Psychotropic Medications in Lactation

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The use of psychotropic medications during lactation has not been investigated in a controlled and systematic fashion. The literature is laden with case reports and small case series containing numerous confounds that render the establishment of definitive treatment guidelines tenuous. The increasing number of women who plan to breast-feed and the high rate of psychiatric illness during the postpartum period underscore the need to develop such guidelines. A MEDLINE search was conducted for key words either in the titles or abstracts of publications citing the use of psychotropic medications in lactating women and describing the pharmacokinetics of medication excretion into breast milk. The publications identified span over three decades. The largest single study by one group of investigators examined 12 mother-infant pairs. The majority of studies report their results as a ratio of the breast milk concentration to the maternal serum concentration (milk/plasma [M/P]) ratio. Estimations that use the M/P ratio of the infant daily dose range from 0.1% to 6.2% of the maternal dose. Few studies attempt to account for the complex variations in the maternal, breast milk, and infant physiologic environments. The major confounds of the studies reviewed include (1) failure to document portion of breast milk assayed (foremilk versus hindmilk), (2) limited metabolite assay, (3) limited assay sensitivity (1–25 ng/mL), not of research quality, (4) concomitant maternal and/or infant medications, and (5) medication exposure during pregnancy. Despite these confounds, there are remarkably few reports of adverse effects on nursing infants exposed to psychotropic medications in breast milk. The limited data confirm that psychotropic medications are excreted into breast milk and that the infant is exposed to these medications. The ideal breast milk study that accounts for the confounds identified has not been completed. The complex matrix of breast milk and the changing infant metabolic capacity will require a more detailed analysis with assays of improved sensitivity. Despite the limited reports of adverse effects on nursing infants, the limitations of the available literature and minimal sample sizes make it premature to recommend specific medications from a given class. There is inadequate data on nursing infant exposure to multiple medications to support changing medication to a different agent in an otherwise stable patient. An individualized risk/benefit assessment with the empirical goal of minimizing infant exposure while maintaining maternal emotional health is the ideal approach.

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The American Academy of Pediatrics has described breast milk as the best and only source of nutrition necessary for newborns for the first 6 months of life.[1] Breastfeeding is supported by most of the professional organizations encountered by women during the antenatal and postnatal periods. The use of psychotropic medications during lactation involves a complex clinical decision that requires thoughtful consideration of the risk/benefit assessment of both treatment, which may include medications, and the impact of untreated maternal mental illness. The majority of pregnant women plan to nurse postpartum; their reasons may include (1) medical benefits of breastfeeding, (2) social pressure, (3) a perception of enhanced mother-infant bonding, and (4) economics. However, maternal plans are often disrupted by new onset or aggravation of psychiatric symptoms that may require treatment with psychotropic medications.

Although the use of psychotropic medications during both pregnancy and lactation has been extensively reviewed,[2–21] the use of pharmacologic interventions specifically during breastfeeding remains an understudied and controversial topic.[22–26] Pregnancy and postpartum are distinct metabolic and developmental periods, and no studies support the extrapolation of data from in utero exposure to

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breast milk exposure. Clinical decisions are further complicated by the lack of definitive treatment guidelines and a body of literature predominantly composed of case reports. We include studies that report infant serum assay or demonstrate the complexity involved in the accurate determination of nursing-infant exposure. Clinical interpretation of the existing and forthcoming data requires an appreciation of the physiologic systems involved. This article describes the pharmacokinetics of medications in breast milk, addresses the benefits of breastfeeding, and reviews the effects of psychotropic medications on nursing infants. We argue for infant monitoring, indicate facets of a careful risk/benefit assessment, and discuss guidelines for selecting a medication and minimizing infant exposure.

PHARMACOKINETICS

The pharmacokinetics of medication excretion into breast milk and ultimately the infant's exposure to a medication can be conceptualized in three components[24]—the mother, breast milk, and infant—each of which changes and matures independently. The amount of medication available to enter the breast milk is dependent on several maternal factors, including (1) maternal rate of drug metabolism, (2) maternal volume of distribution, (3) medication dosing schedule, (4) breastfeeding schedule, and (5) the bioavailability of the medication in her circulation. The physiologic changes associated with pregnancy demonstrate variability in returning to prepregnancy states after childbirth. Medications ingested by a nursing mother enter the bloodstream, where the free non-protein-bound portion will readily pass into breast milk. The individual physicochemical properties of a medication appear to be the best predictors of medication concentrations available in the breast milk.[12] The lipid solubility of an agent typically determines how quickly molecules diffuse into breast milk; more lipophilic medications will diffuse more readily into the milk.[9,22] The molecular weight (MW) of some medications may limit their crossing into the alveolar ducts, though such passive diffusion is typically not a significant factor for psychotropic medications (MW < 500). The amount of a medication available for passage into milk is also determined by the dosage and frequency of medication administration, the rate of absorption of the medication in the mother, and the blood flow to the breast. The maternal serum concentration typically varies after oral ingestion, and the limited number of studies demonstrate a time course for excretion. The major determinant in the breast milk concentration of a medication is the milk composition, which changes with maturity and demonstrates a gradient in lipid content.[22]

Breast milk is a unique fluid that undergoes marked alteration in composition over the course of time. Milk pH is lower than plasma pH, causing weak acids to diffuse slowly and weak bases to diffuse more readily into breast milk. The pK_a of small molecular compounds diffuses down the concentration gradient between the plasma and breast milk. Organic bases, such as ones that are found in many central nervous system agents, become ionized under acidic conditions, and the lower breast milk pH can cause these agents to become trapped in the milk. The composition of breast milk includes protein and lipids that demonstrate a gradient, with the higher concentrations of lipids being in the later portion (hindmilk). Our group has reported that such a gradient has profound effects on the concentration of antidepressants in breast milk, with the higher concentrations being found in hindmilk.[27]

The milk/plasma (M/P) ratio provides a relative assessment of breast milk concentrations of a particular medication. However, providing an accurate comparison of medications will require controlling for both the aliquot (fore/hind milk) and the time after maternal dose to determine the utility of the breast milk concentration.[16] The M/P ratio is variable over time secondary to the changes noted above, and the infant's exposure is directly related to the breast milk concentration and not the M/P ratio.

The neonate possesses a physiologic system that is metabolically immature and continually changing. The newborn is less able than adults to metabolize and excrete most medications. Newborns lack many of the metabolic enzymes of an adult, and metabolites compete for the available enzymes.[22] Both oxidation reactions and glucuronidation are immature and develop at variable rates.[28,29] In the neonate, the glomerular filtration and tubular secretion rates are slower than those of adults, possibly leading to a higher serum steady-state concentration or even accumulation of medications in the infant over time.[8,22] The infant gastrointestinal tract has a higher gastric pH, a changing microbial environment, and a slower bowel motility and elimination rate, thereby producing more irregular and unpredictable absorption.[8,30] The bioavailability of medications is altered in the infant secondary to the different pathophysiologic composition in the bloodstream and altered plasma protein binding.[31] The decreased protein binding in the infant increases the serum concentration of free drug in the infant.[30] The infant has a different volume of distribution and a higher permeability of tissues and organs that may create higher tissue concentrations of a medication. It is of concern that the infant may be capable of producing different metabolic products than adults, as in the case of chlorpromazine.[28]

In summary, the determinants of the actual infant daily exposure to a given medication are highly variable and may contribute to higher infant serum concentrations at steady state. Earlier reviews have utilized terms such as *accumulation* and *toxicity*, but our review of the literature does not find their use substantiated. To demonstrate accumulation, repeated infant serum analyses would be needed to confirm increasing serum concentrations. The few studies of adverse effects on nursing infants report findings

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consistent with the side effect profile of the medication, not with acute toxicity. The infant data[32] on vitamins, anticonvulsants, and psychotropic medications suggest that infants achieve serum concentrations that are considerably higher than would be predicted from daily dose estimations and that may even exceed maternal serum concentrations. The potential for elevated steady-state concentrations in infants compared with adults underscores the need to perform infant serum monitoring and to educate parents about potential side effects. These issues are detailed later in this review.

