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Serum Concentrations of Antidepressants and Benzodiazepines in Nursing Infants: A Case Series

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ABSTRACT. *Objective.* The relative risk of psychotropic medication use in women with puerperal psychiatric illness who are breastfeeding has yet to be quantified adequately. Although the emotional and medical benefits of breastfeeding and adverse effects of maternal depression on infant development are well described, how these absolute benefits weigh against the potential effects of psychotropic drug use during lactation to ultimately guide clinical decisions is still unclear. The objective of this report was to evaluate the extent that psychotropic medications were present in the serum of infants breastfed by mothers treated with antidepressants and benzodiazepines.

Design. Serum samples were obtained from 35 nursing infants whose mothers were treated with psychotropic medications while breastfeeding. When a detectable concentration of medication was reported, information regarding infant behavior was obtained by maternal report.

Setting. The Perinatal and Reproductive Psychiatry Program at Massachusetts General Hospital serves as a regional consultation center for the treatment of psychiatric disorders during pregnancy and the postpartum period.

Patients. Subjects were mothers referred to the Perinatal Psychiatry Program for consultation regarding the relative safety of psychotropic medication use while breastfeeding.

Primary Outcome Measures. Presence of detectable levels of medication in infants whose mothers breastfed while taking psychotropic medications during pregnancy and/or during the puerperium and the well-being (based on maternal report) of infants who had detectable serum concentrations of medication.

Results. Seventy-four percent ($n = 26$) of infants had serum medication concentrations below the laboratory limit of detection (assay sensitivity 5–50 ng/mL). In the remaining 26% of the sample ($n = 9$), serum concentrations of psychotropic medications and/or active metabolites were detected. In each of these cases, infants had been exposed to the medication during pregnancy. Medications were not detected in infant serum when mothers had taken these agents solely during the postpartum period. No readily apparent difficulties with the infants were reported by mothers.

Conclusions. These data support the low incidence of infant toxicity and adverse effects associated with antidepressant and benzodiazepine use during breastfeeding. These data also suggest that infant serum monitoring is helpful in the assessment of medication exposure in children of mothers who breastfeed while using psychotropic medications. Given the limited accumulated data regarding serum concentrations of psychotropic medications in breastfeeding infants, no single agent seems to be safer than another. Therefore, choice of pharmacologic treatment should be guided by the likelihood that it will result in restoration of maternal psychiatric well-being. *Pediatrics* 1999;104(1). URL: <http://www.pediatrics.org/cgi/content/full/104/1/e11>; *breastfeeding, antidepressants, benzodiazepines.*

ABBREVIATION. SSRI, selective serotonin reuptake inhibitor.

Several investigators describe a high prevalence of psychiatric disorders during the postpartum period. Major depression, which occurs in ~10% of postpartum women, is of primary concern.^{1,2} In addition, the puerperium may be a time of particular risk for women with a history of mood disorder.^{3,4} Anxiety disorders, including panic disorder and obsessive compulsive disorder, as well as postpartum psychosis, are less prevalent but also may have a significant impact on maternal functioning.^{5,6} The high prevalence of postpartum psychiatric illness and the extent to which psychotropic medications are prescribed to postpartum women underscore the need to develop treatment guidelines for women who suffer from psychiatric disorders during the postpartum period. For postpartum women who choose to breastfeed, little exists in the way of scientifically derived guidelines that address the use of psychotropic medications during lactation and appropriate monitoring of infant serum concentrations of psychotropic medication. Nonetheless, postpartum women are counseled routinely not to breastfeed when prescribed psychotropic medications. These recommendations are made without data regarding the safety of treatment with a given medication during breastfeeding or are based on anecdotal data that describe symptoms such as colic, irritability, and sedation in infants whose mothers have ingested a particular psychotropic medication while breastfeeding.^{7,8} Despite these anecdotal reports, professional guidelines established by the American Academy of Pediatrics do not preclude the

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use of psychotropic medications in women who breastfeed.⁹

The positive medical and emotional benefits of breastfeeding are well described.¹⁰ In addition, growing evidence suggests that untreated maternal mood disorder may have a significant impact on mother-infant attachment and child development^{11–13} and may increase the risk for chronic depressive illness in the mother.^{14,15} Thus, relative risk assessment in cases of women who wish to breastfeed while using psychotropic medications such as antidepressants and benzodiazepines warrants additional investigation.

