Pooled Analysis of Antidepressant Levels in Lactating Mothers, Breast Milk, and Nursing Infants

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Objective: The available data on antidepressant levels in nursing infants were analyzed in order to calculate average infant drug levels and determine what factors influence plasma drug levels in breast-feeding infants of mothers treated with antidepressants.

Method: Electronic searches of MEDLINE, PreMEDLINE, Current Contents, Biological Abstracts, and PsycINFO from 1966 through July 2002 followed by bibliographic searches identified 67 relevant studies (two unpublished). By consensus the authors identified 57 studies of maternal plasma, breast milk, and/or infant plasma antidepressant levels from nursing mother-infant pairs, measured by liquid chromatography.

Results: Infants with recent prenatal exposure and symptomatic infants included in case reports were analyzed separately. Infant plasma levels were standardized against the average maternal level for each drug. The average infant-maternal plasma ratio was calculated for each drug, and correlations of infant plasma level to maternal dose, maternal plasma level, and breast milk level were calculated. Nortriptyline, paroxetine, and sertraline usually produce undetectable infant levels. Of drugs currently used, fluoxetine produces the highest proportion (22%) of infant levels that are elevated above 10% of the average maternal level. Based on smaller numbers, the data on citalopram indicate that it produces elevated levels in 17% of infants. The milk-to-plasma ratios for 11 antidepressants had a statistically significant negative association with the percentage of the drug bound to protein.

Conclusions: Nortriptyline, paroxetine, and sertraline may be preferred choices in breast-feeding women. Minimizing the maternal dose may be helpful with citalopram. Current data do not support monitoring breast milk levels in individual patients. Future researchers should report maternal, breast milk, *and* infant antidepressant levels along with other appropriate variables.

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Postpartum depression occurs in 13% of mothers (1), and as many as 50% of affected women are treated with antidepressant medication (2). Because 60% of mothers initiate breast-feeding (3), substantial numbers of women with postpartum depression and women who require chronic antidepressant therapy may wish to continue breast-feeding while taking antidepressants. Unfortunately, there is little available information about the potential risk to the infant. The medical literature contains multiple case reports and case series involving measurements of antidepressant levels in maternal plasma, breast milk, and/or infant plasma. Although several published reviews summarize the available data (4–7), they focus on only one class of drug (5), do not directly compare different drugs (6, 7), or were published before data on newer drugs such as citalopram and paroxetine were available (4). We present a pooled analysis of all available data on antidepressant levels in nursing mother-infant pairs.

Method

Published Data

Electronic searches of MEDLINE, PreMEDLINE, Current Contents, Biological Abstracts, and PsycINFO from 1966 through July 2002 were conducted by using the keywords "antidepressant drugs," "antidepressive agents," "human milk," "lactation," and "breast feeding" and the name of each antidepressant drug. Retrieved studies were examined for additional references. The inclusion criterion was the measurement of antidepressant levels in lactating mothers, breast milk, or nursing infants, alone or in any combination. Of 65 studies identified, two (8, 9) were excluded because levels were measured by immunoassay only, which is an inaccurate method of quantification (10, 11). Four others (12–15) were excluded because actual drug levels were not specified. A seventh (16) was excluded because the patient had galactorrhea and was not breast-feeding. An eighth report (17) contained data also included in a subsequent publication (18). Data were analyzed from the remaining 57 articles (Table 1). Some authors measured antidepressant levels in plasma, and others measured levels in serum. Thus, in Table 1 "maternal level" denotes a level measured in plasma or serum; similarly, "infant level" refers to a level measured in plasma or serum.

TABLE 1. Published Studies Included in a Pooled Analysis of Antidepressant Levels in Lactating Mothers, Breast Milk, and Breast-Feeding Infants

Study	Drug(s)	Number of Cases	Case Report	Maternal Levels[a]	Infant Levels[b]	Breast Milk Levels	Limit of Quantification (ng/ml)[c]
Erickson et al., 1979 (19)	Amitriptyline	1		Yes	Yes		28 (blood)
Bader et al., 1980 (20)	Amitriptyline	1		Yes	Yes	Yes	10 (blood, milk)
Brixen-Rasmussen et al., 1982 (21)	Amitriptyline	1		Yes	Yes	Yes	5 (blood), 15 (milk) (for metabolite, 10 in blood and 30 in milk)
Pittard et al., 1986 (22)	Amitriptyline	1		Yes		Yes	—[d]
Breyer-Pfaff et al., 1995 (23)	Amitriptyline	1		Yes	Yes	Yes	5 (blood)
Yoshida et al., 1997 (24)	Amitriptyline	2		Yes		Yes	20 (blood, milk)
	Clomipramine	2		Yes		Yes	20 (blood, milk)
	Dothiepin	2		Yes		Yes	20 (blood, milk)
	Imipramine	4		Yes		Yes	20 (blood, milk)
Briggs et al., 1993 (25)	Bupropion	1		Yes	Yes	Yes	5 (blood, milk) (20 for metabolites)
Jensen et al., 1997 (26)	Citalopram	1		Yes	Yes	Yes	2.4 (blood, milk)
Öhman et al., 1997 (27)	Citalopram	2		Yes		Yes	—[d]
Spigset et al., 1997 (28)	Citalopram	2		Yes		Yes	2 (blood), 4 (milk)
Lepola et al., 2000 (29)	Citalopram	7		Yes		Yes	5 (blood, milk)
Rampono et al., 2000 (30)	Citalopram	7			Yes		1 (blood)
Schmidt et al., 2000 (31)	Citalopram	1		Yes	Yes	Yes	2 (blood, milk)
Nordeng et al., 2001 (32)	Citalopram	3		Yes	Yes	Yes	4 (blood, milk)
	Fluvoxamine	1		Yes		Yes	0.43 (blood, milk)
	Paroxetine	4		Yes	Yes	Yes	5 (blood, milk)
Wisner et al., 1995 (33)	Clomipramine	4		Yes	Yes		10 (blood)
Birnbaum et al., 1999 (34)	Clomipramine	1			Yes		20 (infant)
	Desipramine	4			Yes		10–25 (infant)
	Fluoxetine	13			Yes		20–50 (infant)
	Imipramine	2			Yes		20–25 (infant)
	Nortriptyline	4			Yes		20–25 (infant)
	Paroxetine	2			Yes		20 (infant)
	Sertraline	3			Yes		5 (infant)
Stancer et al., 1986 (35)	Desipramine	1		Yes	Yes	Yes	2 (blood, milk)
Buist et al., 1993 (36)	Dothiepin	12		Yes	Yes	Yes	10 (blood, milk)
Ilett et al., 1992 (37)	Dothiepin	8		Yes	Yes	Yes	2 (blood, milk), 10 (one infant sample)
Kemp et al., 1985 (38)	Doxepin	1		Yes	Yes	Yes	10 (blood)
Matheson et al., 1985 (39)	Doxepin	1	Yes	Yes	Yes	Yes	3 (blood), 7 (milk)
Frey et al., 1999 (40)	Doxepin	1	Yes	Yes	Yes		25 (blood)
Isenberg, 1990 (41)	Fluoxetine	1	Yes	Yes		Yes	—[d]
Burch et al., 1992 (42)	Fluoxetine	1		Yes		Yes	5 (blood, milk)
Lester et al., 1993 (43)	Fluoxetine	1	Yes		Yes	Yes	—[d]
Taddio et al., 1996 (44)	Fluoxetine	10			Yes (one only)	Yes	1 (blood, milk)
Brent et al., 1998 (45)	Fluoxetine	1			Yes	Yes	—[d]
Yoshida et al., 1998 (46)	Fluoxetine	4		Yes	Yes	Yes	2 (blood, milk), 5–20 (some infant samples)
Kristensen et al., 1999 (47)	Fluoxetine	14	Yes (two infants)	Yes	Yes	Yes	15 (blood, milk)
Hendrick et al., 2001 (48)	Fluoxetine	20		Yes	Yes		1 (blood)
Wright et al., 1991 (49)	Fluvoxamine	1		Yes	Yes		2 (blood)
Yoshida et al., 1997 (50)	Fluvoxamine	1		Yes		Yes	—[d]
Arnold et al., 2000 (51)	Fluvoxamine	1		Yes	Yes	Yes	5 (blood, milk)
Hagg et al., 2000 (52)	Fluvoxamine	1		Yes		Yes	43 (blood), 7 (milk)
Piontek et al., 2001 (53)	Fluvoxamine	2		Yes	Yes		2.5 (blood)
Sovner et al., 1979 (54)	Imipramine	1		Yes		Yes	—[d]
Dodd et al., 1999 (55)	Nefazodone	2		Yes		Yes	50 (blood, milk)
Matheson et al., 1988 (56)	Nortriptyline	1		Yes		Yes	15 (blood), 30 (milk)
Wisner et al., 1991 (57)	Nortriptyline	7		Yes	Yes		4–5 (blood)
Wisner et al., 1996 (58)	Nortriptyline	5		Yes	Yes		4 (blood)
Mammen et al., 1997 (59)	Nortriptyline	2		Yes	Yes		4 (blood)
Wisner et al., 1997 (60)	Nortriptyline	7		Yes	Yes		4 (blood), 10 (one infant sample)
Altshuler et al., 1995 (61)	Nortriptyline and sertraline	1		Yes	Yes	Yes for sertraline	10 (blood) for nortriptyline; 0.5 (blood, milk) for sertraline
Spigset et al., 1996 (62)	Paroxetine	1		Yes		Yes	—[d]
Begg et al., 1999 (63)	Paroxetine	10		Yes		Yes	4 (blood, milk)
Öhman et al., 1999 (64)	Paroxetine	7		Yes		Yes	5 (blood, milk)
Stowe et al., 2000 (65)	Paroxetine	16		Yes	Yes		4 (blood, milk)
Hendrick et al., 2000 (66)	Paroxetine	1		Yes	Yes	Yes	1 (blood), 2 (milk)
Misri et al., 2000 (67)	Paroxetine	24		Yes	Yes	Yes	0.1 (blood, milk)