This complex system and the recommendation for infant monitoring must be considered in the review of emerging data and in the risk/benefit assessment. Equally important are the well-documented benefits of breastfeeding for both the infant and mother.

BENEFITS OF BREASTFEEDING

Maternal

Breast milk is portable, economical, and resistant to spoilage while in the breast. Breastfeeding has psychological, physiologic, and possibly preventative benefits for the mother. The sense of enhanced bonding has not been studied in a systematic fashion, but the mother's perception of nursing should be included in treatment planning. Nursing stimulates uterine contractions, as in coitus, and some women report orgasm associated with nursing. Elevated prolactin associated with lactation delays the return of ovulation by inhibiting the ovarian response to follicle-stimulating hormone, and suckling-stimulated oxytocin release promotes uterine contractions contributing to involution of the uterus after delivery.[33] One group[34] reports a decreased incidence of breast cancer in premenopausal women with a longer duration of breastfeeding. The potential maternal benefits of breastfeeding warrant further study. Several women report that breastfeeding also assisted them in losing weight postpartum (Z.N.S. 1997. Unpublished data). In addition, considerable literature documents the short-term and potentially long-term benefits to the neonate.

Infant

Numerous studies have demonstrated the immunologic benefits of breast milk to the infant. A retrospective cohort study with 776 mothers at 6 months postpartum matched for infant age, socioeconomic status, maternal age, and cigarette consumption found that breastfeeding had a protective effect against gastrointestinal illness, respiratory illness, and all other illness in the infants except trauma.[35] The decreased incidence of otitis media associated with breastfeeding has been documented by several groups. Duncan and colleagues[36] reviewed the pediatric records of 1220 infants and found that exclusive breastfeeding for at least 4 months protected infants from both single and recurrent otitis media. A second group[37] proposes that the reduction of otitis media in breastfed babies could be related to (1) reduced exposure to microorganisms, (2) improved nutrition, and/or (3) antibacterial qualities of breast milk, possibly related to interference of attachment of Haemophilus influenzas and Streptococcus pneumonias to nasopharyngeal epithelial cells. These antiadhesive properties may further protect against infections elsewhere in the body as well. Breastfeeding significantly reduced the rate of urinary tract infections during the first month of life, possibly related to an oligosaccharide in the urine of breastfed infants that causes inhibition of Escherichia cold adhesion to uroepithelial cells.[38,39] Follow-up IQ testing at 7.5 to 8 years of age of children born prematurely demonstrates that IQ scores in the preterm infants who were breastfed had an 8.3-point (over half a standard deviation) advantage over nonbreastfed infants.[40] These data suggest that breast milk may have both immunologic and neurodevelopmental advantages to a child.

STUDY LIMITATIONS

A controlled study of psychotropic medication in breastfeeding will most likely never be conducted; hence the clinician will have to base a treatment decision on limited information. Prior to any interpretation of the literature, the clinician should be familiar with the potential confounds prevalent in the available breast milk data and the limitations that will exist in future studies. These limitations include (1) estimation of infant dose based on breast milk samples and time samples were taken after maternal dose of medication, (2) no control for maturity of breast milk, (3) limited analysis of active metabolites, (4) variations in assay sensitivity, and (5) major confounds in infant follow-up data.

Significant confounds in the evaluation of nursing infants exposed to psychotropic medication are (1) the use of medications during pregnancy, (2) concomitant medications while breastfeeding, and (3) cigarette smoking. Ninety-five percent of breastfeeding mothers take at least one medication during the first postpartum week, 17% to 25% of mothers take medications in the 2 weeks surrounding their fourth postpartum month, and up to 5% of mothers will take at least one medication throughout the entire breastfeeding period.[30,41] Cigarette smoking has an adverse impact on infant development, such as an increased incidence of attention-deficit/hyperactivity disorder (ADHD).[42] One group[43] found that 20% to 35% of breastfeeding mothers smoked cigarettes. Two final points to consider are (1) the sensitivity of the assays—the term *undetectable* indicates the limits of the technique; medication may still be present; and (2) the bias of case reports toward adverse effects that may not represent a broad clinical experience. These issues should be considered in reviews of the literature and future studies.

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EFFECTS OF PSYCHOTROPIC MEDICATIONS ON NURSING INFANTS

A recent review[25] focused on nursing infant serum concentrations during maternal treatment with antidepressants. The majority of the literature on breastfeeding and infant serum concentrations involves antidepressants, particularly the tricyclic agents.

Tricyclic Antidepressants (TCAs)

Several reports[44–48] on the use of amitriptyline during breastfeeding found detectable concentrations of amitriptyline and nortriptyline in the breast milk of women taking 75 to 175 mg/day. Infant serum analysis failed to find detectable concentrations of either amitriptyline or nortriptyline with assay sensitivity of 5 to 14 ng/mL. These authors reported no adverse effects in the nursing infants. One group[45] demonstrated M/P ratios for nortriptyline (0.74) and (*E*)-10-hydroxynortriptyline (0.70) and concluded that the metabolites of amitriptyline bind less to both plasma and milk proteins than those of nortriptyline.[45] Similarly, Pittard and O'Neal[48] found a lower M/P ratio for nortriptyline than for amitriptyline and suggested that hepatic reduction into more water-soluble substances may account for this difference.

Clomipramine is the only antidepressant listed as compatible with breastfeeding in the American Academy of Pediatrics Report.[1] A woman treated with 125 mg/day of clomipramine during pregnancy delivered an infant described as having mild hypotonia, tremor, respiratory acidosis, and airtrapping, all of which resolved at 6 days of age.[49] The same infant was breastfed and remained asymptomatic. Maternal and infant serum and breast milk samples were obtained at delivery and 4, 6, 10, 14, and 35 days postpartum. Detectable concentrations of clomipramine, which declined from delivery to achieve a level approximately 6% of the maternal serum concentrations over the course of breastfeeding, were found in the infant. These data suggest that accumulation did not occur and that pregnancy exposure can alter initial infant serum concentrations. The author calculated that if the infant ingested 1000 mL/day of breast milk and the mother took 150 mg/day of clomipramine, the infant dose of clomipramine would be 0.4% of the maternal dose. In four women treated with 75 to 125 mg/day of clomipramine, infant serum concentrations, collected after 3 weeks of stable maternal dose, were below the assay sensitivity of 10 ng/mL for the three metabolites of clomipramine *N*-desmethylclomipramine, 8-hydroxyclomipramine, and 8-hydroxydesmethylclomipramine.[50] All four infants were described as developing normally.

In contrast, a case report[51] on doxepin exposure during breastfeeding described suspected respiratory depression in an 8-week-old infant that temporally correlated with an increased maternal dose. Breastfeeding was discontinued, and the infant's respiration normalized within 24 hours. Consistent with the absorptive phase, peak breast milk concentrations of doxepin and *N*-desmethyldoxepin were observed at 4 to 5 hours after maternal dose and minimum concentrations observed prior to oral dose at 23 to 24 hours. Based on 150 mL of breast milk/kg of infant weight, the infant daily dose was 0.3% of the maternal dose.[28,29] However, infant serum concentrations of *N*-desmethyldoxepin were comparable to maternal levels, with a detectable concentration of doxepin (3 μg/L). A second report[52] obtained maternal and infant plasma and breast milk samples of doxepin and *N*-desmethyldoxepin during an 8-week period.[52] Plasma taken from the infant after 43 days of exposure to the medication showed no detectable concentrations of doxepin (< 5 $\mu g/L^{-1}$) and *N*-desmethyldoxepin (15 $\mu g/L^{-1}$). These authors calculated that the infant would receive 2.2% of the maternal doxepin dose. Discordant reports such as these underscore the need for infant monitoring.