Reports of adverse effects after infant exposure to medications via breast milk are described for a broad range of compounds. Specific reports of antidepressant treatment during breastfeeding were reviewed by Wisner and associates.¹⁶ These case reports or small uncontrolled case series describe the amount of medication present in breast milk or infant serum at a given point in time and associated infant symptoms such as colic, irritability, and sedation.^{7,17} These symptoms are offered frequently as examples of toxicity, although symptoms such as colic, irritability, and a range of alertness are also noted in infants whose mothers do not breastfeed while taking psychotropic medications. In addition, the concurrent use of nonpsychotropic medications for pain relief or infection control makes assignment of a causal relationship between maternal use of a psychotropic drug and observed infant symptoms even more problematic.

The extent to which infant exposure to psychotropic medications might affect infant brain development and functioning is unknown. Some long-term neurobehavioral follow-up after fetal exposure to antidepressants such as fluoxetine are available, but these data are still sparse. Because psychotropic medications affect central nervous system neurotransmitters, it is possible that infant exposure to these agents may cause interference in the development of neurotransmitter receptors.¹⁸

Few studies of women who breastfeed while taking psychotropic medications have evaluated the presence or absence of medication in the infants' serum.^{19,20} To date, the accumulated reports of infants who have breastfed while their mothers used psychotropic medications are limited given the total number of women who breastfeed while using these agents.^{7,16,17,19–41} This article describes a series of infant serum measures obtained in an effort to evaluate the extent to which nursing infants are exposed to psychotropic medications when their mothers are treated with these agents.

METHODS

The Perinatal and Reproductive Psychiatry Clinical Research Program at Massachusetts General Hospital, Boston, serves as a national referral center for the treatment of psychiatric disorders during pregnancy and in the postpartum period. Mothers with a history of affective disorder or those women who suffer from postpartum psychiatric disorders often are referred to the Perinatal Psychiatry Program for consultation regarding the risk of psychotropic use if they choose to breastfeed. During consultation, the possible risks of infant exposure to psychotropic medications are reviewed with mothers and are weighed against the risks of

untreated maternal illness and the benefits of breastfeeding. When mothers elect to take psychotropic medications during lactation, infant monitoring typically includes the determination of infant serum concentrations of psychotropic medication and is part of routine follow-up.

The current investigation was undertaken after approval by the institutional review board at Massachusetts General Hospital. All participants gave informed verbal consent to participate. Subjects typically were patients of community psychiatrists who were referred to the Perinatal Psychiatry Program for consultation regarding perinatal psychiatric care. Several subjects were followed primarily by clinicians within the program (L.S.C., C.B., L.G.). All patients who were seen by physicians in the program and who elected to breastfeed while taking psychotropic medications were invited to participate in the study. Of these patients, 10% to 20% declined because of logistic reasons or refusal to have the infant undergo venipuncture.

The concentrations of psychotropic medications and their metabolites, if any, were measured in serum samples obtained from 35 infants of mothers referred to the Perinatal Psychiatry Program who elected either 1) to continue pharmacologic therapy begun during pregnancy ($n = 25$) or 2) to initiate psychopharmacologic treatment during the puerperium ($n = 10$). Five infants were tested on a second occasion either after an increase in maternal daily dose of psychotropic medication or in situations in which detectable concentrations of psychotropic medications were reported in an initial sample of infant serum. Serum samples were obtained either by antecubital venous sampling or by lateral heel stick. Mothers were treated with a number of psychotropic medications including clomipramine ($n = 1$), desipramine ($n = 4$), imipramine ($n = 2$), nortriptyline ($n = 4$), fluoxetine ($n = 12$), paroxetine ($n = 2$), sertraline ($n = 3$), clonazepam ($n = 11$), trifluoperazine ($n = 1$), and valproic acid ($n = 2$). Several of these women ($n = 6$) were treated with a combination of psychotropic agents.

