Mood Stabilizers During Breastfeeding: A Review

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Background: The postpartum period is an exceptionally high-risk time for recurrence of depression, mania, or psychosis for women with bipolar disorder. Puerperal prophylaxis with mood stabilizers decreases this risk. To allow patients and clinicians to make informed decisions about mood-stabilizer use during breastfeeding, there is a need for a critical review and analysis of the data.

Data Sources: A search of MEDLINE (1966–1998) and the Lithium Database, Madison Institute of Medicine, was conducted to obtain articles about lithium, valproate, carbamazepine, gabapentin, or lamotrigine use during lactation. Search terms used were *pregnancy*, *teratogenesis*, *breastfeeding*, *lactation*, *breast milk levels* and *lithium*, *anticonvulsants*, *mood stabilizers*. No other search restrictions were used. Unpublished data on gabapentin and lamotrigine were provided by the manufacturers.

Results: The search revealed 11 cases of lithium use during breastfeeding, 8 of which reported infant serum levels. Two cases reported symptoms consistent with lithium toxicity in the infants. Thirty-nine cases of valproate use during breastfeeding were found, 8 of which reported infant serum levels. There was 1 report of thrombocytopenia and anemia in an infant. Fifty cases of carbamazepine use during breastfeeding were found, 10 of which reported infant serum levels. Two infants experienced hepatic dysfunction. One unpublished study of gabapentin in breast milk was found. Three reports of lamotrigine use during breastfeeding were found.

Discussion: Available information remains limited to uncontrolled studies and case reports. Carbamazepine and valproate, but not lithium, have generally been considered compatible with breastfeeding. The overall paucity of data, data confounded by polypharmacy and infant age differences, and adverse reactions reported with all established mood stabilizers dictate a reassessment of these recommendations. We propose that a woman's historical response to medication and the clinical circumstances be the primary considerations when choosing a mood stabilizer during breastfeeding, rather than strict adherence to categorical assignments.

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For many women, the postpartum period is an emotionally difficult time. For women with bipolar or other major mental illnesses, it is a time of exceptionally high risk for an episode of depression, mania, or psychosis. Between 5% and 20% of women will experience a postpartum depression within the first 6 months,[1–5] while 0.1% to 0.2% will experience a postpartum psychosis.[3,6] Women with bipolar disorder have a 100-fold greater risk than women with no previous psychiatric history for developing a postpartum psychosis.[3,6] In addition, 40% of women who have bipolar disorder experience postpartum mania or depression. Each postpartum episode of mania or depression increases the risk of a future postpartum episode.[6] Recent studies have shown that puerperal prophylaxis with a mood stabilizer decreases the rate of recurrence to 10%.[7–9] Considering the risks associated with a bipolar episode for both mother and newborn, the use of prophylactic mood stabilizers is advised for women with bipolar disorder during this high-risk time.

Because the negative effects of depressed mothers on their infants are well documented,[10–12] treating these women prophylactically may seem to be the obvious solution. However, this issue is complicated by the fact that many women would like to breast-feed. Many variables in the risk-benefit analysis of breastfeeding while being treated with a mood stabilizer are case-specific. These include factors such as the individual's ability to engage in consistent, closely monitored treatment; the relationship

between the physician and the woman; the woman's social supports; and her emotional commitment to breastfeeding. There are also more global factors to consider such as the benefits of breastfeeding to the mother and infant and the risks of medication exposure via breast milk to the infant.

While some articles have reviewed psychotropic medication use during breastfeeding (with mention of mood stabilizers),[13–16] none have focused on an in-depth evaluation of the pros and cons of mood-stabilizer use during this time. This article will provide a concise yet thorough overview of publications that include milk levels and/or infant serum levels of mood stabilizers. It will also review the risks and benefits of breastfeeding while being treated with lithium, carbamazepine, or valproate. It will cover the limited information available on gabapentin and lamotrigine, 2 newer anticonvulsant mood stabilizers.

DATA SOURCES

An extensive unrestrictive search of MEDLINE (1966–1998) and the Lithium Database (Madison Institute of Medicine, Madison, Wis.) was conducted to obtain articles on lithium, valproate, carbamazepine, gabapentin, and lamotrigine use during lactation. The search terms used were *pregnancy*, *teratogenesis*, *breastfeeding*, *lactation*, *breast milk levels* and *lithium*, *anticonvulsants*, *mood stabilizers*. Unpublished data were also obtained from the manufacturers of gabapentin and lamotrigine.