Stancer and Reed[53] measured desipramine and its metabolite, 2-hydroxydesipramine, in the milk and plasma of an infant and his mother, who was treated with 300 mg/day of desipramine and held at this dose for 1 week at the commencement of sampling. Concentrations in the maternal plasma and breast milk were similar, with serum ratios between the parent and metabolite compound of 0.9 and 0.9 and for the milk 1.2 and 1.0. Neither compound was detected in the 10-week-old infant's serum. The authors calculated that a 4-kg infant would ingest about 1/100 of the maternal dose in a 24-hour time period. No adverse effects were noted in the infant after 3 weeks of exposure.

The largest collection of infant serum measures conducted by a single group is 12.[54,55] The women were treated with 50 to 110 mg/day of nortriptyline, and infant sera were analyzed for nortriptyline and its metabolites, (*E*)-10-hydroxynortriptyline and (*Z*)-10-hydroxynortriptyline. No nortriptyline was detected in any of the infant samples, and 10-hydroxynortriptyline was detected in only two infant sera. The group reported that the parents and pediatricians described these infants' development as normal. The maternal serum concentrations of nortriptyline were as high as 201 ng/mL, and after 50 days of exposure there was no evidence of rising serum concentrations in the breastfed infants. Similarly, Altshuler and colleagues[56] reported on a woman treated with nortriptyline and sertraline; the authors were unable to detect either compound in the infant serum.

Serotonin Selective Reuptake Inhibitors (SSRIs)

The serotonin selective reuptake inhibitors (SSRIs), like the tricyclic agents, have been used in a wide variety of psychiatric illnesses and are all excreted into breast milk. The published data on infant serum concentrations are limited.

Fluoxetine demonstrates a time course of excretion into breast milk that parallels the absorptive phase from the

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gut.[57] In a lactating woman treated with 20 mg/day of fluoxetine for postpartum depression, no adverse effects were noted in the baby's behavior or nursing patterns, and after 2 months of exposure the infant was described as having normal development.[58] No infant serum concentrations were reported. In contrast, a father who is a pediatrician described increased irritability in his son during the initial 2 weeks of nursing exposure to fluoxetine. Still, the infant continued with normal weight gain and achieved all developmental milestones for his age.[59] Lester and colleagues[60] reported a case of colic in a 6-week-old infant whose mother continued to breast-feed while taking 20 mg/day of fluoxetine. The mother kept a diary of the infant's behavior and reported increased crying, decreased sleep, increased vomiting, and watery stools when the infant was exposed to fluoxetine via breast milk. The breast milk concentration of fluoxetine was 69 ng/mL and of norfluoxetine, 90 ng/mL. The infant's serum contained 340 ng/mL of fluoxetine and 208 ng/mL of norfluoxetine. The author suggested that this case may represent potential adverse side effects in a nursing infant due to fluoxetine exposure in breast milk.

In a recent publication, Mammen et al.[61] reported on three nursing infants exposed to sertraline. They found very low concentrations of desmethylsertraline using a highly sensitive assay, and no adverse effects were reported. Our group[27] completed a detailed study of the pharmacokinetics of sertraline excretion into breast milk and nursing infants (N = 12) and demonstrated both a gradient from foremilk to hindmilk as well as a significant time course for excretion into breast milk. Only 3 of the 12 infants had detectable concentrations of sertraline, and no adverse effects were noted. Another group (Birnbaum C. 1997. Unpublished data) has collected serum samples from nursing infants exposed to fluoxetine and sertraline. Detectable concentrations of fluoxetine were found only in those infants exposed during pregnancy. No adverse effects on the nursing infants were observed. Additional reports[62,63] for the remaining SSRIs have not included infant serum measures but have estimated infant dose to be 0.5% of the maternal dose for fluvoxamine and 0.34% of the maternal dose for paroxetine.

Stowe et al.[27] recently analyzed the absorption of sertraline and desmethylsertraline into human breastmilk, examining both gradient and time course. Twelve maternal-infant serum pairs were studied. The majority of the infant samples were below the levels of detection (< 1 ng/mL), and no adverse effects on these infants were noted.

Other Antidepressants

Although a lactating mother taking 100 mg of bupropion three times a day evinced M/P ratios markedly higher than those produced by the use of other psychotropic medications, infant serum collected 3.67 hours after the last breastfeeding and 9.5 hours after the mother's last dose revealed no measurable amount of bupropion or its metabolites at an assay sensitivity of .005 μg/mL.[64] This single report noted no adverse effects or changes in the infant, though bupropion treatment continued for only 1 week after the sampling.

The monoamine oxidase inhibitors (MAOIs) are not often used as first-line treatment in lactating mothers secondary to dietary constraints and potential for hypertensive crisis.[7] Pons et al.[65] examined the use of moclobemide, a reversible monoamine oxidase-A inhibitor, in breastfeeding women to measure the time-course of the medication and its metabolites in breast milk. They found the peak concentration at 3 hours after maternal dose, and 12 hours postdose breast milk concentrations were undetectable. This study was conducted for six lactating women who received a single 300 mg dose within 3 to 5 days postpartum, and no comment on continuing treatment or infant exposure was made.

In summary, the majority of antidepressant studies have documented limited infant sampling. In those studies that assessed infant serum concentrations, these values were typically below the limits of detection of the assay. With the exception of the single reports noted for doxepin and fluoxetine, no acute adverse effects were described.

Anxiolytic Medications

The most commonly prescribed class of medications for the treatment of anxiety is the benzodiazepines. In reviewing the literature on the use of these agents during lactation, it was readily apparent that the data were derived from a mixture of both chronic daily exposure and multiple single exposures seen with as-needed use. Literature exists on many of the benzodiazepine-derivative antianxiety medications in lactation. It is noteworthy that the data on breastfeeding and benzodiazepine use support the majority of hypotheses concerning the pharmacokinetics of excretion and infant metabolism.

Fisher and colleagues[66] reported on a mother who took clonazepam during pregnancy and lactation. The infant was born at 36 weeks gestation with apnea, cyanosis, and hypotonia that all resolved by 10 days postpartum. The mother continued her clonazepam treatment and nursed from Day 3 postpartum until Day 14 postpartum. The breast milk concentrations of clonazepam, taken at several points, were between 11 and 13 ng/mL of the medication. The infant serum, collected at 120 hours after delivery, contained 2.9 ng/mL of clonazepam, and on postpartum Day 14 the concentration had declined to 1 ng/mL. The infant experienced episodes of apnea that resolved after 10 weeks postpartum, and the infant was reportedly normal from a neurodevelopmental standpoint at 5 months postpartum. Because a significant amount of clonazepam crosses the placenta, the authors recommended that any infant exposed to clonazepam during pregnancy or breastfeeding be monitored for apnea or central nervous

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system depression. In another report,[67] a mother was treated with 2 mg of clonazepam and 200 mg of phenytoin twice daily during both pregnancy and lactation. The group tested 10 mL of her foremilk, 10 mL of her hindmilk, her blood, and her infant's blood on postpartum Days 2, 3, and 4. The lower limit of their assay sensitivity was 3.2 μg/L. The highest clonazepam concentration in breast milk was found 4 hours post maternal dose at 10.7 μg/L. Based on the estimation that an infant ingests 0.15 mg/kg of his or her own body weight daily, the authors calculated that an infant would ingest a maximum of 2.5% of the maternal weight-adjusted dose of clonazepam. The infant's serum taken on Days 2 through 4 was mixed, and 4.7 μg/L of clonazepam was found. The authors of this latter study found that the additional medication, phenytoin, may have served as a protective factor for the clonazepam by inducing liver enzymes. The group reported[68] that induced liver enzymes in 18 infants caused the half-life elimination of clonazepam to be similar to adult elimination rates.