(continued)

TABLE 1. Published Studies Included in a Pooled Analysis of Antidepressant Levels in Lactating Mothers, Breast Milk, and Breast-Feeding Infants (continued)

Study	Drug(s)	Number of Cases	Case Report	Maternal Levels[a]	Infant Levels[b]	Breast Milk Levels	Limit of Quantification (ng/ml)[c]
				Type of Data Extracted From the Study			
Epperson et al., 2001 (18)	Sertraline	14		Yes	Yes		2.5 (blood)
Mammen et al., 1997 (68)	Sertraline	3		Yes	Yes		2 (blood)
Stowe et al., 1997 (69)	Sertraline	11		Yes	Yes		1 (blood)
Kristensen et al., 1998 (70)	Sertraline	8			Yes		5 (blood)
Wisner et al., 1998 (71)	Sertraline	8		Yes	Yes		2 (blood)
Dodd et al., 2000 (72)	Sertraline	10		Yes		Yes	5 (blood, milk)
Ilett et al., 1998 (73)	Venlafaxine	3		Yes	Yes	Yes	10 (blood, milk)
Hendrick et al., 2001 (74)	Venlafaxine	2		Yes	Yes		10 (blood)

[a] Some authors measured antidepressant levels in plasma, and others measured levels in serum. Thus, "maternal level" denotes a level measured in plasma or serum.

[b] Some authors measured antidepressant levels in plasma, and others measured levels in serum. Thus, "infant level" denotes a level measured in plasma or serum.

[c] Limit of quantification of the parent drug. Limit may be higher for metabolites. "Blood" represents maternal blood, "infant" represents infant blood. In some cases, the limit of quantification was higher for the infant's blood because of the small volume of blood obtained.

[d] Not reported.

We contacted the seven authors who had published the largest series of data and the manufacturers of each drug produced in the United States. Two additional unpublished papers were discovered, but data on individual cases were not available from these studies.

Within the 57 articles we identified, some data could not be used because they included immunoassay data or drug levels averaged over several patients. One report (63) presented some data only as the calculated area under the curve. Since these data could not be compared to one-time measurements, they were excluded. We were unable to obtain the original blood and breast milk levels for those subjects from the authors.

One subject, patient 9 from a study by one of us (71), was excluded. In this case, the infant's sertraline and norsertraline levels were 64 ng/ml and 68 ng/ml, respectively, which were more than 50% of the mother's levels. In the 58 other published cases involving sertraline, the infant level did not exceed 4.9 ng/ml for sertraline or 24 ng/ml for norsertraline. The original investigators believed the unusually high sertraline levels in this infant were spurious.

Data were extracted by one author (M.D.) and checked on two occasions by another (A.M.W.). Of greatest value were data sets that included maternal blood levels, breast milk levels, and infant blood levels; however, many data sets included two and some only one of these measurements. Only 18 studies (17, 23, 25, 31, 33, 39, 45, 51, 53, 56, 57, 59–61, 66–68, 71) specifically stated the proportion of breast milk versus bottle feedings; 11 infants (67) were more than 80% breast-fed, seven infants (17, 23, 31, 57, 68) were about 60%–80% breast-fed, one (exposed to fluvoxamine) (53) was half breast-fed, and one (exposed to bupropion) (25) was about 30% breast-fed; the other 49 infants were fully breast-fed. Only one publication (51) reported a patient's smoking status, and none commented on alcohol use.

Where possible, we categorized data sets as collected either from patients who were studied because the infant was symptomatic in some way (case reports) or from patients identified for study in other ways (research cases). When possible, we also noted which infants had been exposed to the same antidepressant before birth.

Unpublished Data

In addition to the published cases, data were also available from 36 unpublished cases (Table 2). Dr. Weissman collected maternal blood, breast milk, and infant blood from 11 mother-infant

pairs in which the mothers were taking five different antidepressants. Dr. Wisner collected maternal and infant blood from 15 mother-infant pairs; the mothers in five pairs were taking sertraline and the mothers in 10 pairs were taking nortriptyline as part of ongoing clinical trials. In these studies, after complete description of the study to the subjects, written informed consent was obtained. Blood was collected from mothers and infants by venipuncture. For breast milk samples, the entire output from one breast was collected while the infant nursed at the other breast.

The blood samples were immediately centrifuged, and the plasma was frozen at –70°C. The milk samples were immediately frozen as well. All samples were sent to the laboratory of James M. Perel, Ph.D., at the University of Pittsburgh Medical Center, for analysis.

Concentrations of the drugs and their major active metabolites were assayed with previously validated analytical methods that used high-performance liquid chromatography. The methods entailed solvent extraction from alkaline solution of 1.0-ml plasma samples, followed by back extraction into dilute acid. By using an automated sample processor, these extracts were injected onto a C-18 column and resolved with a phosphate buffer/acetonitrile mobile phase, and the levels were determined by using a variable-wavelength ultraviolet light detector and automatic integration. For fluvoxamine, the limit of quantitative detectability necessary to assay physiologically significant levels for infants was lower than the published range (75). Adjustment of the wavelengths to optimize the signal-to-noise ratio, increasing the percentage of final extract injected, and careful chromatographic conditions permitted validation of all the methods at levels of quantification down to 1.5 to 2.0 ng/ml for the various compounds: sertraline (71, 76), fluoxetine and citalopram (77), and paroxetine (unpublished method of G. Rudolph and J. Perel, 2001; similar to preceding method). The level of detectability was about one-third the level of quantification. In cases where a full milliliter of infant plasma was not available, the levels of quantification and detectability were correspondingly compromised.

Milk samples were assayed by the method of standard addition, so that each sample served as its own matrix. A volume of 0.5 ml of milk was used per extraction tube instead of the 1.0 ml used in the plasma assays. Five 0.5-ml volumes for each milk sample, containing zero or various known amounts of the drug (and metabolites, as appropriate), were extracted and chromatographed as were the 1.0-ml plasma samples. The results were then graphically extrapolated to determine the correct values.

Statistical Analysis

For studies that had more than one value for breast milk levels for the same feeding (i.e., hind milk and fore milk levels or right and left breast levels), the values were averaged. For statistical analysis, levels reported as "not detected" were entered as zero and levels reported as detected but not quantifiable were entered as 0.1 ng/ml less than the limit of quantification. Sensitivity analyses were done by recoding "not detected" from "0" to half the limit of quantification and "detectable but not quantifiable levels" from 0.1 ng/ml below the limit of quantification to half the limit of quantification.

For some studies, several measurements per mother-infant pair were reported. To avoid undue influence from a given patient, we included only one measurement from a given source (maternal plasma, milk, or infant plasma) per subject. If there were several measurements from one source (e.g., milk), we chose the single measurement that corresponded in time to another measurement (e.g., plasma). Few infants had more than one plasma level measurement. For those who did, we used the first infant blood level obtained, since younger infants may metabolize the medication more slowly than older infants. For infants with multiple measurements and a history of prenatal exposure, we used the first measurement taken after the infant was older than five times the adult half-life of the parent drug.