Infant serum was assayed at 11 different hospital and community laboratories, and test results were forwarded to the Perinatal Psychiatry Program. Sensitivities of assays used in different laboratories varied (10–25 ng/mL for tricyclic antidepressants, 5–50 ng/mL for selective serotonin reuptake inhibitors (SSRIs), and 5–14 ng/mL for clonazepam) and are noted in Tables 1 and 2. Typically, newborns were on different feeding schedules when tested. Information regarding gestational age at delivery, weight at the time of testing, and number of feedings per day was obtained. Data regarding maternal daily doses of medications used during the third trimester of pregnancy and during lactation also were obtained. In most cases, maternal daily dose had been stable for >14 days.

The primary aim of this investigation was to assess serum concentrations of medications in infants and not to assess formally infant outcome with a standardized pediatric neurologic examination. Nonetheless, mothers were asked whether they had noticed any infant symptoms including lethargy, difficulty feeding, or jitters. They were also asked whether routine pediatric examinations had revealed any symptoms that the clinician had attributed to maternal ingestion of psychotropic medication(s).

RESULTS

Infants' ages ranged from 1.3 to 44.0 weeks at the time of sampling. Of the 35 mothers, 25 had been treated pharmacologically during the third trimester of pregnancy and in the postpartum period. Results of assays for the infants of these mothers are shown in Table 1. Of the 25 infants tested, medication was noted in 36% ($n = 9$) of infants. Of these cases, 7 were infants whose mothers took fluoxetine during pregnancy and the puerperium. Of note, detectable concentrations of fluoxetine and/or norfluoxetine were noted in 78% ($n = 7$) of infants whose mothers used this medication during pregnancy and in the postpartum period. Two infants whose mothers remained on the same dose of fluoxetine were retested 4 to 5.4 weeks after the initial test. Neither of these infants had a detectable level of fluoxetine or norflu-

TABLE 1. Serum Drug Concentrations in Infants Whose Mothers Used Psychotropic Medications During Trimester III and Lactation

Drug Class	Subject ID No.*	Infant Age When Tested (Week)	Gestational Age at Delivery (Week)	Infant Weight at Testing (kg)	Average No. of Feedings per Day	Mother's Medication During Trimester III and Delivery (mg/day)	Mother's Medication During Lactation (mg/day)	Infant Serum Concentration (Metabolite) (ng/mL)†
Tricyclic antidepressants	1a‡	2.3	36.1	3.8	7-9	Desipramine 200	Desipramine 200	<25
	1b‡	14.9	36.1	6.9	7-9	Desipramine 200	Desipramine 200 Fluoxetine 20	<25 <20 (<20 Norfluoxetine)
	2	5.4	39.4	N/A	10-12	Desipramine 150	Desipramine 200	<20
	3	5.9	39.5	5.1	10-12	Imipramine 75	Imipramine 75	<25 (<25 Desipramine)
	4	17.0	37.0	5.9	10-12	Imipramine 10	Imipramine 150	<20 (<35 Desipramine)
	5	1.7	40.4	3.8	7-9	Nortriptyline 60	Nortriptyline 60	<25
	6	4.3	39.5	4.8	10-12	Nortriptyline 75	Nortriptyline 75	<20
SSRIs	7	11.9	40.0	5.7	4-6	Nortriptyline 75	Nortriptyline 75	<25
	8a	1.3	39.8	3.1	7-9	Fluoxetine 20	Fluoxetine 20	<25 (112 Norfluoxetine)
	8b	6.7	39.8	4.7	7-9	Fluoxetine 20	Fluoxetine 20	<25 (<25 Norfluoxetine)
	9	2.3	39.6	3.9	4-6	Fluoxetine 40	Fluoxetine 60	<50
	10	2.4	37.4	3.2	10-12	Fluoxetine 50	Fluoxetine 50	28 (250 Norfluoxetine)
	11	2.4	38.0	2.7	7-9	Fluoxetine 40	Fluoxetine 40	82 (53 Norfluoxetine)
	12a	3.0	39.8	N/A	7-9	Fluoxetine 40	Fluoxetine 60	76 (<25 Norfluoxetine)
	12b	6.4	39.8	N/A	7-9	Fluoxetine 40	Fluoxetine 80	60 (<25 Norfluoxetine)
	13a	6.0	40.4	4.3	10-12	Fluoxetine 20	Fluoxetine 20	<20 (21 Norfluoxetine)
	13b	10.0	40.4	4.9	10-12	Fluoxetine 20	Fluoxetine 20	<20 (<20 Norfluoxetine)
Benzodiazepines	14	6.1	39.4	3.2	10-12	Fluoxetine 20	Fluoxetine 20	<20 (38 Norfluoxetine)
	15	5.6	40.3	4.2	7-9	Paroxetine 30	Paroxetine 30	<20
	16	1.4	38.8	3.7	7-9	Clonazepam 0.75	Clonazepam 0.75	<5
	17‡	1.9	40.8	3.4	10-12	Clonazepam 0.5	Clonazepam 0.5	22
	18	3.0	40.5	3.4	7-9	Clonazepam 1.5	Clonazepam 1.5	<5
	19	6.9	40.4	5.5	4-6	Clonazepam 0.75	Clonazepam 1.0	<14
	20	44.0	39.0	9.5	7-9	Clonazepam 0-1.0	Clonazepam .75	<10
Combination	21	1.9	40	3.9	10-12	Clonazepam 0.25 Trifluoperazine 10 Valproic acid 500	Clonazepam 0.25 Trifluoperazine 10 Valproic acid 500	<5 1 <3.5 ng/mL
	22	2.0	38.8	2.6	10-12	Clonazepam 0.5	Clonazepam 0.5 Fluoxetine 20	<5 <25 (<25 Norfluoxetine)
	23‡	3.4	37.0	3.8	4-6	Clonazepam 2.5	Clonazepam 2.0	<5
	24	4.1	39.0	4.5	7-9	Nortriptyline 75 Fluoxetine 20	Nortriptyline 75 Fluoxetine 20	<25 <20 (48 Norfluoxetine)
	25	9.3	37.0	4.5	10-12	Clonazepam 1.0	Clonazepam 1.0 Valproic acid 500 Paroxetine 20 Clonazepam 1.5	<10 <5 <20 <5