The infant of a breastfeeding mother treated with 10 mg of diazepam three times a day experienced lethargy and weight loss.[69] Infant urine tested positive for oxazepam, and the infant's electroencephalogram showed patterns consistent with the use of a sedative medication. Due to the limits of sensitivity, the assay run on the breast milk could not detect the level of diazepam or oxazepam in the breast milk. Erkkola and Kanto[70] studied diazepam and the primary metabolite, 10-desmethyldiazepam, in the mother, the breast milk, and the baby. Three patients were treated with 10 mg of diazepam three times a day. On the fourth and sixth postpartum days, samples were collected. The breast milk concentrations of diazepam and 10-desmethyldiazepam increased from Days 4 to 6. Significantly larger amounts of diazepam and *N*-desmethyldiazepam were found in the maternal serum than in either the breast milk or the infant serum. No free oxazepam was detected in any of the media. No lethargy or hypoventilation was observed in these three infants. The authors note that babies with any kind of distress may be more susceptible to potential adverse effects. The authors also note that the competition between bilirubin and diazepam in the metabolic pathway may cause neurologic damage or possibly kernicterus; hyperbilirubinemia has been observed in infants whose mothers took diazepam before labor.

Morselli et al.[71] studied the effect of diazepam on premature and full-term infants, and children. They found a decreased ability to hydroxylate diazepam and a decreased ability to excrete other metabolites of diazepam in premature and full-term infants compared with adults. Diazepam was administered to the subjects at a dosage of 0.3 mg/kg. Blood and urine assays were conducted for the presence of diazepam, oxazepam, and *N*-desmethyloxazepam. Diazepam concentrations were higher and present longer in premature infants than in children. Further evidence of delayed clearance is provided by Eliot and colleagues,[72] who showed that even after a single dose of diazepam to a mother in labor, both diazepam and desmethyldiazepam can be detected in the infant at 10 days postpartum. Another group[73] treated nine nursing mothers with diazepam and collected breast milk, maternal serum, and infant serum. Three cases of mild jaundice were noted, though this is not an unusual number of cases. Maternal milk and plasma levels of diazepam and desmethyldiazepam averaged a 2:1 ratio. Both compounds were found in all fluids in all subjects. A significant level was found on the 10th postpartum day in one infant whose mother had received a dose of diazepam during delivery. Dusci et al.[74] studied a case of a woman taking high doses of diazepam and oxazepam. Her breast milk levels, her plasma levels, and her 1-year-old nursing infant's plasma levels of diazepam, *N*-desmethyldiazepam, temazepam, and oxazepam were examined. Ratios of the following maternal plasma to milk levels were found: diazepam 0.2, *N*-desmethyldiazepam 0.13, temazepam 0.14, and oxazepam 0.10. The authors calculated on a mg/kg^{-1} basis that the infant received 4.7% of the maternal dose. Readily detectable concentrations of *N*-desmethyldiazepam (20 and 21 $\mu g/L^{-1}$), temazepam (7 $\mu g/L^{-1}$), and oxazepam (7.5 and 9.6 $\mu g/L^{-1}$) were found in the infant's serum. The infant did not show adverse physical or mental sequelae of benzodiazepine intoxication.

The excretion of other benzodiazopines into human breast milk has been demonstrated, but studies did not include infant serum analysis.

Sedative Hypnotic Medication

Lebedevs and colleagues[75] studied breast milk and maternal and infant serum levels for temazepam in 10 mother-infant pairs. Temazepam (10–20 mg dose) was given at bedtime for at least 2 days before samples were taken. The amount of medication found in the maternal serum was comparable to steady-state concentrations of the medications. The study mentioned that several of the women were taking other medications and that the time of sampling was within 2 weeks postpartum, a time of breast milk composition variability. The M/P ratio for the samples was 0.12 in one of the ten patients and ranged between < 0.09 and < 0.63 in the other patients. Milk concentration was below the level of detection, 5 $\mu g/L^{-1}$, in several samples. The assay also tested for oxazepam, which was below the limits of detection for all the samples assayed. The researchers noted that infants are less able to eliminate temazepam by the adult method of glucuronidation and that it may be eliminated at three to four times the adult elimination rate. Even if the medication were ingested, at the ratios seen it is likely that the infant would receive negligible amounts of temazepam.

Zolpidem, a hypnotic, sleep-inducing medication, acts on the omega-1 receptor sites. The excretion of this medi-

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cation into breast milk was examined by Pons et al.[76] Five women received a single 20-mg dose 30 minutes after dinner. Milk and maternal plasma levels were taken 17, 7, and 4 hours before dosing and at 1.5, 3, 13, and 16 hours after dosing. The half-life elimination was 2.6 hours. The amount of medication found in the breast milk ranged from 0.004% to 0.019% of the ingested dose. The M/P ratio was measured at 3 hours after dose, and the average clearance rate was 1.48 mL/hour. This medication has rapid onset, a short half-life, and rapid absorption; the indication is that most of the zolpidem excretion in the breast milk took place within 3 hours after maternal dose. No infant serum concentrations were obtained, and the authors did not report any adverse effects.

Mood Stabilizers

The use of mood stabilizers is not limited to patients with bipolar disorder but may also include augmentation strategies in patients with other neuropsychiatric conditions. Most studies of these patients typically involved exposure during pregnancy, confounding infant assessment for adverse events related to breastfeeding.

Goldfield and Weinstein[77] suggested that lithium not be used in breastfeeding women, because the levels in the breast milk approach the levels found in the maternal serum. They cautioned against potential dehydration of the infant and the potential slowed and less effective excretion of lithium by the newborn. Schou and Amdisen[78] studied the amount of lithium in the serum of infants whose mothers were taking lithium while lactating and found that the lithium concentration in breast milk was approximately half the concentration found in the maternal serum. They also examined infant serum and found that, during the first postpartum week, the infant serum concentration was about 50% of the mother's serum concentration, and after the first week, it declined to about 33% of the maternal serum concentrations. Sykes et al.[79] reported on a woman who had been taking 800 mg/day of lithium carbonate and learned of her pregnancy at 8 weeks gestation. The woman's dose was reduced twice during pregnancy. The infant was mildly hypotonic for 2 days after birth. The mother chose to breast-feed. The infant serum lithium level was similar to the mother's serum level at birth but fell to 0.03 mmol/L by the sixth postpartum day and increased slightly once breastfeeding was established. The mother's serum and breast milk concentrations rose, but there was not an appreciable increase in the infant serum concentration. The infant was assessed as having normal development. The author noted that breastfeeding was stopped at 10 weeks postpartum due to the known inhibiting effect lithium has on 3'5'-cyclic adenosine monophosphate and the potential risk of this factor on the infant's still-developing brain. Linden and Rich[80] stated that infants who are receiving lithium through breast milk should be monitored for hypotonia, lethargy, and cyanosis. The use of lithium during breastfeeding has been repeatedly discouraged in the literature. While the data are limited, evidence suggests that management of women taking lithium while breastfeeding warrants careful monitoring of the infant's hydration status.