Infants selected for study because they were symptomatic were analyzed separately from the others. Infants with prenatal exposure whose only measurements were taken within five half-lives of the parent drug were excluded from the primary analysis. This allowed us to examine data that reflected primarily breast-feeding drug exposure, rather than prenatal drug exposure. To compute correlations between mothers' and infants' levels, we used mother and infant levels from blood samples taken simultaneously.

We included metabolite levels in some analyses by computing a weighted sum of the parent drug plus metabolite levels, using the metabolite's biological activity relative to the parent drug as the weighting factor (Table 3). However, because metabolites were often not measured, the analyses we will describe are based on parent drug levels alone except where otherwise stated.

A one-way analysis of variance (ANOVA) was used to compare infant plasma levels across medications. To standardize the infant plasma concentrations so that results with one drug could be compared to results with another, we divided each infant plasma level by the average maternal plasma level for each drug. We would have preferred to divide by the minimum therapeutic level for each drug, but minimum therapeutic levels have not been defined for antidepressants other than tricyclics.

Correlations of the milk level with the mother's plasma level and of the infant's plasma level with the mother's dose and blood level were computed for each medication. Only correlations based on five or more observations are reported. Correlations for all subjects combined were adjusted for medication by using indicator variables.

Results

The complete database of published and unpublished cases included drug levels for 15 antidepressants and their major active metabolites (Table 3). The database contained 337 research cases, including measurements for 238 infants. An additional six cases that had been studied because of suspected adverse effects in the infant were classified as case reports (39–41, 43, 45, 47) (Table 4).

These cases were excluded in the calculation of average blood or breast milk drug levels but were included in examination of predictors of breast milk and infant drug levels. Two of the infants in the research cases had also displayed adverse effects (31, 32) (Table 4), but these infants had not been selected for study on this basis and were included in all analyses.

In addition to excluding the case reports, the analyses in Table 5 and Table 6 also excluded data from infants with prenatal exposure who were younger than five times the average adult half-life of the parent drug. Table 5 presents the mean dose, maternal plasma level, breast milk level, and milk/plasma ratio for each drug. Drug levels were detectable in breast milk for all antidepressants studied. Pearson correlations between maternal plasma and breast milk levels were statistically significant for citalopram, dothiepin, fluvoxamine, and paroxetine. Despite large study groups, the correlation between maternal plasma and breast milk levels did not reach statistical significance for fluoxetine or sertraline.

Table 6 compares the infant plasma levels with the maternal plasma and breast milk levels for each drug. The standardized infant plasma level for each drug (infant level divided by the average maternal plasma level for that drug) is given on the left side of the table. We defined elevated infant levels as those above 10% of the average maternal level. Other than dothiepin, which was studied in only three infants, fluoxetine produced the highest proportion of elevated infant levels and the highest mean standardized infant level (Table 6). Citalopram also produced a relatively high percentage of elevated infant levels. Repeating the analysis of infant levels with the weighted sum of the metabolites included did not substantially change the results (data not shown). Of note, the only infant with an elevated paroxetine level, 31.4 ng/ml (32), was 5 days old and had a history of prenatal exposure to paroxetine, which may have caused the high level. However, that infant's mother also had an unusually high level of paroxetine in her breast milk. All other infant paroxetine levels were zero (limit of quantification, 4–5 ng/ml), and these infants included three with prenatal exposure who were 4.0–5.6 weeks old.

In the ratios of infant to maternal plasma levels for each individual mother-infant pair, fluoxetine and citalopram again produced relatively high proportions of elevated infant levels (Table 6). Fluvoxamine and clomipramine each produced an elevated level in one infant out of the three studied. For venlafaxine, which had substantial infant metabolite levels, we repeated the analysis with the weighted sum of the metabolites. When the metabolites were included in the analysis, venlafaxine produced a mean standardized infant level of 0.06 ng/ml in the five infants studied, and one infant had an elevated plasma level. The infant-to-mother ratio for venlafaxine was 0.12, with elevated ratios for two of the five infants. These five infants all had substantial metabolite levels (16–225 ng/ml) despite having levels of the parent drug of zero. For the other

TABLE 2. Previously Unpublished Antidepressant Plasma and Breast Milk Levels in 36 Breast-Feeding Mother-Infant Pairs

Mother-Infant Pair	Infant's Age (weeks)	Infant's Sex	Infant's Birth Weight (kg)	Infant's Current Weight (kg)	Mother's Weight (kg)	Mother's Antidepressant Treatment			
						Drug	Dose (mg/day)	Duration (weeks)	Time Between Last Dose and Blood Sampling (hours)
1	4.8	F	3.270	4.45	77.2	Fluoxetine	20	6	9
2	5.1	M	2.410	3.19	65.5	Sertraline	50	5	8
3	29.1	F	3.510	8.27	62.4	Fluvoxamine	250	94	9
4	1.6	F	3.736	3.85	73.4	Citalopram	20	26	9
5	11.7	F	3.580	5.74	65.3	Citalopram	20	12	10
6	19.6	M	3.540	6.77	53.7	Sertraline	50	14	8
7	9.9	F	3.810	5.41	135.8	Paroxetine	30	156	10
8	7.3	M	3.520	4.71	66.9	Paroxetine	20	140	8
9	11.4	M	2.810	5.03	52.4	Sertraline	100	4	10
10	9.9	F	3.300	4.77	98.0	Sertraline	50	2	8
11	28.1	F	4.250	8.03	91.2	Paroxetine	10	10	8
12	4.0	—	3.830	—	—	Sertraline	50	4	12
13	4.0	M	3.260	—	—	Sertraline	50	4	1
14	4.0	—	3.660	—	—	Sertraline	50	4	4
15	4.0	—	3.740	—	—	Sertraline	50	4	1
16	4.0	F	3.150	—	—	Sertraline	50	4	3
17	4.0	M	3.090	—	—	Sertraline	50	4	27
18	4.0	M	3.200	—	—	Sertraline	50	4	25
19	2.0	F	0.910	—	—	Nortriptyline	100	3	12
20	—	F	—	—	—	Nortriptyline	100	3	14
21	7.0	F	2.690	—	—	Sertraline	100	3	9
22	7.0	M	3.690	—	—	Nortriptyline	100	3	11
23	10.0	F	3.690	—	—	Sertraline	100	3	12
24	11.0	F	3.710	—	—	Sertraline	100	3	13
25	7.0	F	3.290	—	—	Nortriptyline	50	3	14
26	7.0	M	3.200	—	—	Nortriptyline	50	3	12
27	7.0	F	3.710	—	—	Sertraline	100	3	14
28	9.0	F	2.290	—	—	Sertraline	100	3	13
29	6.0	F	4.340	—	—	Sertraline	100	3	12
30	5.0	F	2.860	—	—	Sertraline	100	3	14
31	15.0	F	4.220	—	—	Nortriptyline	50	3	12
32	11.0	M	3.260	—	—	Nortriptyline	50	3	11
33	9.0	F	—	—	—	Nortriptyline	50	3	13
34	15.0	F	3.060	—	—	Sertraline	100	3	11
35	8.0	M	3.030	—	—	Nortriptyline	50	3	12
36	12.0	M	3.800	—	—	Nortriptyline	50	3	7

[a] E-Nortriptyline and Z-nortriptyline are stereoisomers of nortriptyline. Their full names are E-10-hydroxynortriptyline and Z-10-hydroxynortriptyline.