* Letters a and b refer to first and second evaluation, respectively, of a given infant.

† Boldface type indicates infants with detectable concentration of a psychotropic medication or its metabolite.

‡ Hyperbilirubinemia at birth.

oxetine when retested. Clonazepam and trifluoperazine were also detected in 2 infants whose mothers took these agents during pregnancy and the puerperium. No adverse effects were reported by mothers of any of these infants. Neither medication nor metabolite was detected in infants whose mothers were treated with desipramine ($n = 3$), imipramine ($n = 2$), nortriptyline ($n = 4$), or paroxetine ($n = 2$).

Ten mothers were treated pharmacologically exclusively during the postpartum period. Results of assays of infant serum from this group of mothers are shown in Table 2. Of the 10 infants tested, none

had a detectable serum concentration of medication or metabolite. Mothers of these infants were treated with clomipramine ($n = 1$), desipramine ($n = 2$), fluoxetine ($n = 3$), sertraline ($n = 3$), and clonazepam ($n = 1$).

DISCUSSION

Anecdotal reports of infant adverse effects are described in cases in which children have breastfed while their mothers used psychotropic medications. These reports exist across classes of compounds including benzodiazepines, tricyclic antidepressants,

TABLE 2. Serum Drug Concentrations in Infants Whose Mothers Used Psychotropic Medications Exclusively During Lactation

Drug Class	Subject ID No.*	Infant Age When Tested (Week)	Gestational Age at Delivery (Week)	Infant Weight When Tested (kg)	Average Number of Feedings per Day	Mother's Medication During Lactation (mg/day)	Infant Serum Concentration (Metabolite) (ng/mL)
Tricyclic antidepressants	26a	7.7	39.0	5.0	7-9	Clomipramine 100	<20
	26b	12.4	39.0	5.5	7-9	Clomipramine 150	<20 Desmethylclomipramine
	27	12.3	36.0	N/A	4-6	Desipramine 150	<20 Desmethylclomipramine
SSRIs	28	33.1	39.1	5.9	0-3	Desipramine 37	<10
	29†	2.6	40.0	3.9	7-9	Fluoxetine 20	<20
	30	4.9	40.5	4.7	10-12	Fluoxetine 20	<40
	31†	6.9	41.0	5.7	4-6	Fluoxetine 10	(<40 Norfluoxetine)
	32	1.7	38.6	3.2	10-12	Sertraline 100	<20
	33	6.7	42.0	5.9	0-3	Sertraline 100	<5
	34	17.3	31.0	4.8	7-9	Sertraline 50	<5
Benzodiazepines	35	10.9	42.0	5.4	10-12	Clonazepam 0.75	<5

* Letters a and b refer to first and second evaluation, respectively, of a given infant.