In contrast, both valproate and carbamazepine are considered compatible with breastfeeding by the American Academy of Pediatrics.[1] Alexander[81] reported on a woman who took sodium valproate in pregnancy and continued this treatment while breastfeeding. The serum concentration of valproate in the infant was similar to the mother's level at delivery but fell to purportedly insignificant levels by the fifth postpartum day and was below the limits of detection at 29 days postpartum. Valproate was present in the breast milk on the fifth day postpartum at 50 mmol/L and fell to 21 mmol/L by postpartum Day 29. The authors suggested that sodium valproate would be found in the breast milk at a level 5% to 10% of the maternal serum level. No adverse sequelae were noted in the infant as a result of the breast milk exposure to valproate.

Transient cholestatic hepatitis in an infant, caused by carbamazepine use in pregnancy and lactation, was documented by Frey et al.[82] The infant's mother was taking 200 mg of carbamazepine three times daily during pregnancy and the postpartum period. The child was admitted to the hospital at 3 weeks postpartum due to persistent jaundice and was found to have cholestatic hepatitis. This condition resolved after nursing was discontinued. Carbamazepine-induced hepatitis has been noted previously in adults and children treated with the medication. M/P ratios of 0.24 to 0.69 have been reported, along with infant serum concentrations of 1.7 μmol/L.[32] This condition may be a risk for infants exposed to carbamazepine through breast milk. Merlob and colleagues[83] reported a case of an infant exposed to carbamazepine in utero and through breast milk. The mother received 400 mg/day of carbamazepine throughout pregnancy and the postpartum period. Jaundice was noted in the infant on the first day of life. The hepatic enzyme levels were normal, with the exception of a very high gamma-glutamyltransferase that decreased slowly in the following postpartum days. The infant was fed only breast milk for 9 days, when supplemental feeding was added. On postpartum Day 2, carbamazepine concentrations were 5.5 μg/mL in maternal serum, 2.8 μg/mL in the breast milk, and 1.8 μg/mL in the infant serum. On postpartum Day 63, concentrations were 6.5 μg/mL in the maternal serum, 2.2 μg/mL in the breast milk, and 1.1 μg/mL in the infant serum. The infant appeared to be developing normally at 2-, 4-, and 6-month follow-up visits.

Antipsychotic Medications

The recent review by Altshuler and colleagues[56] suggests that the aliphatic phenothiazines may have adverse effects when used during pregnancy. A common side effect of typical antipsychotic agents is increased prolactin

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and, in some cases, galactorrhea. Despite the availability of antipsychotic medications for over 4 decades with no clear adverse impact on milk production, remarkably limited data on their excretion into breast milk and sparse infant serum assessments are available.

Blacker et al.[84] reported the breast milk and maternal plasma concentrations of a woman initially treated with a single dose of 1200 mg of chlorpromazine. A blood sample was taken before the initial dose, and then at 30, 60, 90, and 180 minutes postdose. Breast milk samples were obtained at 60, 120, and 180 minutes postdose. The peak plasma concentration of 0.75 μg/mL was found at the 90-minute postdose collection. The peak milk level was 0.29 μg/mL, found at the 120-minute postdose collection. From this information, the group calculated that the 7-pound baby would receive a 3 μg/kg daily dose. The woman was continued on chlorpromazine therapy, and her dosage was changed to 600 mg twice a day. This change in dosage resulted in the plasma and milk sample concentrations being lowered below the group's assay sensitivity. The group suggested that splitting dosing may result in lower concentrations of chlorpromazine in the breast milk and perhaps enhanced safety to nursing infants. Wiles and colleagues[85] also evaluated plasma and milk sample concentrations of chlorpromazine in four lactating mothers. Chlorpromazine was found in all samples with a range of 7 to 98 ng/mL. Metabolites were also found in the samples; 7-hydroxychlorpromazine was found in two subjects, monodesmethylated chlorpromazine was found in one sample, and chlorpromazine sulfoxide was found in all four samples. Plasma concentrations were lower than breast milk levels in two patients. Only two of the mothers were actually breastfeeding. One of these mothers reported no adverse effects (milk level of 7 ng/mL), but the second mother reported drowsiness and lethargy in her infant (milk level of 92 ng/mL). Mothers who nurse while taking chlorpromazine should monitor their infants for side effects.

Olesen et al.[86] reported on a case of the neuroleptic medication perphenazine and lactation. A mother was given 12 mg of perphenazine twice a day for postpartum psychosis. The dose was reduced to 8 mg twice a day due to maternal side effects and high serum concentrations of the medication. The group measured the breast milk and serum of the woman at both of these doses of medication at different time intervals. Maternal serum and milk levels increased and decreased congruently, and levels were similar at all intervals. The mean M/P ratios were 0.7 and 1.1. Based on the results of their comparison between the milk and serum concentrations, they calculated that the infant would receive about 0.1% of the maternal dose of perphenazine. The child continued to breast-feed during the mother's entire 3.5-month course of perphenazine treatment and showed normal development, with no signs of adverse medication effects.

A few studies exist on haloperidol excretion in breast milk. The first study was done by Stewart and colleagues.[87] They found breast milk concentrations of haloperidol in one woman to be 5 ng/mL, 11 hours after a 6-day average 29.2 mg/day dose, and breast milk concentrations on the 12th day were 2 ng/mL 9 hours after a 12-mg dose. The woman took 7 mg/day of haloperidol from Day 13 to Day 19 and then discontinued the medication. Three days after discontinuation, no haloperidol could be detected in her breast milk. The group calculated that an infant ingesting 0.5 to 1.5 liters of milk per day, based on the levels above, would receive a maximum dose of 0.0075 ng/day of haloperidol. Whalley et al.[88] also studied haloperidol excretion in a woman taking 5 mg twice a day. Her infant continued to breast-feed during maternal treatment. On the 16th postpartum day the mother began taking 100 mg/day of chlorpromazine, which continued for 4 days. This therapy did not appear to be effective so she was treated with haloperidol. Maternal plasma and breast milk samples were obtained on the 1st, 6th, 7th, and 21st days after haloperidol treatment began. The milk concentrations ranged from 0 to 23.5 μg/L. In contrast to the earlier report, the author concluded from the observed concentrations that the infant was potentially exposed to sizeable amounts of haloperidol. No adverse effects were noted, and the infant was reportedly developing normally at his 6-month and 1-year physician check-ups. The mother continued to nurse for 5 months and remained on the medication only until the sixth postpartum week.

A study[89] was conducted on newborn rabbits after 7 days of exposure to haloperidol from their nursing mothers. The mothers were taking 1 mg/kg/day of haloperidol. The report pointed out that newborn rabbits are similar developmentally to the human infant during the third trimester of pregnancy. The haloperidol-exposed offspring had muscular weakness, movement problems, and appeared less exploratory compared with control baby rabbits. These differences resolved as the rabbits grew older. The authors theorized that these effects were probably due to the dopamine-blocking properties of haloperidol, which may have blocked neural message pathways or feedback pathways. This study gives credence to the enhanced possibility of adverse effects of psychotropic medications in nursing preterm infants and underscores the need to scrutinize the breast milk data with respect to exposure during pregnancy.

Barnas and colleagues[90] reported on a woman who took 100 mg/day of clozapine through most of her pregnancy but took 50 mg/day in the last 9 weeks. The breast milk was not given to the infant, but breast milk and maternal plasma samples were collected. The day after delivery the maternal plasma level of clozapine was 14.7 ng/mL, and the foremilk concentration was 63.5 ng/mL. Three days after delivery the maternal dose was raised back to 100 mg/day. On postpartum Day 7, clozapine concentration in

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maternal plasma was 41.4 ng/mL and in breast milk was 115.6 ng/mL. The authors attributed the higher M/P ratio to the high lipid solubility and lipophilic properties of the clozapine and warned that nursing infants exposed to clozapine may be at risk for accumulation or "floppy infant syndrome."