RESULTS

Advantages of Breastfeeding

There are many advantages to breastfeeding for both the mother and infant. In 1997, the American Academy of Pediatrics published its policy statement in support of breastfeeding.[17] It noted the recent advancements in scientific research including the benefits of breastfeeding in developed countries such as the United States.

For the mother, the medical benefits from lactation include faster postpartum weight loss,[18] lactation amenorrhea,[19] decreased risk of epithelial ovarian cancer, decreased risk of obesity, decreased risk of osteoporosis, and protection against premenopausal breast cancer.[20,21] At least one study suggests that the relative risk of breast cancer in breastfeeding women is almost half that of non-breastfeeding women.[22] Lactation amenorrhea decreases menstrual blood loss and contributes to a delay in ovulation resumption. Hence, for the first 6 months postpartum, breastfeeding may have the added benefit of being a form of contraception.[19]

Psychologically, women who breast-feed have been found to have feelings of increased intimacy with their infants[23] and to develop increased self-esteem and assertiveness.[20] Furthermore, the psychological impact of breastfeeding may be one of empowerment, since this special nourishment is something that only the mother can provide for her infant. Another benefit to breastfeeding is financial. The American Academy of Pediatrics estimates that the savings is approximately $400 per child for the first year.[17] For a mother on a limited budget, this savings may be considerable.

For the infant, breast milk is the ultimate nutrition because of its species-specific nutritive value. It has unique protein and fat compositions, growth factors that promote development of the gastrointestinal tract, enzymes that facilitate digestion, immunoprotective components, and bioactive substances such as hormones, enzymes, and live cells.[24] Breast milk also contains all of the vitamins, essential minerals, and trace elements required by a normal-term infant.[25]

Breastfed infants have been shown to have lower mortality rates from sudden infant death syndrome and necrotizing enterocolitis.[21] They have decreased risks for respiratory infections, gastroenteritis, otitis media, allergies, type I diabetes, Crohn disease,[17,21,26] and childhood lymphoma.[27] One study suggests that children who were breastfed for more than 6 months were significantly less likely to develop cancer than bottle-fed infants or infants breastfed for less than 6 months.[27] This study also showed that non-breastfed infants had almost double the risk of developing cancer (odds ratio [OR] = 1.75) and, more specifically, 5 times greater risk of developing lymphoma (OR = 5.62) than infants breastfed for more than 6 months. With regard to more common illness such as diarrhea, coughs or wheezes, and ear infections, one study found that fully breastfed infants had significantly fewer illnesses and sick-baby medical visits than non-breastfed infants (OR = 0.78).[28] More specifically, these infants had less diarrhea (OR = 0.54), coughs or wheezes (OR = 0.83), vomiting (OR = 0.71), ear infections (OR = 0.49), colds (OR = 0.67), and fevers (OR = 0.71) than non-breastfed infants. Furthermore, infants who were partially breastfed also experienced a protective effect from breastfeeding for diarrhea, coughs or wheezes, and ear infections.[28] These findings did not differ among income groups, thus challenging the argument that breastfeeding is not beneficial in developed, affluent communities. Another study[29] similarly found that non-breastfed infants have an 80% increased risk of developing diarrhea and a 70% increased risk of developing ear infections when compared with exclusively breastfed infants.

Research has also pointed to possible benefits of breastfeeding on neurodevelopment, especially in preterm infants.[30] Similarly, studies have shown benefits to full-term infants including benefits to the central nervous systems as evidenced by the more rapid development of visual acuity in breastfed infants.[31] Breastfed infants have also been found to be in a "more stable state" as evidenced by longer periods of quiet sleep and slower heart rate in

active sleep than bottle-fed infants.[32] This study found that the "total mother-infant interaction during breastfeeding" rather than the individual components (for example, breast milk, holding time, sucking time) positively affected the infants. This finding reinforces the importance of the interaction between mother and infant that has been found to affect bonding.[33] While it is difficult to quantify this effect, it intuitively makes sense that breastfeeding enhances the interaction because of the physical closeness, the total dependence of the infant on the mother, and the limitations on distraction that the mother can incur and continue to nurse the infant.

