, Lohr KN, et al. Perinatal depression: prevalence, screening accuracy, and screening outcomes. Summary, Evidence Report/Technology. 2005 Assessment No. 119. AHRQ Publication No. 05-E006-1.
2. Bennett HA, Einarson A, Taddio A, et al. Prevalence of depression during pregnancy: systematic review. Obstet Gynecol. 2004; 103(4):698–709. [Erratum appears in Obstet Gynecol. 2004 Jun; 103(6):1344]. [PubMed: 15051562]
3. Reefhuis J, Rasmussen SA, Friedman JM. Selective serotonin-reuptake inhibitors and persistent pulmonary hypertension of the newborn. New Engl J Med. 2006; 354(20):2188–2190. author reply 2188–2190. [PubMed: 16707761]
4. Heikkinen T, Ekblad U, Palo P, et al. Pharmacokinetics of fluoxetine and norfluoxetine in pregnancy and lactation. Clin Pharmacol Ther. 2003; 73(4):330–337. [PubMed: 12709723]
5. Kim J, Riggs KW, Misri S, et al. Stereoselective disposition of fluoxetine and norfluoxetine during pregnancy and breast-feeding. Br J Clin Pharmacol. 2006; 61(2):155–163. [PubMed: 16433870]
6. Wisner KL, Perel JM, Wheeler SB. Tricyclic dose requirements across pregnancy. Am J Psychiatry. 1993; 150(10):1541–1542. [PubMed: 8379562]
7. Wadelius M, Darj E, Frenne G, et al. Induction of CYP2D6 in pregnancy. Clin Pharmacol Ther. 1997; 62(4):400–407. [PubMed: 9357391]
8. Rochat B, Amey M, Gillet M, et al. Identification of three cytochrome P450 isozymes involved in *N*-demethylation of citalopram enantiomers in human liver microsomes. Pharmacogenetics. 1997; 7(1):1–10. [PubMed: 9110356]