The Kirk group[91] reported on the breast milk and plasma concentrations from women taking cis-(*Z*)-flupentixol. Maternal doses were 2 mg, 40 mg, and 60 mg/day. Two mothers gave one set of serum and milk samples, and a third mother gave two sets of serum and milk samples. The data showed that the milk concentration of the medication was approximately 30% higher than the serum concentration. The group calculated that an infant who ingested 1 liter of breast milk a day would receive a dosage of 2 µg/day.

INFANT MONITORING

Previous reviews have not discussed the necessity or clinical significance of infant serum monitoring. The extent of monitoring, such as performing repeated serum measures, should be considered in the risk/benefit assessment. The single consistent finding in the literature has been that the nursing infant is exposed to any psychotropic medication taken by the mother. What constitutes clinically significant exposure in a nursing infant remains an enigma. There is a propensity in the literature to describe "negligible exposure" or suggest that a detectable infant serum concentration of a particular medication has clinical relevance. Unfortunately, it is difficult to assign significance beyond the finding itself until cause and effect investigations have been completed. In a recent report[92] on four nursing infants exposed to sertraline, no alterations in platelet 5-hydroxytyramine were observed, providing some reassurance that exposure during breastfeeding may not produce all the chemical effects observed in adults. However, until further developmental data are obtained, the clinician would be ill-advised to assume that the effects of a particular medication are limited to a medication's primary mechanism of action, as multiple neurotransmitter systems are affected by most medications. Similarly, the clinician should be cautious about extrapolating the limited data in a general fashion, as infant metabolic capacity and maturity are highly variable. The extent and degree of infant monitoring may involve either single or repeated infant serum collection, the risk of which must be incorporated into the treatment decision.

For example, previous reviews on the use of antidepressants during breastfeeding have supported the use of secondary amine tricyclic agents. While the breastfeeding data on tricyclics have not revealed any adverse cardiac effects, and infant serum concentrations have typically been below the limits of detection, the question remains as to whether there were any alterations in the infant's electrocardiogram (ECG). This may appear excessive, yet the number of cases to date has not ruled out the potential for ECG changes seen in children and adolescents exposed to TCAs.[93] In addition, though lithium is currently contraindicated in breastfeeding by most reviews, the literature provides little definitive evidence for adverse effects when infant hydration status is unaltered. The potential effects of lithium require monitoring of infant electrolytes, thyroid function, and lithium serum concentrations, thereby complicating its use, but no data support its exclusion.

Infant monitoring should be consistent with standard practice guidelines for the management of psychotropic medications in adults, with some additions: (1) Parents should be educated about potential side effects of medication; (2) infant laboratory assessment should include medication concentration at least once (for comparison to existing data) and monitoring of other organ systems that may be affected by the medication (e.g., liver enzymes for anticonvulsants); (3) clinicians should consider repeat infant serum measurement and/or suspension of nursing if side effects are observed; (4) infant hydration status may affect serum concentrations and dehydration may precipitate adverse effects; and (5) communication with the pediatrician needs to be ongoing, as infants are often treated with medications such as acetaminophen, ibuprofen, and antibiotics that may enhance the potential for drug-drug interactions. While seemingly excessive for such purported limited exposure, it is reasonable to provide the nursing infant with the same level of care and safety that is provided to the mother. Continuing consultation and liaison with the infant's clinician is an important component in minimizing the risks of medication exposure during breastfeeding.

RISK/BENEFIT ASSESSMENT

The discussion of the risk/benefit assessment begins with the individual's psychiatric history, including (1) severity of illness, (2) history of risk for self-harm, and (3) the level of functional impairment when ill. It is important to include the factors motivating the mother to breast-feed and the utility/availability of nonpharmacologic interventions. Table 1 provides an outline for these discussions.

No clinical decision is risk-free, and the treatment options and risk/benefit assessment should be documented in the medical record. Patients need to be cautioned about potential conception, and the method currently being used for birth control should be documented.

DISCUSSION

The available literature does not provide sufficient data for the inclusion or exclusion of any given medication for use during lactation. The complex pharmacokinetics of medication excretion into breast milk, the potential con-

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Table 1. Factors to Consider in a Risk/Benefit Assessment of Taking Psychotropic Medications While Breastfeeding

Known Data
> 60% of women plan to breast-feed during the puerperium
5% of all nursing women take a prescription medication during breastfeeding
20%–22% of nursing women smoke cigarettes
Breastfeeding provides immunologic benefits to infant
Breastfeeding is supported by most professional organizations as ideal form of newborn nutrition
The postnatal period is a high-risk time for onset/relapse of maternal psychiatric illness
Untreated maternal mental illness adversely affects mother-infant attachment and infant development
All psychotropic medications are excreted in breast milk; therefore infant is exposed
Emerging Data
Adverse effects of psychotropic agents on infants are limited to case reports
Nursing infant daily dose of psychotropic agents is less than maternal daily dose
Infant monitoring may require serum sampling
The pharmacokinetics of psychotropic medication excretion into breast milk is complicated
Commercial laboratory sensitivity may be inadequate for accurate determination of infant serum concentrations for most psychotropic medications
Unknown Data
The clinical significance of detectable infant serum concentrations remains an open question
Little is known about the long-term neurobehavioral effects of breastfeeding exposure to psychotropic medications

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founds of sampling techniques, and the limitations of assay sensitivity restrict definitive conclusions. It is readily apparent that reliance on the M/P ratio provides only a very coarse estimate of the infant daily dose and is of little clinical value. In addition, the necessity and clinical significance of infant monitoring during exposure to psychotropic medications during breastfeeding has yet to be addressed.

Considering these issues, we have provided a guideline and rationale for choosing a medication from a particular class, listed in order of relative importance:

1) Document all environmental exposures to medication, alcohol, and drugs during pregnancy, and minimize factors that may affect infant development. The clinician should encourage women to discontinue tobacco use, limit the use of over-the-counter medications, and document exposures that occurred prior to treatment.
2) Use the medication of prior response, with limited exceptions. The postpartum period is not the time to experiment with new treatments. With no guarantee that a similar medication will be an effective treatment, the clinician may face the option either of exposing the developing infant to a new medication or of only partially treating a patient's illness, while the unknown risks of both illness and medication exposure remain. Exceptions would include the use of MAOIs, lithium, and clozapine secondary to the risk of side effects and the need for more extensive monitoring.
3) Use a medication for which some data exist. In the absence of a prior treatment history, a medication with prior use in breastfeeding is preferable to a novel agent with no information. As newer medications are developed, it is important to remember that relative safety cannot be extrapolated across medication classes. Improved pharmacokinetic profiles, limited metabolites, and greater receptor selectivity are not substitutes for data.
4) First try monotherapy. Avoid medications that typically require second medications for the treatment of side effects. While data may exist for each agent individually, data on combination therapy during lactation are virtually nonexistent.
5) Limit invasive monitoring. We support monitoring of infant serum medication concentrations for comparison to the available literature. However, medications such as clozapine and lithium warrant more frequent infant venous sampling, which involves risk. The clinician should consider the utility of infant serum concentrations and the availability of research quality assays in the context of interpreting infant serum measures.
6) Use flexible dosing. The empirical goal of minimizing infant exposure supports the use of medications for which multiple capsule or tablet sizes allow for careful dose titration to the minimum effective dose.
7) Use a familiar medication. Clinicians should choose a medication with known efficacy and side effects. In this way, the clinician may identify any adverse effects and provide reassurance for the nursing mother.