Disadvantages of Breastfeeding

The total reliance by the infant on the mother to provide 24-hour-a-day nutrition may be a disadvantage of breastfeeding. In women with bipolar illness, this need for nursing at all hours may increase their susceptibility to mood destabilization due to increased sleep disruption. However, depending on the situation, some women may experience less sleep disruption because of the immediate nature and availability of breast milk rather than preparing bottles of formula.

The most obvious disadvantage to breastfeeding while being treated with a mood stabilizer is the excretion of medication into the breast milk and the exposure of the infant to medication.

Medications in Breast Milk

Psychotropic medications are excreted in breast milk. Factors that affect the passage of drugs into breast milk include route of administration, absorption rate, half-life and peak serum time, dissociation constant, volume of distribution, molecular size, degree of ionization, pH of plasma (7.4) and milk (6.8), solubility of the drug in water and in lipids, and greater binding to plasma protein than to milk protein.[34,35]

The amount of drug received by the infant depends on multiple factors as well. These include milk yield, composition of the milk (i.e., colostrum versus mature milk), concentration of the drug in the milk, which breast is being suckled (the yield is not equal from each breast), and how well the breast was emptied during the previous feeding.[35] The mammary alveolar epithelium is most permeable during the colostral phase (first week postpartum), and, thus, the concentration of the drug is typically highest during this time.[34] However, the mean volume of milk transferred to the infant is lower during the first 2 days after delivery and increases rapidly on days 3 and 4. It then increases more slowly to a maximum of approximately 800 mL/day at 6 months of age.[36] To calculate the amount of drug transferred to an infant, the following formula is used: dose/24 hours = concentration of drug in milk × weight in kg of the baby × volume of milk per kg ingested in 24 hours. Clinically, this calculation may be difficult to employ, but it can be used to approximate the amount of drug the infant is receiving.[34]

An infant's ability to absorb, detoxify, and excrete the drug are important factors.[34] Less mature infants are less able to clear drugs because of their immature renal and liver functions.[35] The age of the infant also affects the amount of milk consumed, since older infants have their nourishment supplemented with cereal, solids, and other liquids. Other factors that may affect drug concentrations include any medical problems that the infant may experience and any other medications that the infant may be receiving.

Most research on mood stabilizers revolves around the ratio of milk to mother's serum drug level. Lawrence,[34] an expert on breastfeeding, notes that the use of this ratio as the reference point presumes that the relationship is constant, which it is not. The ratio depends on many variables including dose strength, duration of dosing, maternal variation in drug disposition, maternal diseases, drug interactions, and racial variation. These variables are important to keep in mind when reviewing the literature since most studies do not address them when making recommendations.

Lithium. In the past 10 years, the use of lithium while breastfeeding has been generally discouraged. The American Academy of Pediatrics Committee on Drugs initially (1983) classified lithium as compatible with breastfeeding,[37] but revised its classification in 1989, with lithium being contraindicated during breastfeeding.[38] The last set of recommendations, in 1994, continues to use this classification.[39] The primary concern about potential lithium toxicity in infants is that lithium has been found consistently in both breast milk and infants' serum. Lithium concentrations in breast milk have been reported to be approximately 40% (range, 24%–72%) of the mothers' serum concentrations[40–45] (Table 1). In only one case, as the mother's serum lithium level increased, the milk lithium level increased up to 1.5 times higher than the maternal serum level.[46] Generally, infants' serum lithium concentrations have been found to be approximately equal to or less than that of the milk and 5% to 200% of the mother's serum concentration[40–45] (see Table 1). There have been 2 case reports of nursing infants who experienced adverse events that were attributed to lithium.[42,45]

The first report,[42] in 1972, described a baby who developed cyanosis, hypothermia, hypotonia, and a heart murmur within a few hours of birth.[42] No lithium levels were reported until day 5, when the baby experienced a cyanotic episode. At that time, the baby's serum and the breast milk had lithium levels of 0.6 mEq/L, and the mother had a serum lithium level of 1.5 mEq/L. The baby had been breast-feeding since birth and continued to do so until the cyanotic episode on day 5. On day 6, the infant showed signs of lethargy. On day 7, the infant had a serum lithium concentration of 0.21 mEq/L and T-wave changes on an electrocardiogram (ECG). The baby improved and was