† Hyperbilirubinemia at birth.

and older and newer SSRIs.^{42,43} However, systematic investigation of the safety of breastfeeding while using psychotropics is lacking.

Although all psychotropic medications are secreted into breastmilk,⁴⁴ infant absorption of these medications varies. Characteristics of a medication that determine the extent of its transport into breastmilk include molecular weight, protein binding, lipid solubility, ionization, pH, and half-life.¹⁰ Factors that affect the extent of infant exposure to medication taken by a lactating mother include individual medication characteristics, variability of maternal and infant metabolism, composition of breast milk, and timing of feedings.¹⁰ Wisner and Perel⁴⁵ describe the absence of medication in serum of 5 newborns whose mothers breastfed while taking nortriptyline, although the hydroxy metabolite of nortriptyline was noted in two of the samples (assay sensitivity <1-5 ng/mL). Wisner and colleagues¹⁹ also describe the absence of clomipramine and its metabolites in the serum of 4 infants whose mothers breastfed while taking this medication. Other investigators⁴⁶ have reported trace concentrations of SSRIs in the serum of 12 infants whose mothers used these agents while breastfeeding (assay sensitivity <1 ng/mL). One additional report²⁹ of a mother treated with sertraline while breastfeeding failed to detect drug levels in a newborn (assay sensitivity <0.5).

In the current series, medication or its metabolite was detected in 9 of 35 infants. Of these infants' mothers, 7 had been treated with fluoxetine during pregnancy and the postpartum period. Adverse effects were not reported in any of these infants. Although there have been reports of perinatal toxicity-associated fluoxetine use during pregnancy⁴⁷ and lactation,⁴⁸ no adverse effects were noted in any of the infants described in the current series. Other data supporting the absence of perinatal toxicity associated with fluoxetine use during pregnancy have been described more recently. Inconsistent findings regarding the risk for perinatal toxicity associated with use of this drug during pregnancy and/or lactation

may derive from the still relatively small numbers of exposures to this drug and to differential sensitivity to drug across infants. Use of fluoxetine during pregnancy was common in our sample given the abundant reproductive safety data available for this compound compared with other SSRIs. Fluoxetine has an elimination half-life of 4 to 6 days after chronic administration, and its active metabolite (norfluoxetine) has an elimination half-life of up to 16 days after chronic administration. These long elimination half-lives suggests that the potential exists for medication to be detected in newborns with histories of antenatal drug exposure. This might be observed for several weeks after delivery and depends on individual mother and infant characteristics, as well as maternal dosage and duration of treatment before delivery. Therefore, presence of fluoxetine in newborn serum during the acute postpartum period after maternal use of the medication during the third trimester of pregnancy is not surprising given the extended half-life of fluoxetine and norfluoxetine. However, the absence of higher infant plasma concentrations of antidepressant during retesting (infants 8, 12, and 13) is of interest. The absence of infant accumulation of fluoxetine/norfluoxetine in these particular infants suggests that postnatal exposure via breastmilk did not increase plasma concentrations of the drug or its metabolite. Because fluoxetine has a longer time to drug elimination after discontinuation of this compound compared with other SSRIs with shorter duration of activity that might clear infant plasma more quickly, treatment with SSRIs, at this time, is best guided by the amount of information available regarding reproductive safety and risk for perinatal toxicity,⁴⁹ which is extensive for fluoxetine.⁴⁹

Clonazepam has a relatively long half-life and was detected in an infant (infant 17) whose mother used the medication during the third trimester of pregnancy and in whom there also was evidence of immature infant hepatic function (hyperbilirubinemia). Both prematurity and medical conditions associated with immature hepatic metabolism are assumed to

increase likelihood of medication detection in infant serum when the mother has breastfed while using psychotropic medication.¹⁶ Clonazepam was not detected in the 9 other infants whose mothers used clonazepam during pregnancy and in the postpartum period. Neither fluoxetine nor clonazepam was detected in the sera of infants whose mothers were treated with these medications exclusively during the puerperium.