The guidelines listed above and the risk/benefit assessment should provide clinicians with a mechanism to achieve the goal of treatment during lactation, minimizing infant exposure and adverse effects while maintaining maternal mental health. The increasing number of publications with improved methodology and the increased awareness of the importance of maternal mental health will eventually provide the basis for definitive medication recommendations in the absence of a treatment history.

Drug names: acetaminophen (Tylenol and others), amitriptyline (Elavil and others), bupropion (Wellbutrin), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clomipramine (Anafranil), clonazepam (Klonopin), clozapine (Clozaril), desipramine (Norpramin and others), diazepam (Valium and others), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), haloperidol (Haldol and others), ibuprofen (Advil and others), nortriptyline (Pamelor and others), oxazepam (Serax and others), paroxetine (Paxil), perphenazine (Trilafon), phenytoin (Dilantin and others), sertraline (Zoloft), temazepam (Restoril and others), zolpidem (Ambien).

REFERENCES

1. American Academy of Pediatrics Committee on Drugs. The transfer of drugs and other chemicals into human milk. Pediatrics 1994;93:137–150
2. Cohen LS, Heller VL, Rosenbaum JF. Treatment guidelines for psychotropic drug use in pregnancy. Psychosomatics 1989;30:25–33
3. Cohen LS. Psychotropic drug use in pregnancy. Hosp Community Psychiatry 1989;40:566–567
4. Kerns LL. Treatment of mental disorders in pregnancy: a review of psychotropic drug risks and benefits. J Nerv Ment Dis 1986;174:652–659
5. Miller LJ. Clinical strategies for the use of psychotropic drugs during pregnancy. Psychiatric Medicine 1991;9:275–298
6. Miller LJ. Psychiatric medication during pregnancy: Understanding and minimizing the risks. Psychiatric Annals 1994;24:69–75
7. Wisner KL, Perel JM. Psychopharmacologic agents and electroconvulsive therapy during pregnancy and the puerperium. In: Cohen RL, ed. Psychiatric Consultation in Childbirth Settings: Parent- and Child-Oriented Approaches. New York, NY: Plenum Medical Book Company; 1988
8. Morselli PL, Franco-Morselli R, Bossi L. Clinical pharmacokinetics in newborns and infants: age related differences and therapeutic implications. Clin Pharmacokinet 1980;5:485–527
9. Mortola JF. The use of psychotropic agents in pregnancy and lactation. Women's Disorders 1989;12:69–87
10. Robinson GE, Stewart DE, Flak E. The rational use of psychotropic drugs in pregnancy and postpartum. Can J Psychiatry 1986;31:183–190
11. Stowe ZN, Nemeroff CB. Psychopharmacology during pregnancy and lactation. In: Schatzberg AF, Nemeroff CB, eds. Textbook of Psychopharmacology. Washington, DC: American Psychiatric Press; 1995
12. Kacew S. Adverse effects of drugs and chemicals in breast milk on the nursing infant. J Clin Pharmacol 1993;33:213–220
13. Knowles JA. Excretion of drugs in milk: a review. Pediatric Pharmacology and Therapeutics 1965;66:1068–1082
14. Vorherr H. Drug excretion in breast milk. Postgrad Med 1974;56:97–104
15. O'Brien TE. Excretion of drugs in human milk. Am J Hosp Pharm 1974;31: 844–854
16. Anderson PO. Drug use during breast-feeding. Clinical Pharmacy 1991;10: 594–624
17. Ito S, Blajchman A, Stephenson M, et al. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. Am J Obstet Gynecol 1993;168:1393–1399
18. Misiri S, Sivertz K. Tricyclic drugs in pregnancy and lactation: a preliminary report. Int J Psychiatry Med 1991;21:157–171
19. Wilson JT. Determinants and consequences of drug excretion in breast milk. Drug Metab Rev 1983;14:619–652
20. VanBlerk GA, Majerus TC, Myers RAM. Teratogenic potential of some psychopharmacologic drugs: a brief review. Int J Gynaecol Obstet 1980; 17:399–402
21. Murray L, Seger D. Drug therapy during pregnancy and lactation. Emerg Med Clin North Am 1994;12:129–148
22. Buist A, Norman TR, Dennerstein L. Breastfeeding and the use of psychotropic medication: a review. J Affect Disord 1990;19:197–206
23. Baum AL, Misri S. Selective serotonin-reuptake inhibitors in pregnancy and lactation. Harv Rev Psychiatry 1996;4:117–125
24. Pons G, Rey W, Matheson I. Excretion of psychoactive drugs into breast milk. Clinical Pharmacokinetics in Special Populations 1994;27:270–289
25. Wisner KL, Perel JM, Findling RL. Antidepressant treatment during breastfeeding. Am J Psychiatry 1996;153:1132–1137
26. Ananth J. Side effects in the neonate from psychotropic agents excreted through breast-feeding. Am J Psychiatry 1978;135:801–805
27. 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
28. Atkinson HC, Begg EJ, Darlow BA. Drugs in human milk: clinical pharmacokinetic considerations. Clin Pharmacokinet 1988;14:217–240
29. Atkinson AJ, Stec G, Lertora J, et al. Impact of active metabolites on monitoring plasma concentrations of therapeutic drugs. Ther Drug Monit 1980; 2:19–27
30. O'Dea RF. Medication use in the breastfeeding mother. NAACOG Clinical Issues in Perinatal and Women's Health Nursing 1992;3:598–604
31. Morselli PL. Clinical pharmacokinetics in neonates. Clin Pharmacokinet 1976;1:81–98
32. Briggs GG, Pharm B, Freeman RK, et al. Update: drugs in pregnancy and lactation. Drugs in Pregnancy and Lactation Update 1996;9:9–18
33. Bonnar J, Franklin M, Nott PN, et al. Effect of breast-feeding on pituitary-ovarian function following childbirth. BMJ 1975;4:82–84
34. Byers T, Graham S, Rzepka T, et al. Lactation and breast cancer: evidence for a negative association in premenopausal women. Am J Epidemiol 1985;121:664–674
35. Beaudry M, Dufour R, Marcoux S. Relation between infant feeding and infections during the first six months of life. J Pediatr 1995;2:191–197
36. Duncan B, Ely J, Holberg CJ, et al. Exclusive breast-feeding for at least 4 months protects against otitis media. Pediatrics 1993;91:867–872
37. Sassen ML, Brand R, Grote JJ. Breast-feeding and acute otitis media. Am J Otolaryngology 1994;15:351–357
38. Pisacane A, Graziano L, Mazzarella G, et al. Breast-feeding and urinary tract infection. J Pediatr 1992;120:87–89
39. Coppa GV, Gabrielli O, Giorgi P, et al. Preliminary study of breastfeeding and bacterial adhesion to uroepithelial cells. Lancet 1990;335:569–571
40. Lucas A, Morley R, Cole TJ, et al. Breast milk and subsequent intelligence quotient in children born preterm. Lancet 1992;339:261–264
41. Cunningham A, Jelliffe D, Jelliffe E. Breast-feeding and health in the 1980's: a global epidemiologic review. J Pediatr 1991;118:659–666
42. Milberger S, Biederman J, Faraone SV, et al. Is maternal smoking during pregnancy a risk factor for attention deficit hyperactivity disorder in children? Am J Psychiatry 1996;153:1138–1142
43. Pichini S, Altieri I, Zuccaro P, et al. Drug monitoring in nonconventional biological fluids and matrices. Clin Pharmacokinet 1996;30:211–228
44. Bader TF, Newman K. Amitriptyline in human breast milk and the nursing infant's serum. Am J Psychiatry 1980;137:855–856
45. Breyer-Pfaff U, Nill K, Enenmann A, et al. Secretion of amitriptyline and metabolites into breast milk. Am J Psychiatry 1995;152:812–813
46. Brixen-Rasmussen L, Halgrener J, Jorgensen A. Amitriptyline and nortriptyline excretion in human breast milk. Psychopharmacology (Berl) 1982; 76:94–95
47. Erickson SH, Smith GH, Heidrich F. Tricyclics and breastfeeding [letter]. Am J Psychiatry 1979;136:1483–1484
48. Pittard WB, O'Neal W. Amitriptyline excretion in human milk. J Clin Psychopharmacol 1986;6:383–384
49. Schimmell MS, Katz EZ, Shaag Y, et al. Toxic neonatal effects following maternal clomipramine therapy. Clinical Toxicology 1991;29:479–484
50. Wisner KL, Perel JM, Foglia JP. Serum clomipramine and metabolite levels in four nursing mother-infant pairs. J Clin Psychiatry 1995;56:17–20
51. Matheson I, Pande H, Alertsen AR. Respiratory depression caused by N-desmethyldoxepin in breast milk [letter]. Lancet 1985;2:1124
52. Kemp J, Ilett KF, Booth J, et al. Excretion of doxepin and N-desmethyldoxepin in human milk. Br J Clin Pharmacol 1985;20:497–499
53. 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
54. Wisner KL, Perel JM. Serum nortriptyline levels in nursing mothers and their infants. Am J Psychiatry 1991;149:1234–1236
55. Wisner KL, Perel JM. Nortriptyline treatment of breast-feeding women [letter]. Am J Psychiatry 1996;153:295
56. Altshuler LL, Cohen L, Szuba MP, et al. Pharmacologic management of psychiatric illness in pregnancy: dilemmas and guidelines. Am J Psychiatry 1996;153:592–606
57. Taddio A, Ito S, Koren G. Excretion of fluoxetine and its metabolite norfluoxetine in human breast milk. J Clin Pharmacol 1996;36:42–47
58. Burch KJ, Wells BG. Fluoxetine/norfluoxetine concentration in human milk. Pediatrics 1992;89:676–677
59. Isenberg KE. Excretion of fluoxetine in human breast milk [letter]. J Clin Psychiatry 1990;51:169
60. Lester BM, Cucca J, Andreozzi L, et al. Possible association between fluoxetine hydrochloride and colic in an infant. J Am Acad Child Adolesc Psychiatry 1993;32:1253–1255
61. Mammen OK, Perel JM, Rudolph G, et al. Sertraline and norsertraline levels in three breastfed infants. J Clin Psychiatry 1997;58:100–103
62. Wright S, Dawling S, Ashford JJ. Excretion of fluvoxamine in breast milk [letter]. Br J Clin Pharmacol 1991;31:209
63. Spigset O, Carleborg L, Norström A, et al. Paroxetine level in breast milk [letter]. J Clin Psychiatry 1996;57:39
64. Briggs GG, Samson JH, Ambrose PJ, et al. Excretion of bupropion in breast milk. Ann Pharmacother 1993;27:431–433
65. Pons G, Schoerlin MP, Tam YK, et al. Moclobemide excretion in human breast milk. Br J Clin Pharmacol 1990;29:27–31
66. Fisher JB, Edgren BE, Mammel MC, et al. Neonatal apnea associated with