9. Tracy TS, Venkataramanan R, Glover DD, et al. National Institute for Child Health and Human Development Network of Maternal-Fetal-Medicine U. Temporal changes in drug metabolism (CYP1A2, CYP2D6 and CYP3A Activity) during pregnancy. Am J Obstet Gynecol. 2005; 192(2): 633–639. [PubMed: 15696014]
10. Sit DK, Perel JM, Helsel JC, et al. Changes in antidepressant metabolism and dosing across pregnancy and early postpartum. [see comment]. J Clin Psychiatry. 2008; 69(4):652–658. [PubMed: 18426260]
11. Kobayashi K, Ishizuka T, Shimada N, et al. Sertraline *N*-demethylation is catalyzed by multiple isoforms of human cytochrome P-450 in vitro. Drug Metab Dispos. 1999; 27(7):763–766. [PubMed: 10383917]
12. Hostetter A, Stowe ZN, Strader JR Jr, et al. Dose of selective serotonin uptake inhibitors across pregnancy: clinical implications. Depress Anxiety. 2000; 11(2):51–57. [PubMed: 10812529]
13. Freeman MP, Nolan PE Jr, Davis MF, et al. Pharmacokinetics of sertraline across pregnancy and postpartum. J Clin Psychopharmacol. 2008; 28(6):646–653. [PubMed: 19011433]
14. Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Human cytochromes mediating sertraline biotransformation: seeking attribution [Editorial]. J Clin Psychopharmacol. 1999; 19:489–493. [PubMed: 10587282]
15. Tanaka E. Gender-related differences in pharmacokinetics and their clinical significance. J Clin Pharm Ther. 1999; 24(5):339–346. [PubMed: 10583696]
16. Nakai A, Sekiya I, Oya A, et al. Assessment of the hepatic arterial and portal venous blood flows during pregnancy with Doppler ultrasonography. Arch Gynecol Obstet. 2002; 266(1):25–29. [PubMed: 11998960]
17. Keller F, Griesshammer M, Haussler U, et al. Pregnancy and renal failure: the case for application of dosage guidelines. Drugs. 2001; 61(13):1901–1920. [PubMed: 11708763]
18. Weinstein, M. Lithium Treatment of Women During Pregnancy and in the Post-delivery Period. Lancaster, England: MTP Press; 1980.
19. Anderson GD. Pregnancy-induced changes in pharmacokinetics: a mechanistic-based approach. Clin Pharmacokinet. 2005; 44(10):989–1008. [PubMed: 16176115]
20. Scordo MG, Spina E, Dahl ML, et al. Influence of CYP2C9, 2C19 and 2D6 genetic polymorphisms on the steady-state plasma concentrations of the enantiomers of fluoxetine and norfluoxetine. Basic Clin Pharmacol Toxicol. 2005; 97(5):296–301. [PubMed: 16236141]
21. Eap CB, Bondolfi G, Zullino D, et al. Concentrations of the enantiomers of fluoxetine and norfluoxetine after multiple doses of fluoxetine in cytochrome P4502D6 poor and extensive metabolizers. J Clin Psychopharmacol. 2001; 21(3):330–334. [PubMed: 11386497]
22. Margolis JM, O'Donnell JP, Mankowski DC, et al. (*R*)-, (*S*)-, and racemic fluoxetine *N*-demethylation by human cytochrome P450 enzymes. Drug Metab Dispos. 2000; 28(10):1187–1191. [PubMed: 10997938]
23. von Moltke LL, Greenblatt DJ, Duan SX, et al. Human cytochromes mediating *N*-demethylation of fluoxetine in vitro. Psychopharmacology. 1997; 132(4):402–407. [PubMed: 9298519]
24. Fjordside L, Jeppesen U, Eap CB, et al. The stereoselective metabolism of fluoxetine in poor and extensive metabolizers of sparteine. Pharmacogenetics. 1999; 9(1):55–60. [PubMed: 10208643]
25. Ring BJ, Eckstein JA, Gillespie JS, et al. Identification of the human cytochromes p450 responsible for in vitro formation of *R*- and *S*-norfluoxetine. J Pharmacol Exp Ther. 2001; 297(3): 1044–1050. [PubMed: 11356927]
26. Henry ME, Schmidt ME, Hennen J, et al. A comparison of brain and serum pharmacokinetics of *R*-fluoxetine and racemic fluoxetine: A 19-F MRS study. Neuropsychopharmacology. 2005; 30(8): 1576–1583. [PubMed: 15886723]
27. Wong DT, Bymaster FP, Reid LR, et al. Norfluoxetine enantiomers as inhibitors of serotonin uptake in rat brain. Neuropsychopharmacology. 1993; 8(4):337–344. [PubMed: 8512621]
28. Fuller RW, Snoddy HD, Krushinski JH, et al. Comparison of norfluoxetine enantiomers as serotonin uptake inhibitors in vivo. Neuropharmacology. 1992; 31(10):997–1000. [PubMed: 1279447]
29. Lundmark J, Reis M, Bengtsson F. Serum concentrations of fluoxetine in the clinical treatment setting. Ther Drug Monit. 2001; 23(2):139–147. [PubMed: 11294514]

30. Harvey AT, Preskorn SH. Fluoxetine pharmacokinetics and effect on CYP2C19 in young and elderly volunteers. J Clin Psychopharmacol. 2001; 21(2):161–166. [PubMed: 11270912]

31. Jannuzzi G, Gatti G, Magni P, et al. Plasma concentrations of the enantiomers of fluoxetine and norfluoxetine: sources of variability and preliminary observations on relations with clinical response. Ther Drug Monit. 2002; 24(5):616–627. [PubMed: 12352933]

32. First, MB.; Spitzer, RL.; Gibbon, M., et al. Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition. Washington, D.C.: American Psychiatric Press; 1996.

33. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry. 1960; 23:56–62. [PubMed: 14399272]

34. Post RM, Roy-Byrne PP, Uhde TW. Graphic representation of the life course of illness in patients with affective disorder. Am J Psychiatry. 1988; 145(7):844–848. [PubMed: 3381929]

35. Piperaki S, Parissi-Poulou M. Use of cyclodextrins as chiral selectors for direct resolution of the enantiomers of fluoxetine and its metabolite norfluoxetine by HPLC. Chirality. 1993; 5:258–266.