Table 1. Lithium Use in Women Who Breast-Feed

Study	Number of Cases	Maternal Serum Level (mEq/L)	Milk Level (mEq/L)	Milk/Maternal Serum Level, %	Infant Serum Level (mEq/L)	Infant Serum/ Maternal Serum Level, %	Infant Age	Infant Complications
Weinstein and Goldfield[40] (1969)	1	0.84	…	…	0.04	5	Day 17	No
		0.5	0.12	24	…	…	10 weeks	No
Fries[41] (1970)	1	…	0.3	…	0.3	…	1 week	No
Tunnessen and Hertz[42] (1972)	1	1.5	0.6	40	0.6	40	Day 5	Cyanotic episode
		…	…	…	0.21	…	Day 7	T-wave inversion; lethargy
Schou and Amdisen[43] (1973)	5 total							
	1	0.34	0.16	47	0.22	65	1 week	No
	1	0.9	0.3	33	0.3	33	2 weeks	No
	1	0.84	0.56	66	0.15	18	2 weeks	No
	1[a]	0.57	0.24	42	…	…	3 weeks	No
	1	…	0.5	…	0.1	…	4 weeks	No
Sykes et al[44] (1976)[b]	1	0.35	0.2	57	0.03	9	Day 6	No
		0.9	0.6	72	0.1	11	Day 28	No
		1.0	0.3	30	0.1	10	Day 42	No
Skausig and Schou[45] (1977)	1	0.7	…	…	1.4	200	2 months	Signs of "lithium toxicity"

[a]Means of determinations on 5 consecutive days.
[b]Approximate values from graph in Sykes et al.[44]

"completely normal" by day 8. On the basis of this infant's experience, the authors discouraged breastfeeding.

Limited inferences can be made about lithium exposure from breast milk from this case because the infant had symptoms consistent with lithium toxicity at birth. In utero, maternal serum and fetal plasma concentrations of lithium are essentially equal. The mother had been maintained at lithium levels of 1.07 to 1.38 mEq/L during pregnancy; thus, the newborn probably had similar levels in utero. The decrease in symptoms over the first week is consistent with reports that serum lithium levels decrease over the first week postpartum in infants exposed in utero as well as postpartum.[43,44,47,48] The initial high lithium levels could have been caused by the infant's slow excretion of the drug because of her immature kidney function. The toxicity on days 5 through 7 could have been a combination of the high maternal serum concentration while breastfeeding and the remaining lithium concentration from birth. This case highlights the risk of neonatal lithium toxicity due to the combination of lithium exposure in utero and through breast milk.

The second often-cited report[45] described a baby who had been breast-feeding without problems for 2 months and had maintained a lithium level approximately 50% of the mother's serum level. During an upper respiratory infection at about 2 months of age, the baby developed a lithium level of 1.4 mmol/L. The mother had a serum level of 0.7 mmol/L. The infant showed signs of toxicity, but recovered with the discontinuation of breastfeeding. The specific signs of toxicity were not published in the English abstract. This report supports an association between breastfeeding and lithium toxicity. However, the infection and the probable dehydration most likely predisposed the infant to the toxicity. The presence of these intermediary variables would dictate extra caution and concern for a nursing infant and may warrant either total or partial discontinuation of breastfeeding during an infant's illness or infection.

In 1973, Schou and Amdisen[43] reviewed 8 reports, including 3 that had been previously published,[40–42] of infants breast-fed by women who were taking lithium. They reported that infants' serum lithium levels were approximately 50% that of the mothers' during the first week postpartum. During the following weeks, the infants' serum levels were about 33% of the mothers' serum levels. Table 1 provides the details of this study. Schou and Amdisen[43] recommended bottle-feeding despite their statement that a child has already been exposed to higher lithium concentrations in utero and that it is unlikely that a few more months of exposure will harm the infant.

Sykes et al.[44] described an infant exposed to lithium in utero who was mildly hypotonic during the first 2 days postpartum. The baby began breastfeeding within 6 days and over the course of 63 days showed no negative effects from the lithium exposure. During that time, despite fluctuations in the mother's serum and breast milk lithium levels, the baby's serum level remained relatively constant (see Table 1). Thus, the author purported that the benefits from breastfeeding "appeared to outweigh any possible risk from lithium in the neonatal period."