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maternal clonazepam therapy: a case report. Obstet Gynecol 1985;66: 34S–35S
67. Soderman P, Matheson I. Clonazepam in breast milk. J Pediatr 1987;147: 212–213
68. Andre M, Boutroy MJ, Dubruc C, et al. Clonazepam pharmacokinetics and therapeutic efficacy in neonatal seizures. Eur J Clin Pharmacol 1986; 30:585–589
69. Patrick MJ, Tilstone WJ, Reavey P. Diazepam and breast-feeding. Lancet 1972;1:542–543
70. Erkkola R, Kanto J. Diazepam and breast-feeding. Lancet 1972;1: 1235–1236
71. Morselli PL, Principi N, Tognoni G, et al. Diazepam elimination in premature and full term infants and children. J Perinat Med 1973;1:133–141
72. Eliot BW, Hill JG, Cole AP, et al. Continuous pethidine/diazepam infusion during labour and its effects on the newborn [letter]. Br J Obstet Gynaecol 1974;82:126
73. Cole AP, Hailey DM. Diazepam and active metabolite in breast milk and their transfer to the neonate. Arch Dis Child 1975;50:741–742
74. Dusci LJ, Good SM, Hall RW, et al. Excretion of diazepam and its metabolites in human milk during withdrawal from combination high dose diazepam and oxazepam. Br J Clin Pharmacol 1990;29:123–126
75. Lebedevs TH, Wojnar-Horton RE, Yapp P, et al. Excretion of temazepam in breast milk. Br J Clin Pharmacol 1992;33:204–206
76. Pons G, Francoual C, Guillet P, et al. Zolpidem excretion in breast milk. Eur J Clin Pharmacol 1989;37:245–248
77. Goldfield MD, Weinstein MR. Lithium carbonate in obstetrics: guidelines for clinical use. Am J Obset Gynecol 1973;116:15–22
78. Schou M, Amdisen A. Lithium and pregnancy, III: lithium ingestion by children breast-fed by women on lithium treatment. BMJ 1973;2:138
79. Sykes PA, Quarrie J, Alexander FW. Lithium carbonate and breast-feeding. BMJ 1976;2:1299
80. Linden S, Rich CL. The use of lithium during pregnancy and lactation. J Clin Psychiatry 1983;44:358–361
81. Alexander FW. Sodium valproate and pregnancy [letter]. Arch Dis Child 1979;54:240
82. 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
83. Merlob P, Mor N, Litwin A. Transient hepatic dysfunction in an infant of an epileptic mother treated with carbamazepine during pregnancy and breastfeeding. Ann Pharmacother 1992;26:1563–1565
84. Blacker KH, Weinstein BJ, Ellman GG. Mother's milk and chlorpromazine. Am J Psychiatry 1962;119:178–180
85. Wiles DH, Orr MW, Kolakowska T. Chlorpromazine levels in plasma and milk of nursing mothers. Br J Clin Pharmacol 1978;5:272–273
86. Olesen OV, Bartels U, Poulsen JH. Perphenazine in breast milk and serum. Am J Psychiatry 1990;147:1378–1379
87. Stewart RB, Karas B, Springer PK. Haloperidol excretion in human milk. Am J Psychiatry 1980;137:849–850
88. Whalley LJ, Blain PG, Prime JK. Haloperidol secreted in breast milk. BMJ 1981;282:1746–1747
89. Lundborg P. Abnormal ontogeny in young rabbits after chronic administration of haloperidol to the nursing mother. Brain Res 1972;44:684–687
90. Barnas C, Bergant A, Hummer M, et al. Clozapine concentrations in maternal and fetal plasma, amniotic fluid, and breastmilk [letter; comment]. Am J Psychiatry 1994;151:945
91. Kirk L, Jorgensen A. Concentrations of cis(Z)-flupentixol in maternal serum, amniotic fluid, umbilical cord serum, and milk. Psychopharmacology (Berl) 1980;72:107–108
92. Epperson CN, Anderson GM, McDougle CJ. Sertraline and breast-feeding [letter]. N Engl J Med 1997;336:1189–1190
93. Leonard H, Meyer M, Savedo S, et al. Electrocardiographic changes during desipramine and clomipramine treatment in children and adolescents. J Am Acad Child Adolesc Psychiatry 1995;34:1460–1468

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