36. Shemesh E, Shneider BL, Savitzky JK, et al. Medication adherence in pediatric and adolescent liver transplant recipients. Pediatrics. 2004; 113(4):825–832. [PubMed: 15060234]

37. Ververs FF, Voorbij HA, Zwarts P, et al. Effect of cytochrome P450 2D6 genotype on maternal paroxetine plasma concentrations during pregnancy. Clin Pharmacokinet. 2009; 48(10):677–683. [PubMed: 19743889]

38. Hamelin BA, Turgeon J, Vallee F, et al. The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin. Clin Pharmacol Ther. 1996; 60(5):512–521. [PubMed: 8941024]

39. Goldstein DB, Need AC, Singh R, et al. Potential genetic causes of heterogeneity of treatment effects. Am J Med. 2007; 120 suppl 1(4):S21–S25. [PubMed: 17403378]

40. Pato MT, Murphy DL, DeVane CL. Sustained plasma concentrations of fluoxetine and/or norfluoxetine four and eight weeks after fluoxetine discontinuation. Jo Clin Psychopharmacol. 1991; 11(3):224–225.

41. Wisner KL, Perel JM, Peindl KS, et al. Effects of the postpartum period on nortriptyline pharmacokinetics. Psychopharmacol Bull. 1997; 33(2):243–248. [PubMed: 9230637]

**TABLE 1**

Chiral and Racemic Fluoxetine and Norfluoxetine Measures by Weeks Since Conception

| Chirals | Week 20 N = 9 | Week 30 N = 9 | Week 36 N = 8 | Delivery N = 0 | 12 Weeks PP N = 6 | *P* |
|---|---|---|---|---|---|---|
| *R*-FLX | 1.0 ± 0.5<br>(0.3–2.0) | 0.8 ± 0.5<br>(0.0–1.4) | 0.8 ± 1.3<br>(0.0–3.7) | | 1.3 ± 0.5<br>(0.9–2.0) | 0.0354* |
| | 0.7, 1.3 | 0.4, 1.1 | 0.0, 1.0 | | 1.0, 1.9 | |
| *S*-FLX | 3.0 ± 2.5<br>(0.7–7.1) | 2.8 ± 2.4<br>(0.1–6.5) | 2.7 ± 3.7<br>(0.0–10.7) | | 5.7 ± 2.7<br>(1.3–9.4) | 0.0160† |
| | 0.9, 5.3 | 1.1, 4.1 | 0.2, 3.9 | | 5.1, 7.6 | |
| *R*-FLX + *S*-FLX | 4.0 ± 2.8<br>(0.9–9.0) | 3.6 ± 2.8<br>(0.1–7.6) | 3.5 ± 4.9<br>(0.0–14.4) | | 7.0 ± 2.9<br>(2.3–10.4) | 0.0255† |
| | 1.5, 6.1 | 1.9, 5.2 | 0.2, 4.6 | | 6.2, 9.6 | |
| *R*-NOR | 1.5 ± 0.8<br>(0.4–2.4) | 1.2 ± 0.8<br>(0.1–2.2) | 1.9 ± 3.0<br>(0.0–9.2) | | 1.9 ± 0.8<br>(0.7–3.1) | 0.4055 |
| | 0.8, 2.0 | 0.5, 2.0 | 0.4, 1.7 | | 1.3, 2.4 | |
| *S*-NOR | 3.1 ± 1.6<br>(1.2–5.7) | 3.0 ± 1.9<br>(0.3–5.8) | 3.5 ± 3.9<br>(0.6–12.5) | | 3.5 ± 1.9<br>(1.9–6.8) | 0.7539 |
| | 2.0, 4.2 | 1.1, 4.3 | 1.1, 4.1 | | 2.2, 4.4 | |
| *R*-NOR + *S*-NOR | 4.5 ± 2.2<br>(1.6–7.6) | 4.2 ± 2.6<br>(0.4–7.8) | 5.4 ± 6.9<br>(0.7–21.8) | | 5.4 ± 2.6<br>(3.2–9.9) | 0.6440 |
| | 2.6, 6.6 | 2.6, 6.5 | 1.8, 5.8 | | 3.2, 6.8 | |
| (*R*-FLX + *S*-FLX) / (*R*-NOR + S-NOR) | 1.0 ± 0.7<br>(0.2–2.5) | 0.9 ± 0.8<br>(0.3–2.9) | 0.6 ± 0.8<br>(0.0–2.4) | | 1.4 ± 0.7<br>(0.7–2.4) | 0.0010‡ |
| | 0.6, 1.2 | 0.5, 1.0 | 0.1, 0 6 | | 0.7, 1.9 | |
| *R*-FLX + *R*-NOR | 2.5 ± 1.2<br>(0.6–3.9) | 2.0 ± 1.3<br>(0.1–3.4) | 2.7 ± 4.3<br>(0.0–13.0) | | 3.3 ± 1.2<br>(1.5–5.0) | 0.1930 |
| | 1.7, 3.3 | 0.9, 3.1 | 0.5, 2.7 | | 2.3, 4.0 | |
| *S*-FLX + *S*-NOR | 6.1 ± 3.4<br>(1.9–12.7) | 5.7 ± 3.5<br>(0.4–12.0) | 6.2 ± 7.3<br>(0.8–23.2) | | 9.2 ± 3.3<br>(3.2–11.9) | 0.1920 |
| | 3.2, 8.3 | 4.1, 7.7 | 1.2, 6.8 | | 7.9, 11.6 | |
| *R*-FLX + *R*-NOR + *S*-FLX + *S*-NOR | 8.5 ± 4.2<br>(2.5–16.6) | 7.8 ± 4.7<br>(0.6–15.3) | 8.9 ± 11.5<br>(1.1–36.2) | | 12.4 ± 4.2<br>(5.5–16.9) | 0.1940 |
| | 6.1, 10.0 | 5.0, 10.2 | 1.9, 9.0 | | 9.4, 14.8 | |
| **Racemates** | **N = 7** | **N = 8** | **N = 7** | **N = 4** | **N = 2** | |