Drug or Metabolite Measured[a]	Maternal Plasma Level (ng/ml)	Breast Milk Level (ng/ml)	Infant Plasma Level (ng/ml)
Fluoxetine	106	578	0.0
Norfluoxetine	203	111	13.0
Sertraline	10	30	0.0
Norsertraline	21	35	1.9
Fluvoxamine	370	380	0.0
Citalopram	44	41	1.8
Desmethylcitalopram	16	25	1.4
Didesmethylcitalopram	6	11	0.0
Citalopram	63	68	2.1
Desmethylcitalopram	19	26	1.4
Didesmethylcitalopram	6	12	0.0
Sertraline	42	90	0.0
Norsertraline	75	71	0.0
Paroxetine	77	50	0.0
Paroxetine	68	54	0.0
Sertraline	22	12	0.0
Norsertraline	31	12	2.9
Sertraline	17	18	0.0
Norsertraline	20	21	0.0
Paroxetine	17	10	0.0
Sertraline	20	—	0.0
Norsertraline	41	—	0.0
Sertraline	28	—	0.0
Norsertraline	69	—	1.9
Sertraline	15	—	0.0
Norsertraline	28	—	1.8
Sertraline	31	—	0.0
Norsertraline	38	—	1.5
Sertraline	62	—	1.5
Norsertraline	115	—	5.1
Sertraline	15	—	0.0
Norsertraline	42	—	11.9
Sertraline	23	—	0.0
Norsertraline	33	—	1.5
Nortriptyline	106	—	0.0
E-Nortriptyline	21	—	0.0
Z-Nortriptyline	117	—	0.0
Nortriptyline	10	—	0.0
E-Nortriptyline	17	—	0.0
Z-Nortriptyline	105	—	1.9
Sertraline	42	—	0.9
Norsertraline	53	—	2.9
Nortriptyline	110	—	0.0
E-Nortriptyline	14	—	0.0
Z-Nortriptyline	66	—	1.9
Sertraline	13	—	0.0
Norsertraline	20	—	0.0
Sertraline	4	—	0.0
Norsertraline	7	—	1.9
Nortriptyline	160	—	0.0
E-Nortriptyline	17	—	0.0
Z-Nortriptyline	141	—	0.0
Nortriptyline	58	—	2.0
E-Nortriptyline	9	—	1.9
Z-Nortriptyline	38	—	7.1
Sertraline	28	—	0.0
Norsertraline	82	—	3.4
Sertraline	53	—	1.5
Norsertraline	145	—	5.6
Sertraline	74	—	1.5
Norsertraline	150	—	1.5
Sertraline	29	—	0.0
Norsertraline	60	—	2.0
Nortriptyline	39	—	0.0
E-Nortriptyline	4	—	0.0
Z-Nortriptyline	50	—	4.6
Nortriptyline	72	—	1.9
E-Nortriptyline	7	—	0.0
Z-Nortriptyline	110	—	1.9
Nortriptyline	73	—	0.0
E-Nortriptyline	10	—	0.0
Z-Nortriptyline	79	—	3.9
Sertraline	27	—	0.0
Norsertraline	45	—	1.9
Nortriptyline	150	—	0.0
E-Nortriptyline	14	—	0.0
Z-Nortriptyline	164	—	1.9
Nortriptyline	111	—	0.0
E-Nortriptyline	71	—	0.0
Z-Nortriptyline	65	—	1.9

drugs studied, including the metabolites produced no substantial changes in the analysis (data not shown).

We analyzed the correlations of the infant plasma level to the mother's dose, mother's plasma level, breast milk level, and infant age for the five drugs for which five or more infant levels were reported (Table 7). We found that the maternal dose was highly correlated with the infant plasma level for citalopram and was weakly correlated for sertraline. Maternal dose did not predict infant level for fluoxetine, nortriptyline, or paroxetine. The maternal plasma level was moderately correlated with the infant level for sertraline but not citalopram, fluoxetine, or nortriptyline. Maternal breast milk level was significantly correlated with infant plasma level for citalopram, fluoxetine, and paroxetine. However, the correlation between breast milk and infant plasma level for paroxetine is high because the 5-day-old infant (32) with a paroxetine level of 31.4 ng/ml was exposed to unusually high levels of paroxetine in the breast milk (153 ng/ml versus an average of 28 ng/ml for the other infants with measurable levels). The level was zero for the other 24 infants. It is interesting that infant age was not correlated with infant plasma level for any drug. (Again, infants with recent prenatal exposure were excluded from this analysis.) Including the metabolites in the analysis produced no significant changes in the correlations (data not shown).

Of the 15 excluded infants (those with prenatal exposure who were younger than five times the average half-life of the parent drug), 12 had mothers taking fluoxetine and had measurable infant plasma levels. The mean plasma level for these 12 infants was 35.5 ng/ml, compared to a mean plasma level of 7.9 ng/ml for the 36 fluoxetine infants who were not excluded (t=2.52, df=46, p=0.03).

We also compared the mean infant fluoxetine plasma levels for infants with and without prenatal exposure who were older than five half-lives of the parent drug. The 22 older infants with prenatal exposure to fluoxetine had a mean level of 7.9 ng/ml, compared to 2.8 ng/ml for nine older infants with no prenatal exposure. This is not a statistically significant difference. Similar comparisons for paroxetine, citalopram, sertraline, and nortriptyline did not reveal any significant differences between infants with and without prenatal exposure who were older than 5 half-lives of the parent drug (data not shown).

Six infants originally selected for study because of symptoms were excluded from the preceding analysis. Of these, four were exposed to fluoxetine and two to doxepin. The symptomatic infants exposed to citalopram (31) and paroxetine (32) were included in our analyses because they were studied prospectively and then found to have symptoms (Table 4).

For 11 antidepressants we had both ratios of milk to maternal plasma levels and published information on percentage of free drug, which allowed us to calculate protein binding (80, 81). For these 11 drugs, the ratio of milk to maternal plasma levels had a statistically significant nega-

TABLE 3. Typical Doses and Major Metabolites of Antidepressants Taken by Mothers in Studies of Breast-Feeding Mother-Infant Pairs

Drug Taken by Mother	Typical Dose (mg/day)	Half-Life of Parent Drug (78, 79) (hours)	Metabolite 1		Metabolite 2		Metabolite 3	
			Name	% Biological Activity Compared to Parent Drug	Name	% Biological Activity Compared to Parent Drug	Name	% Biological Activity Compared to Parent Drug
Amitriptyline	150	20	Nortriptyline	100				
Bupropion	300	21	Erythrohydro-bupropion	50	Hydroxybupropion	50	Threohydro-bupropion	50
Citalopram	20	35	Norcitalopram	13	Didesmethyl-citalopram	13		
Clomipramine	200	32	*N*-Desmethyl-clomipramine	100	8-Hydroxy-clomipramine	100	8-Hydroxy-desmethyl-clomipramine	100
Desipramine	150	20	2-Hydroxy-desipramine	100				
Dothiepin	100	19	Nordothiepin (northiaden)	50[a]	Dothiepin-*S*-oxide	50[a]	Nordothiepin-*S*-oxide	50[a]
Doxepin	150	9	*N*-Desmethyldoxepin	100				
Fluoxetine	20	96	Norfluoxetine	100				
Fluvoxamine	150	16	—[b]					
Imipramine	150	12	Desipramine	100				
Nefazodone	300	17	Hydroxynefazodone	100	Dione metabolite (BMS-180492A)	0	*m*-Chlorophenyl-piperazine (*m*-CPP)	0
Nortriptyline	75	37	E-Nortriptyline[c]	50[a]	Z-Nortriptyline[d]	50[a]		
Paroxetine	20	22	—[b]					
Sertraline	100	26	Norsertraline	10				
Venlafaxine	150	5	*O*-Desmethyl-venlafaxine	100				

[a] Unknown; value is an estimate.
[b] No active metabolite.
[c] E-10-Hydroxynortriptyline.
[d] Z-10-Hydroxynortriptyline.

tive association with the percentage of the drug bound to protein (r_s=–0.69, N=11, p=0.02).

Our methods of data extraction could have led to over- or underestimation of the infant plasma levels. Initially, we coded undetectable infant levels as zero, which could lead to underestimation, and we coded detectable but not quantifiable infant levels as 0.1 ng/ml less than the limit of detectability, which could lead to overestimation of infant levels. We therefore repeated the analyses in Table 6 and Table 7 under different conditions to assess the robustness of our results.

First, undetectable infant levels were recoded from zero to half the level of quantification. The standardized infant levels (Table 6) were now elevated (>10% of the average maternal level) in one of four amitriptyline infants, the one bupropion infant, the one dothiepin infant, three of 36 nortriptyline infants (8%), and three of 47 paroxetine infants (6%). The proportion of infants with elevated standardized levels changed from 22% to 25% for fluoxetine. The correlations in Table 7 changed slightly. Two correlations changed in statistical significance: the correlation between maternal dose and infant level for paroxetine became significant at r=0.35 (p<0.05), and the correlation between maternal dose and infant level for sertraline became nonsignificant at r=0.25.