The current report is limited by lack of information regarding feeding schedule, as well as regarding time and duration of maternal dose. Varying infant age precluded meaningful calculation of intensity of infant exposure.⁴⁶ Data regarding the relationship between time of medication ingestion and the time of feedings also were not available. Infant serum concentrations of medication were obtained at various community and hospital-based laboratories with assays that differed in sensitivity, and the assay protocol was not standardized. Some infants were exposed to medication in utero, whereas others were not. Follow-up serum concentrations for infants who had detectable serum concentrations of medication were not always obtained. In addition, maternal serum levels of medications were not obtained to confirm compliance with prescribed regimens. Another limitation of this study was that maternal interviews regarding infant adverse effects were not standardized. Nonetheless, the current report describes the single largest series of cases in which mothers breastfed while using psychotropics and in which concentrations of medication in infant serum are described, in particular, the SSRI fluoxetine ($n = 12$ infants) and the benzodiazepine clonazepam ($n = 11$ infants). No readily noticeable infant adverse effects were reported by mothers across the sample. In addition, there was no evidence of infant accumulation of longer half-life medications such as fluoxetine or its metabolite norfluoxetine after retesting infants who were noted initially to have detectable drug (or metabolite) concentrations in serum during index screening. These data seem to support the low incidence of infant toxicity and adverse effects associated with antidepressant and benzodiazepine use during breastfeeding, particularly for fluoxetine and clonazepam which were used most commonly in our sample.

Decisions regarding whether women should breastfeed while using psychotropics must be made on a case by case basis. Properties of each medication as well as the renal and hepatic function of both infant and mother must be considered. Some investigators have suggested that immature infant hepatic function should be a relative contraindication to breastfeeding while taking psychotropic medication.¹⁶ Given the limited accumulated data regarding serum concentrations of psychotropic medications noted in children whose mothers are treated with these agents for postpartum illness, no single agent seems to be particularly safer than another with respect to risk for infant toxicity. Therefore, decisions regarding choice of medication for women who suffer from postpartum illness should be guided by the likelihood that its use will result in improvement of

maternal mood and functioning. Factors that may predict response to antidepressants include past or family history of response to a given medication. Lithium carbonate, which has been reported consistently to have relatively high concentrations in breastmilk, is an exception.⁵⁰ Its use during lactation is avoided frequently.

Women who are treated with psychotropic medications and who breastfeed should be counseled regarding the benefits of this activity and the small known risk of severe infant adverse effects as well as the unknown, but possible, impact on brain development. Women who choose to breastfeed while taking psychotropic medication should work collaboratively with a psychiatrist and a pediatrician. Infant serum should be assayed for the presence of medication after ~2 to 4 weeks. For women who have been treated with longer acting psychotropics such as fluoxetine during pregnancy, testing may be more informative at 6 to 8 weeks postpartum. This extension of the time of testing minimizes the likelihood of detecting residual medication (or its metabolite) derived from maternal use of the agent during pregnancy.

Most assays available from commercial and hospital-based laboratories have sensitivities ranging from 2 to 50 ng/mL depending on the medication being tested and the laboratory technique used. Pending greater routine availability of assays with heightened sensitivity compared with those used by most commercial and hospital-based laboratories, clinicians may use currently available assays foremost as a measure of potential toxicity. Although the results of these assays may not confirm an absolute presence or absence of medication in the infant, they may be helpful in ruling out situations in which there is idiosyncratic significant secretion of medication into breastmilk or an inability of the infant to metabolize psychotropic medication.