| Chirals | Week 20 N = 9 | Week 30 N = 9 | Week 36 N = 8 | Delivery N = 0 | 12 Weeks PP N = 6 | *P* |
|---|---|---|---|---|---|---|
| FLX | 4.4 ± 3.0<br>(2.4–10.1) | 4.8 ± 2.6<br>(2.5–8.8) | 4.1 ± 2.2<br>(1.8–7.4) | 2.3 ± 3.3<br>(0.5–7.3) | 4.3 ± 5.4<br>(0.5–8.1) | 0.1936 |
| | 2.5, 7.0 | 2.6, 7.1 | 1.9, 6.9 | 0.6, 4.0 | 0.5, 8.1 | |
| NOR | 4.2 ± 1.4<br>(1.8–5.7) | 4.7 ± 2.0<br>(2.0–7.5) | 4.5 ± 1.9<br>(1.8–7.4) | 2.1 ± 0.9<br>(1.3–3.1) | 3.7 ± 2.1<br>(2.2–5.2) | 0.0491[§] |
| | 3.3, 5.5 | 2.8, 6.2 | 2.9, 6.3 | 1.4, 2.8 | 2.2, 5.2 | |
| FLX + NOR | 8.6 ± 2.4<br>(5.8–13.5) | 9.6 ± 2.3<br>(5.5–12.0) | 8.6 ± 2.7<br>(5.9–13.2) | 4.4 ± 3.0<br>(2.0–8.8) | 8.0 ± 7.5<br>(2.7–13.3) | 0.1355 |
| | 7.2, 9.0 | 7.7, 11.4 | 6.3, 11.0 | 2.6, 6.2 | 2.7, 13.3 | |
| FLX / NOR | 1.4 ± 1.4<br>(0.4–3.9) | 1.4 ± 1.5<br>(0.4–4.2) | 1.3 ± 1.3<br>(0.4–4.2) | 1.4 ± 2.2<br>(0.2–4.7) | 0.9 ± 0.9<br>(0.2–1.6) | 0.1884 |
| | 0.5, 3.0 | 0.5, 2.2 | 0.5, 1.2 | 0.2, 2.6 | 0.2, 1.6 | |

Data presented as mean ± SD, (min-max), and median, IQR.

Visits significantly different from one another (adjusted Tukey, $P < 0.05$).

[*] Week 20/week 36.

[†] Week 36/12 weeks pp.

[‡] Week 20/week 36; week 30/week 36; week 36/12 weeks pp.

[§] Week 30/Delivery.

pp indicates postpartum.