We then recoded detectable but nonquantifiable infant levels, reducing them from 0.1 ng/ml less than the limit of quantification to half the limit of quantification. The standardized infant levels (Table 6) were now elevated (>10% of the average maternal level) in six (17%) of 36 fluoxetine infants instead of 22% and in 0% of sertraline infants instead of 7%. The correlations in Table 7 again changed slightly, but there were no changes in statistical significance.

Discussion

There are many factors potentially affecting breast milk and infant plasma levels of maternally ingested antidepressants. These include protein binding, CYP2D6 polymorphisms, lipophilicity, and the presence of other drugs (including herbs) ingested by the nursing mother. We found a strong negative relationship between antidepressant protein binding and potential transmission to the fetus that to our knowledge has not been addressed in previous studies. According to currently available data, breast-feeding infants exposed to nortriptyline, paroxetine, or sertraline seem unlikely to develop detectable or elevated plasma levels, while infants exposed to fluoxetine appear to be at higher risk of developing elevated levels, especially following prenatal exposure or if levels are high in the breast milk. Citalopram may produce elevated levels in

TABLE 4. Case Reports of Adverse Effects of Antidepressants in Breast-Feeding Infants

Study	Drug	Age (weeks)	Symptoms	Infant Levels (ng/ml)[a] Drug	Metabolite	Prenatal Exposure
Schmidt et al., 2000 (31)	Citalopram	6.6	Uneasy sleep (resolved after dose was halved)	12.7[b]	—	No
Matheson et al., 1985 (39)	Doxepin	8	Respiratory depression, drowsiness; recovered 24 hours after exposure ceased	3	62	No
Frey et al., 1999 (40)	Doxepin	1.6	Hypotonia, vomiting, poor sucking and swallowing, weight loss; recovered 24 hours after exposure ceased	10	0	No
Isenberg, 1990 (41)	Fluoxetine	14.9[c]	Irritability	—	—	No
Lester et al., 1993 (43)	Fluoxetine	10.3	Crying, decreased sleep, increased vomiting, watery stools; diary documented that symptoms returned on rechallenge and resolved after discontinuation of breast milk	340	208	No
Brent et al., 1998 (45)	Fluoxetine, carbamazepine, and buspirone		Possible seizure, recurring after drug exposures stopped			
Fluoxetine						Yes
Time 1		1.9		0	58	
Time 2		3.0		61	57	
Carbamazepine						Yes
Time 1		1.9		0.5	—	
Time 2		3.0		<0.5	—	
Buspirone						Yes
Time 1		1.9		—[d]	—	
Time 2		3.0		—[d]	—	
Kristensen et al., 1999 (47)						
Infant 10	Fluoxetine	6.4	Uncontrollable crying, irritability, and poor feeding	0	187	Yes
Infant 14[e]	Fluoxetine	1.7	Uncontrollable crying, irritability, and poor feeding	252	185	Yes
Nordeng et al. (32) and Nordeng (personal communication), 2001	Paroxetine	0.7	Lethargy, poor weight gain, hypotonia that persisted through first 4–6 weeks of life	31.4	31.4	Yes

[a] Some authors measured antidepressant levels in plasma, and others measured levels in serum. Thus, "infant level" denotes a level measured in plasma or serum.
[b] Level decreased to 4.5 ng/ml with half the dose.
[c] Authors reported that 2 weeks of fluoxetine treatment began when the mother was 3 months postpartum.
[d] Not detectable.
[e] Also exposed to methadone.

some infants, especially if the maternal dose or breast milk level is high, but more data are needed before firm conclusions can be drawn. Although our research does not show that the elevated levels have consequences for infants, a conservative approach to management may be to prescribe only medications that do not appear in infants' plasma.

Short-Term Effects of Antidepressant Exposure

Short-term but potentially serious adverse effects of breast-feeding exposure to antidepressants have been noted in individual case reports (Table 4). Of note, the 10-week-old infant studied by Lester et al. (43) had no history of prenatal exposure to fluoxetine yet developed plasma levels higher than the average maternal plasma level in our database. This measurement may have been spuriously high because it was obtained at a commercial laboratory rather than a research laboratory (4), but the infant's symptoms correlated with withdrawal and reexposure to the mother's breast milk. The fluoxetine-exposed infant studied by Brent and Wisner (45) had levels that increased between 2 and 3 weeks of age. These findings support our conclusion that fluoxetine is more likely than other antidepressants to accumulate in nursing infants.

The symptomatic infant with citalopram exposure reported by Schmidt et al. (31) is interesting because the symptoms occurred in an infant with no history of prenatal exposure whose level was 13% of the average maternal plasma level in our database. This supports our classification of infant levels above 10% of the maternal level as of potential clinical significance.

Long-Term Effects of Antidepressant Exposure

This pooled analysis focused only on infant plasma and breast milk levels. However, plasma levels or even brain tissue levels may not accurately predict the biochemical effect of an antidepressant on the brain (82, 83). Therefore, a low or undetectable infant plasma concentration by itself cannot reassure us that the antidepressant will have no effect on the rapidly developing brain. The larger question—whether chronic exposure to low doses of antidepressant medication poses long-term neurodevelopmental risks to the infant—remains unanswered. The limited information available from small controlled (24, 69, 84) and uncontrolled (46, 50) studies of asymptomatic infants is reassuring. Platelet serotonin uptake is not decreased in breast-fed infants exposed to sertraline; by inference, breast-feeding exposure to sertraline should therefore not

TABLE 5. Maternal Antidepressant Dose and Plasma and Breast Milk Levels in Breast-Feeding Mother-Infant Pairs in 57 Studies

Antidepressant	Maternal Dose			Maternal Plasma Level			Breast Milk Level			Ratio of Milk to Plasma Level			Pearson Correlation of Milk and Plasma Levels[b]
		Dose (mg/day)			Level (ng/ml)			Level (ng/ml)			Ratio		
	N	Mean	Range	N	Mean	Range	N	Mean	Range	N	Mean[a]	Range	
Amitriptyline	6	129	75–175	6	112	41–228	4	80	38–143	5	0.8	0–1.6	0.46
Bupropion	1	300		1	11		1	78		1	7.1		
Citalopram	18	29	20–60	14	98	32–250	18	157	41–451	14	1.7	0.9–2.8	0.93**
Clomipramine	6	96	75–125	5	122	60–160	2	141	139–143	2	0.9	0.8–0.9	
Desipramine	5	177	37–300	1	264		1	322		1	1.2		
Dothiepin	12	142	50–225	19	93	11–712	19	130	0–1119	19	1.3	0–3.2	0.98**
Doxepin	1	150		1	46		1	61		1	1.4		
Fluoxetine	33	28	10–80	28	165	21–506	20	76	23–189	28	0.2	0–1.1	0.53
Fluvoxamine	8	159	50–300	7	188	12–370	6	174	18–478	6	0.9	0.3–1.4	0.82*
Imipramine	7	129	75–200	5	146	21–334	5	190	16–435	4	1.4	1.1–2.0	
Nefazodone	2	275	150–400	2	333	49–617	2	254	57–450	2	4.6	0.1–9.2	
Nortriptyline	35	78	50–150	33	102	10–201	1	230		1	1.6		
Paroxetine	68	21	10–50	55	47	0–276	50	28	0–153	39	0.6	0–2.4	0.79**
Sertraline	77	83	25–200	65	35	4–134	15	45	7–207	27	0.9	0–5.2	0.22
Venlafaxine	5	225	75–450	5	174	28–550	3	955	565–1700	3	2.5	0–5.2	

[a] Significant difference among mean ratios (ANOVA: F=7.79, df=14, 140, p<0.001).
[b] Correlations determined only for antidepressants with at least five cases.
*p<0.05.   **p<0.001.

affect serotonin metabolism in the infant brain (18). However, Chambers et al. (85) found a small growth deficit of 392 g at 6 months of age in infants exposed to fluoxetine through breast milk. Although antenatal exposure is different from breast-feeding exposure, the available data on antenatal exposure points toward little or no long-term effect on developmental outcomes (86). Clearly, further work needs to be done before we can be confident that antidepressant exposure poses no important long-term neurodevelopmental risks to the nursing infant.