Whether women choose to stop breastfeeding when laboratories with extremely sensitive assays (ie, 1–2 ng/mL) detect small amounts of medication is a decision to be made collaboratively between the patient and the physician. The impact of untreated maternal depression on infants is well described and must be factored critically into any decision regarding the treatment of postpartum mood disorder. However, the possibility that chronic exposure to even very low doses or trace amounts of psychotropic medications during the infant period might affect longer term neurobehavioral development must also be considered and must be balanced with the wishes and needs of mothers and families. The latter issue is an important one. Currently, data are not available to support the conclusion that neonatal exposure to trace amounts of any particular medication is associated with different effect on the outcome variable of ultimate interest, namely long-term neurobehavioral function. Even if it could be demonstrated that maternal use of a particular SSRI was associated consistently with lower infant plasma levels of the medication, how the variable effects of these agents at the receptor translate into measurable differences in behavior is a subject about which it is

only possible to speculate at this time. Controlled, prospective neurobehavioral evaluation of infants of mothers who choose to breastfeed while taking psychotropic medications and for whom extent of exposure is well documented is needed and ultimately may help to refine our understanding of the risks and benefits of psychotropic medication use in postpartum women who wish to breastfeed.

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REFERENCES

- Cohen LS, Sichel DA, Dimmock JA, Rosenbaum JR. Postpartum course in women with preexisting panic disorder. *J Clin Psychiatry*. 1994;55:289–292
- O'Hara MW, Neunaber DJ, Zekoski EM. Prospective study of postpartum depression: prevalence, course, and predictive factors. *J Abnorm Psychol*. 1984;93:158–171
- O'Hara MW. Social support, life events, and depression during pregnancy and the puerperium. *Arch Gen Psychiatry*. 1986;43:569–573
- O'Hara MW, Schlechte JA, Lewis DA, et al. Controlled prospective study of postpartum mood disorders: psychological, environmental, and hormonal factors. *J Abnorm Psychol*. 1991;100:63
- Kendell RE, Chalmers JC, Platz C. Epidemiology of puerperal psychoses. *Br J Psychiatry*. 1987;150:662–673
- Klein DF. False suffocation alarms, spontaneous panics, and related conditions. *Arch Gen Psychiatry*. 1993;50:306–317
- 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
- Matheson I, Skjaeraasen J. Milk concentrations of flupentixol, nortriptyline and zuclopentixol and between-breast differences in two patients. *Eur J Clin Pharmacol*. 1988;35:217–220
- American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk. *Pediatrics*. 1994;93:137–150
- Riordan J. Drugs and breastfeeding. In: Riordan J, Auerbach KG, eds. *Breastfeeding and Human Lactation*. Boston, MA: Jones and Bartlett; 1993:135–152
- Cogill SR, Caplan HL, Alexandra H, Robson KM, Kumar R. Impact of maternal depression on cognitive development of young children. *Br Med J*. 1986;292:1165–1167
- Cohn JF, Tronick E. Specificity of infants' response to mothers' affective behavior. *J Am Acad Child Adolesc Psychiatry*. 1989;28:242–248
- Zuckerman B, Bauchner H, Parker S, Cabral H. Maternal depressive symptoms during pregnancy, and newborn irritability. *J Dev Behav Pediatr*. 1990;11:190–194
- Post RM. Sensitization and kindling perspectives for the course of affective illness: toward a new treatment with the anticonvulsant carbamazepine. *Pharmacopsychiatry*. 1990;23:3–17
- Ballenger JC. Pharmacotherapy. *J Clin Psychiatry*. 1986;47:27–32
- Wisner KL, Perel JM, Findling RL. Antidepressant treatment during breastfeeding. *Am J Psychiatry*. 1996;153:1132–1137
- Matheson I, Panele H, Alertsen AR. Respiratory depression caused by N-desmethyldoxepin in breast milk. *Lancet*. 1985;2:1124
- Lauder J. Neurotransmitters as growth regulatory signals: role of receptors and second messengers. *Trends Neurosci*. 1993;16:233–240
- Wisner KL, Perel JM, Foglia JP. Serum clomipramine and metabolite levels in four nursing mother-infant pairs. *J Clin Psychiatry*. 1995;56:17–20
- Wisner KL, Perel JM. Serum nortriptyline levels in nursing mothers and their infants. *Am J Psychiatry*. 1991;148:1234–1236
- Bader T, Newman K. Amitriptyline in human breast milk and nursing infants' serum. *Am J Psychiatry*. 1980;137
- Erickson S, Smith G, Heidrich F. Tricyclics and breast feeding. *Am J Psychiatry*. 1979;136:1483
- Brixen-Rasmussen L, Halgrener J, Jorgensen A. Amitriptyline and nortriptyline in human breast milk. *Psychopharmacology*. 1982;76:94–95
- Breyer-Pfaff U, Nill K, Entenmann A, Gaertner HJ. Secretion of amitriptyline and metabolites into breastmilk. *Am J Psychiatry*. 1995;152:812–813. Letter
- Stancer H, Reed K. Desipramine and 2-hydroxy-desipramine in human breast milk and the nursing infant's serum. *Am J Psychiatry*. 1986;143:1597–1600
- 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
- 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
- Ilett KF, Lebedevs TH, Wojnar-Horton RE, et al. The excretion of dothiepin and its primary metabolites in breastmilk. *J Clin Pharmacol*. 1993;33:635–639
- Altshuler LL, Burt VK, McMullen M, Hendrick V. Breastfeeding and sertraline: a 24 hour analysis. *J Clin Psychiatry*. 1995;56:243–245
- Griggs GG, Samson JH, Ambrose PJ, Schroeder DH. Excretion of bupropion in breast milk. *Ann Pharmacother*. 1993;27:431–433
- Aaes-Jorgensen T, Bjorndal F, Bartels U. Zuclopentixol levels in serum and breast milk. *Psychopharmacology*. 1986;90:417–418
- Blacker KH, Weinstein BJ, Ellman GJ. Mother's milk and chlorpromazine. *Am J Psychiatry*. 1962;119:178–179
- Brandt R. Passage of diazepam and desmethyldiazepam into breast milk. *Arzneim-Forsch*. 1976;26:454–457
- Burch KJ, Wells BG. Fluoxetine/norfluoxetine concentrations in human milk. *Pediatrics*. 1992;89:676–677
- Erkkola R, Kanto J. Diazepam and breast feeding. *Lancet*. 1972; i:1235–1236
- Frey B, Schubiger G, Musy JP. Transient cholestatic hepatitis in a neonate associated with carbamazepine exposure during pregnancy and breast-feeding. *Eur J Pediatr*. 1990;150:136–138
- Froesch W, Eichelbaum M, Niesen M, Dietrich K, Rausch P. Carbamazepine levels in breast milk. *Ther Drug Monit*. 1984;6:226–271
- Gelenberg AJ. Amoxapine, a new antidepressant, appears in human milk. *J Nerv Ment Dis*. 1979;167:635–636
- Patrick MJ, Tilstone WJ, Reavey P. Diazepam and breast feeding. *Lancet*. 1972; i:542–543
- Pynnonen S, Sillanpaa M. Carbamazepine and mother's milk. *Lancet*. 1975;1:63
- Summerfield RJ, Nielsen MS. Excretion of lorazepam into breast milk. *Br J Anaesth*. 1985;57:1042–1043
- Dahl ML, Olhager E, Ahlner J. Paroxetine withdrawal syndrome in a neonate. *Br J Psychiatry*. 1997;171:391–394. Letter
- Suri RA, Altshuler LL, Burt VK, Hendrick VC. Managing psychiatric medications in the breastfeeding woman. *Medscape Women Health*. 1998;3
- Llewellyn A, Stowe ZN. Psychotropic medications in lactation. *J Clin Psychiatry*. 1998;59:41–52
- Wisner KL, Perel JM. Nortriptyline treatment of breastfeeding women. *Am J Psychiatry*. 1996;153:295
- Stowe ZN, Owens MJ, Landry JC, et al. Sertraline and desmethylsertraline in human breast milk and nursing infants. *Am J Psychiatry*. 1997; 154:1255–1260
- Chambers CD, Johnson KA, Dick LM, Felix RJ, Lyons Jones K. Birth outcomes in pregnant women taking fluoxetine. *N Engl J Med*. 1996;335:1010–1015
- Spencer M. Fluoxetine hydrochloride (Prozac) toxicity in the neonate. *Pediatrics*. 1993;92:721–722
- Cohen L, Altshuler L. Pharmacologic management of psychiatric illness during pregnancy and the postpartum period. In: Dunner D, Rosenbaum J, eds. *The Psychiatric Clinics of North America Annual of Drug Therapy*. Philadelphia, PA: WB Saunders Company; 1997:21–60
- Schou M. Lithium treatment during pregnancy, delivery, and lactation: an update. *J Clin Psychiatry*. 1990;51:410–413

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