Limitations

This pooled analysis included all the currently available data we could find on antidepressant levels in breast-feeding mothers and infants, as well as data from 36 unpublished cases. Most data sets did not include maternal, breast milk, *and* infant levels. Infant levels were especially lacking. Because the neonatal liver undergoes a marked increase in metabolic capacity during the first weeks of life, from very low to above the adult range (87), the infant's ability to metabolize the drug can be a much stronger determinant of plasma level than the amount of drug ingested through breast milk. Despite the correlations we have presented, the current knowledge is not sufficient to support monitoring of breast milk levels in order to estimate individual infant plasma levels, and researchers should not rely on breast milk levels alone to estimate the extent of exposure of the infant.

Other data elements that were not routinely reported include the maternal weight, time after a maternal dose, whether the infant had been exposed to the drug before birth, the limit of quantifiability of the assay, and the use of other medications, including herbs, that may affect metabolism. Variation in pharmacogenetics may also be important, but these studies are unlikely to be done in the near future, given the current invasive nature of these assays. The pharmacokinetics of drug transfer by breast milk can be understood only if the presence or absence of prenatal exposure is reported, since prenatal exposure provides a "loading dose" that far exceeds any exposure from breast milk.

Many reported breast milk levels are unreliable because of variations in milk collection procedures. In some studies, an unspecified aliquot from a given feeding was collected or only fore or hind milk levels were determined, and these may not accurately reflect the overall drug concentration ingested by the infant. Because antidepressants tend to be lipophilic, breast milk concentrations for some drugs may vary more than twofold between the watery fore milk and the fattier hind milk (56, 64), while others vary very little (35).

Other possible confounding factors include cigarette smoking, a known inducer of cytochromes CYP1A1 and CYP1A2 (88). Almost none of the reports indicated whether the mothers used cigarettes, which can potentially affect infant metabolism and maternal metabolism. Similarly, alcohol use was not reported.

The studies we reviewed primarily made contemporaneous measurements of maternal, breast milk, and infant drug levels. However, the peak level in breast milk may lag behind the maternal plasma peak by 2 or more hours and can be two to three times as high as the trough level (39, 44, 47). Different drugs peak in breast milk at different intervals after a maternal dose, and this interval may vary between patients taking the same drug (63, 69). The peak drug level in the infant would be expected sometime after the feeding that contains a peak or near-peak level in the milk. Thus, one-time measurements may not accurately reflect the extent of infant exposure to the drug. Using the calculated area under the curve overcomes this problem

TABLE 6. Relation of Antidepressant Levels in Infants' Plasma to Maternal Plasma and Breast Milk Levels for Breast-Feeding Mother-Infant Pairs in 57 Studies

Antidepressant	Standardized Infant Plasma Level[a]					Ratio of Infant Plasma to Maternal Plasma Level					Ratio of Infant Plasma to Breast Milk Level		
	Level			Elevated Ratio[b]			Ratio		Elevated Ratio[b]			Ratio	
	N	Mean	Range	N	%	N	Mean[c]	Range	N	%	N	Mean[d]	Range
Amitriptyline	4	0.00		0	0	4	0.00		0	0	3	0.00	
Bupropion	1	0.00		0	0	1	0.00		0	0	1	0.00	
Citalopram	12	0.03	0.00–0.13	2	17	5	0.07	0.03–0.17	1	20	5	0.04	0.02–0.06
Clomipramine	4	0.02	0.00–0.08	0	0	3	0.04	0.00–0.11	1	33	0		
Desipramine	5	0.00		0	0	1	0.00		0	0	1	0.00	
Dothiepin	3	0.12	0.00–0.37	1	33	1	0.00		0	0	1	0.00	
Doxepin	1	0.00		0	0	1	0.00		0	0	1	0.00	
Fluoxetine	36	0.06	0.00–0.63	8	22	22	0.07	0.00–0.59	4	18	5	0.04	0.00–0.19
Fluvoxamine	4	0.02	0.00–0.05	0	0	3	0.16	0.00–0.45	1	33	2	0.18	0.00–0.36
Imipramine	2	0.00		0	0	0					0		
Nortriptyline	36	0.01	0.00–0.10	0	0	32	0.01	0.00–0.24	1	3	0		
Paroxetine[e]	47	0.01	0.00–0.66	1	2	40	0.00		0	0	27	0.01	0.00–0.20
Sertraline	60	0.02	0.00–0.14	4	7	53	0.02	0.00–0.15	3	6	5	0.00	
Venlafaxine[f]	5	0.00		0	0	5	0.00		0	0	3	0.00	

[a] Each infant blood level was divided by the average of all maternal plasma levels for that medication.
[b] Elevated was defined as above 0.10.
[c] Significant difference among mean ratios (ANOVA: $F=2.68$, $df=12, 158$, $p<0.05$).
[d] Significant difference among mean ratios (ANOVA: $F=2.08$, $df=10, 43$, $p<0.05$).
[e] The values for paroxetine are skewed by one 5-day-old infant with prenatal exposure and an elevated plasma level: all other paroxetine infant levels were zero (see text).
[f] Metabolites are not included in this analysis. The infant levels of venlafaxine were all zero, but infant levels of the metabolite *O*-desmethyl-venlafaxine were substantial.

TABLE 7. Correlations of Antidepressant Levels in Infants' Plasma With Mother's Dose, Mother's Plasma Level, Breast Milk Level, and Infant Age Among Breast-Feeding Mother-Infant Pairs in 57 Studies

Antidepressant	Pearson Correlation With Infant Plasma Level[a]							
	Maternal Dose		Maternal Plasma Level		Breast Milk Level		Infant Age	
	N	r	N	r	N	r	N	r
Citalopram	5	0.99*	5	0.69	5	0.91*	<5	—
Fluoxetine	30	0.28	22	0.08	5	0.93*	36	–0.17
Nortriptyline	34	0.01	32	–0.28	<5	—	35	–0.17
Paroxetine[b]	47	0.28	42[c]	—	29	0.72*	47	–0.20
Sertraline	60	0.27*	53	0.63*	<5	—	56	–0.11
Overall[d]	176	0.31*	154	0.21*	44	0.55*	178	–0.12

[a] Correlations are shown only for antidepressants for which five or more mother-infant pairs were reported. Data on medications with fewer than five observations were included in the overall correlation.
[b] The correlations for paroxetine are skewed by one 5-day-old infant with an elevated plasma level (31.4 ng/ml) who had prenatal exposure and exposure to high levels of paroxetine in the breast milk (153 ng/ml versus an average of 28 ng/ml in the breast milk from the mothers of the other four infants with measurable levels). All other paroxetine infant levels were zero (see text).
[c] There were 42 mother-infant pairs; the infant level was zero for every pair. Thus, Pearson's correlations could not be calculated.
[d] The dose of a given medication was divided by the typical dose for that medication before computation of the overall correlation. Infants were excluded from the overall correlation if they were exposed to a medication for which no infants had elevated blood levels.
*$p<0.05$.

but requires obtaining multiple samples from the same patient during a dosing interval. We are not aware of any study of multiple infants that has determined the area under the curve of an infant's blood level. Given the logistics involved and quantity of blood that would be required, it is unlikely this will be done.

Conclusions

According to currently available data, breast-feeding infants exposed to nortriptyline, paroxetine, or sertraline are unlikely to develop detectable or elevated plasma drug levels, while infants exposed to fluoxetine appear to be at higher risk of developing elevated levels, especially following prenatal exposure. Citalopram may produce elevated levels in some infants, but additional data are needed before firm conclusions can be drawn. Current knowledge does not support clinical monitoring of maternal plasma or breast milk antidepressant levels in an attempt to estimate individual infant plasma levels. Further research is needed before we can be confident that antidepressant exposure produces no significant long-term risks to the infant; however, on the basis of current knowledge, breast-feeding women may reasonably choose to use antidepressants. In order to clarify factors influencing infant exposure to antidepressants through breast milk, investigators in future studies must measure infant levels and report relevant information such as the history of prenatal expo-

sure, infant age, infant weight, and concomitant use of other medications.

Infant drug levels are just one factor potentially affecting the infant. Given the paucity of published reports of infant drug levels, the lack of studies that consistently take into account the many factors potentially influencing drug levels, and the numbers of women who may benefit from antidepressants during the time that breast-feeding is recommended, larger studies are imperative in the future in order to be able to give nursing mothers the best possible advice concerning use of and potential effects of antidepressants.

Because rare, adverse effects may not have been picked up by the small numbers of case reports and published studies, nursing mothers choosing to use antidepressants should be alert to subtle changes or worrisome infant behaviors, such as irritability, poor feeding, or uneasy sleep, that may indicate adverse infant effects from maternally ingested medication. Infants born prematurely and those with impaired metabolite efficiency are likely to have higher levels and should be watched closely for side effects.

References

1. O'Hara M, Swain A: Rates and risk of postpartum depression—a meta-analysis. Int Rev Psychiatry 1996; 8:37–54

2. Georgiopoulos AM, Bryan TL, Wollan P, Yawn BP: Routine screening for postpartum depression. J Fam Pract 2001; 50:117–122; correction, 50:470

3. Ryan A: The resurgence of breastfeeding in the United States. Pediatrics 1997; 99:e12

4. Wisner KL, Perel JM, Findling RL: Antidepressant treatment during breast-feeding. Am J Psychiatry 1996; 153:1132–1137

5. Misri S, Burmann A, Kostaras D: Are SSRIs safe for pregnant and breastfeeding women? Can Fam Phys 2000; 46:626–633

6. Llewellyn A, Stowe Z: Psychotropic medications in lactation. J Clin Psychiatry 1998; 59(suppl 2):41–52

7. Ito S: Drug therapy for breast-feeding women. N Engl J Med 2000; 343:118–126

8. Schimmell MS, Katz EZ, Shaag Y, Pastuszak A, Koren G: Toxic neonatal effects following maternal clomipramine therapy. J Toxicol Clin Toxicol 1991; 29:479–484

9. Rees J, Glass R, Sporne G: Serum and breast-milk concentrations of dothiepin (letter). Practitioner 1976; 217:686

10. Banger M, Hermes B, Hartter S, Hiemke C: Monitoring serum concentrations of clomipramine and metabolites: fluorescence polarization immunoassay versus high performance liquid chromatography. Pharmacopsychiatry 1997; 30:128–132

11. Hackett LP, Dusci LJ, Ilett KF: A comparison of high-performance liquid chromatography and fluorescence polarization immunoassay for therapeutic drug monitoring of tricyclic antidepressants. Ther Drug Monit 1998; 20:30–34

12. Moretti ME, Sharma A, Bar Oz B, Koren G, Ito S: Fluoxetine and its effects on the nursing infant: a prospective cohort study (abstract). Clin Pharmacol Ther 1999; 65:141

13. Verbeeck R, Ross S, McKenna E: Excretion of trazodone in breast milk. Br J Clin Pharmacol 1986; 22:367–370

14. Pons G, Schoerlin MP, Tam YK, Moran C, Pfefen JP, Francoual C, Pedarriosse AM, Chavinie J, Olive G: Moclobemide excretion in human breast milk. Br J Clin Pharmacol 1990; 29:27–31

15. Dodd S, Maguire KP, Burrows GD, Norman TR: Nefazodone in the breast milk of nursing mothers: a report of two patients (letter). J Clin Psychopharmacol 2000; 20:717–718

16. Gelenberg A: Amoxapine, a new antidepressant, appears in human milk. J Nerv Ment Dis 1979; 167:635–636

17. Epperson CN, Anderson GM, McDougle CJ: Sertraline and breast-feeding (letter). N Engl J Med 1997; 336:1189–1190

18. Epperson N, Czarkowski KA, Ward-O'Brien D, Weiss E, Gueorguieva R, Jatlow P, Anderson GM: Maternal sertraline treatment and serotonin transport in breast-feeding mother-infant pairs. Am J Psychiatry 2001; 158:1631–1637

19. Erickson SH, Smith GH, Heidrich F: Tricyclics and breast feeding. Am J Psychiatry 1979; 136:1483–1484

20. Bader TF, Newman K: Amitriptyline in human breast milk and the nursing infant's serum. Am J Psychiatry 1980; 137:855–856

21. Brixen-Rasmussen L, Halgrener J, Jorgensen A: Amitriptyline and nortriptyline excretion in human breast milk. Psychopharmacology (Berl) 1982; 76:94–95

22. Pittard WB III, O'Neal W Jr: Amitriptyline excretion in human milk (letter). J Clin Psychopharmacol 1986; 6:383–384

23. Breyer-Pfaff U, Nill K, Entenmann A, Gaertner HJ: Secretion of amitriptyline and metabolites into breast milk (letter). Am J Psychiatry 1995; 152:812–813

24. Yoshida K, Smith B, Craggs M, Kumar RC: Investigation of pharmacokinetics and of possible adverse effects in infants exposed to tricyclic antidepressants in breast-milk. J Affect Disord 1997; 43:225–237

25. Briggs GG, Samson JH, Ambrose PJ, Schroeder DH: Excretion of bupropion in breast milk. Ann Pharmacother 1993; 27:431–433

26. Jensen PN, Olesen OV, Bertelsen A, Linnet K: Citalopram and desmethylcitalopram concentrations in breast milk and in serum of mother and infant. Ther Drug Monit 1997; 19:236–239

27. Öhman I, Norstedt Wikner B, Vitols S: Citalopram and metabolite levels in plasma and breast milk in two nursing women. Eur J Clin Pharmacol 1997; 52(suppl A):A179

28. Spigset O, Carieborg L, Ohman R, Norstrom A: Excretion of citalopram in breast milk. Br J Clin Pharmacol 1997; 44:295–298

29. Lepola U, Penttinen J, Koponen H, Nohr Poulsen M, Fredricson Overø K: Citalopram treatment and breastfeeding, in NCDEU Poster Abstracts. Rockville, Md, National Institute of Mental Health, 2000, number 152

30. Rampono J, Kristensen JH, Hackett LP, Paech M, Kohan R, Ilett KF: Citalopram and desmethylcitalopram in human milk; dis-

tribution, excretion and effects in breast fed infants. Br J Clin Pharmacol 2000; 50:263–268

31. Schmidt K, Olesen O, Jensen P: Citalopram and breast-feeding: serum concentration and side effects in the infant. Biol Psychiatry 2000; 47:164–165

32. Nordeng H, Bergsholm YK, Bohler E, Spigset O: [The transfer of selective serotonin reuptake inhibitors to human milk]. Tidsskr Nor Laegeforen 2001; 121:199–203 (Norwegian)

33. Wisner K, Perel J, Foglia J: Serum clomipramine and metabolite levels in four nursing mother-infant pairs. J Clin Psychiatry 1995; 56:17–20

34. Birnbaum CS, Cohen LS, Bailey JW, Grush LR, Robertson LM, Stowe ZN: Serum concentrations of antidepressants and benzodiazepines in nursing infants: a case series. Pediatrics 1999; 104:e11

35. Stancer HC, Reed KL: Desipramine and 2-hydroxydesipramine in human breast milk and the nursing infant's serum. Am J Psychiatry 1986; 143:1597–1600

36. Buist A, Norman T, Dennerstein L: Plasma and breast milk concentrations of dothiepin and northiaden in lactating women. Hum Psychopharmacol 1993; 8:29–33

37. Ilett KF, Lebedevs TH, Wojnar-Horton RE, Yapp P, Roberts MJ, Dusci LJ, Hackett LP: The excretion of dothiepin and its primary metabolites in breast milk. Br J Clin Pharmacol 1992; 33:635–639

38. Kemp J, Ilett KF, Booth J, Hackett LP: Excretion of doxepin and N-desmethyldoxepin in human milk. Br J Clin Pharmacol 1985; 20:497–499

39. Matheson I, Pande H, Alertsen A: Respiratory depression caused by N-desmethyldoxepin in breast milk (letter). Lancet 1985; 2:1124

40. Frey O, Scheidt P, von Brenndorff A: Adverse effects in a newborn infant breast-fed by a mother treated with doxepin. Ann Pharmacother 1999; 33:690–693

41. Isenberg K: Excretion of fluoxetine in human breast milk (letter). J Clin Psychiatry 1990; 51:169

42. Burch K, Wells B: Fluoxetine/norfluoxetine concentrations in human milk. Pediatrics 1992; 89(4, part 1):676–677

43. Lester BM, Cucca J, Andreozzi L, Flanagan P, Oh W: Possible association between fluoxetine hydrochloride and colic in an infant. J Am Acad Child Adolesc Psychiatry 1993; 32:1253–1255

44. Taddio A, Ito S, Koren G: Excretion of fluoxetine and its metabolite, norfluoxetine, in human breast milk. J Clin Pharmacol 1996; 36:42–47

45. Brent N, Wisner K: Fluoxetine and carbamazepine concentrations in a nursing mother/infant pair. Clin Pediatr 1998; 37:41–44

46. Yoshida K, Smith B, Craggs M, Kumar RC: Fluoxetine in breast-milk and developmental outcome of breast-fed infants. Br J Psychiatry 1998; 172:175–178

47. Kristensen JH, Ilett KF, Hackett LP, Yapp P, Paech M, Begg EJ: Distribution and excretion of fluoxetine and norfluoxetine in human milk. Br J Clin Pharmacol 1999; 48:521–527

48. Hendrick V, Stowe ZN, Altshuler LL, Mintz J, Hwang S, Hostetter A, Suri R, Leight K, Fukuchi A: Fluoxetine and norfluoxetine concentrations in nursing infants and breast milk. Biol Psychiatry 2001; 50:775–782

49. Wright S, Dawling S, Ashford J: Excretion of fluvoxamine in breast milk (letter). Br J Clin Pharmacol 1991; 31:209

50. Yoshida K, Smith B, Kumar R: Fluvoxamine in breast-milk and infant development (letter). Br J Clin Pharmacol 1997; 44:210–211

51. Arnold L, Suckow R, Lichtenstein P: Fluvoxamine concentrations in breast milk and in maternal and infant sera. J Clin Psychopharmacol 2000; 20:491–493

52. Hagg S, Granberg K, Carleborg L: Excretion of fluvoxamine into breast milk (letter). Br J Clin Pharmacol 2000; 49:286–288

53. Piontek CM, Wisner KL, Perel JM, Peindl KS: Serum fluvoxamine levels in breastfed infants. J Clin Psychiatry 2001; 62:111–113

54. Sovner R, Orsulak PJ: Excretion of imipramine and desipramine in human breast milk. Am J Psychiatry 1979; 136(4A):451–452

55. Dodd S, Buist A, Burrows GD, Maguire KP, Norman TR: Determination of nefazodone and its pharmacologically active metabolites in human blood plasma and breast milk by high-performance liquid chromatography. J Chromatogr B Biomed Sci Appl 1999; 730:249–255

56. Matheson I, Skjaeraasen J: Milk concentrations of flupenthixol, nortriptyline and zuclopenthixol and between-breast differences in two patients. Eur J Clin Pharmacol 1988; 35:217–220

57. Wisner KL, Perel JM: Serum nortriptyline levels in nursing mothers and their infants. Am J Psychiatry 1991; 148:1234–1236

58. Wisner KL, Perel JM: Nortriptyline treatment of breast-feeding women (letter). Am J Psychiatry 1996; 153:295

59. Mammen O, Perel JM, Wheeler SB: Antidepressants and breast-feeding (letter). Am J Psychiatry 1997; 154:1174–1175

60. Wisner KL, Perel JM, Findling RL, Hinnes RL: Nortriptyline and its hydroxymetabolites in breastfeeding mothers and newborns. Psychopharmacol Bull 1997; 33:249–251

61. Altshuler LL, Burt VK, McMullen M, Hendrick V: Breastfeeding and sertraline: a 24-hour analysis. J Clin Psychiatry 1995; 56:243–245

62. Spigset O, Carleborg L, Norstrom A, Sandlund M: Paroxetine level in breast milk (letter). J Clin Psychiatry 1996; 57:39

63. Begg EJ, Duffull SB, Saunders DA, Buttimore RC, Ilett KF, Hackett LP, Yapp P, Wilson DA: Paroxetine in human milk. Br J Clin Pharmacol 1999; 48:142–147

64. Öhman R, Hagg S, Carleborg L, Spigset O: Excretion of paroxetine into breast milk. J Clin Psychiatry 1999; 60:519–523

65. Stowe ZN, Cohen LS, Hostetter A, Ritchie JC, Owens MJ, Nemeroff CB: Paroxetine in human breast milk and nursing infants. Am J Psychiatry 2000; 157:185–189

66. Hendrick V, Stowe ZN, Altshuler LL, Hostetter A, Fukuchi A: Paroxetine use during breast-feeding (letter). J Clin Psychopharmacol 2000; 20:587–589

67. Misri S, Kim J, Riggs KW, Kostaras X: Paroxetine levels in postpartum depressed women, breast milk, and infant serum. J Clin Psychiatry 2000; 61:828–832

68. Mammen OK, Perel JM, Rudolph G, Foglia JP, Wheeler SB: Sertraline and norsertraline levels in three breastfed infants. J Clin Psychiatry 1997; 58:100–103

69. Stowe ZN, Owens MJ, Landry JC, Kilts CD, Ely T, Llewellyn A, Nemeroff CB: Sertraline and desmethylsertraline in human breast milk and nursing infants. Am J Psychiatry 1997; 154:1255–1260

70. Kristensen JH, Ilett KF, Dusci LJ, Hackett LP, Yapp P, Wojnar-Horton RE, Roberts MJ, Paech M: Distribution and excretion of sertraline and N-desmethylsertraline in human milk. Br J Clin Pharmacol 1998; 45:453–457

71. Wisner KL, Perel JM, Blumer J: Serum sertraline and N-desmethylsertraline levels in breast-feeding mother-infant pairs. Am J Psychiatry 1998; 155:690–692

72. Dodd S, Stocky A, Buist A, Burrows GD, Maguire K, Norman TR: Sertraline in paired blood plasma and breast-milk samples from nursing mothers. Hum Psychopharmacol 2000; 15:261–264

73. Ilett KF, Hackett LP, Dusci LJ, Roberts MJ, Kristensen JH, Paech M, Groves A, Yapp P: Distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk. Br J Clin Pharmacol 1998; 45:459–462

74. Hendrick V, Altshuler L, Wertheimer A, Dunn WA: Venlafaxine and breast-feeding (letter). Am J Psychiatry 2001; 158:2089–2090

75. Foglia J, Birder L, Perel J: Determination of fluvoxamine in human plasma by high-performance liquid chromatography with ultraviolet detection. J Chromatogr 1989; 495:295–302

76. Axelson D, Perel JM, Rudolph G, Birmaher B, Brent D: Sertraline pediatric/adolescent PK-PD parameters: dose/plasma level ranging for depression (abstract). Clin Pharmacol Ther 2000; 67(2):169

77. Perel JM, Rudolph G, Foglia JP, Cornellus J, Birmaher B: Chirality and TDM of fluoxetine (FL), norfluoxetine (NFL) and citalopram (Cit) (abstract). Clin Pharmacol Ther 1996; 59(2):213

78. Drug Facts and Comparisons 2001. St Louis, Facts and Comparisons, 2001

79. AHFS Drug Information 2001. Bethesda, Md, American Society of Health-System Pharmacists, 2001

80. Perry PJ, Alexander B, Liskow BI: Psychotropic Drug Handbook, 7th ed. Washington, DC, American Psychiatric Press, 1997, p 143

81. Milne RJ, Goa KL: Citalopram: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. Drugs 1991; 41:450–477

82. Wikell C, Apelqvist G, Carlsson B, Hjorth S, Bergqvist PB, Kugelberg FC, Ahlner J, Bengtsson F: Pharmacokinetic and pharmacodynamic responses to chronic administration of the selective serotonin reuptake inhibitor citalopram in rats. Clin Neuropharmacol 1999; 22:327–336

83. Bourdeaux R, Pannetier P, Younos C, Desor D, Lehr PR, Capolaghi B: [Fluoxetine: relations between plasma concentration and therapeutic effects in 32 patients with major depression and treated with 20 mg/day.] Encephale 1998; 24:57–61 (French)

84. Buist A, Janson H: Effect of exposure to dothiepin and northiaden in breast milk on child development. Br J Psychiatry 1995; 167:370–373

85. Chambers CD, Anderson PO, Thomas RG, Dick LM, Felix RJ, Johnson KA, Jones KL: Weight gain in infants breastfed by mothers who take fluoxetine. Pediatrics 1999; 104:e61

86. Nulman I, Rovet J, Stewart DE, Wolpin J, Gardner HA, Theis JG, Kulin N, Koren G: Neurodevelopment of children exposed in utero to antidepressant drugs. N Engl J Med 1997; 336:258–262

87. Kearns G: Impact of developmental pharmacology on pediatric study design: overcoming the challenges. J Allergy Clin Immunol 2000; 106(suppl 3):S128–S138

88. Spigset O, Carleborg L, Hedenmalm K, Dahlqvist R: Effect of cigarette smoking on fluvoxamine pharmacokinetics in humans. Clin Pharmacol Ther 1995; 58:399–403