Lithium is eliminated via renal excretion with an elimination half-life in adults of about 24 hours (longer in the elderly). Owing to infants' immature excretory systems, there is concern about the increased possibility of adverse reactions to lithium. These reactions include increased sensitivity to alterations in fluid and electrolyte balance, cardiac arrhythmia, hypothyroidism, goiter, tremor, muscle weakness, sedation, gastrointestinal problems, and neph-

rotoxicity.[49] Further concern is based on animal studies. Rats have shown alterations in renal function with postnatal lithium exposure; however, the effects lessened with age.[50,51] Similarly, there is less concern as an infant grows because glomerular filtration and tubular secretory processes mature over the first month of life.[35] A final reason for recommendations against breastfeeding while taking lithium is the possibility of lithium accumulation in developing bone of the infant.[52–54] Lithium accumulation is of concern because it is accompanied by a decrease in bone calcium.[55] Research with mice has shown that the amount of lithium taken up in bone is dose dependent.[56] Neither animal nor adult human studies have demonstrated any long-term effects on bone mass,[55,57] and the risk to nursing infants is unknown.

Because of possible lithium toxicity in infants, limited information about its effect on the developing infant, and the lack of sufficient data to support a clear recommendation, the experts' recommendations vary with regard to breastfeeding. They range from strong statements against breastfeeding while taking lithium to supporting a mother's informed choice.

Most physicians are conservative and follow the recommendations against breastfeeding. However, given the paucity of information about the actual negative effects of lithium on the breastfed infant and the increasing literature on the benefits to both mother and infant from breastfeeding, this strong contraindication should be more fully evaluated. The mother and doctor must fully understand the limitations of the current recommendations.

Valproate. Valproic acid and divalproex sodium, hereafter referred to as valproate, are excreted into human breast milk.[58–67] As of 1994, valproate was classified by the American Academy of Pediatrics Committee on Drugs as compatible with breastfeeding.[39] The recommendation is based almost exclusively on case reports and studies of epileptic women. There are only 2 case reports of breastfeeding women who used valproate solely for psychiatric purposes.[63]

Valproate has been considered compatible with breastfeeding because of its consistently low concentration in milk. Breast milk contains concentrations that are between less than 1% and 10% of the mothers' serum valproate level[59–62,65,67] (Table 2). While this may seem reassuring, it is important to note that the studies that generated these data were of very small sample size (the largest involved 16 women). Furthermore, many of the women were receiving combinations of anticonvulsants.

The data on nursing infants' serum valproate levels are even sparser, with only 10 reported cases, one of which does not provide the mother's levels for comparison.[60–64] The data show that the infants' serum levels ranged from undetectable to 40% of the maternal serum level. Five of the 8 infants' serum levels were between 4% and 12% of the mother's serum levels (see Table 2).

The half-life of valproate in infants less than 2 months old and neonates is significantly longer than in adults. The mean half-life in newborns receiving valproate transplacentally is 47 hours, while in infants 10 days to 2 months old, the half-life ranges from 9 to 22 hours, compared with a half-life in adults of 7 to 12 hours.[68] Thus, depending on the age and ability to metabolize valproate, the amount of valproate in breast milk would not necessarily reflect the amount in the infants' sera. This may be especially true during the first postpartum week because of possible exposure to valproate in utero as well as from breastfeeding.

Table 2 displays data from the most detailed studies. One study that did not list specific case information describes 4 epileptic women on valproate monotherapy.[60] The concentrations of valproate in milk were found to be 5% to 10% of the maternal serum concentrations. In one woman, during 1 day, the amount of valproate in the milk fluctuated from 1.5% to 7.6% of her serum concentration. On the same day, the woman's 3-month-old infant's serum level was 7.6% of the maternal serum concentration.

A review article not listed in Table 2 referenced valproate levels in breast milk that were equal to or greater than maternal plasma levels.[69] This report was not available in English for critical review. It appears to be in contrast to other reports, and the results have not been replicated to date.

We found only one published report of an adverse event in a nursing infant of a mother treated with valproate.[70] The 3-month old developed thrombocytopenia and anemia while the mother received sodium valproate monotherapy. The infant's serum valproate level was 46 μmol/L or 6.6 μg/mL. The maternal serum and milk concentrations were not reported. The hematologic abnormalities resolved between 12 and 35 days after discontinuation of breastfeeding. Despite extensive investigation, no other etiology for the abnormalities was discovered.

The 2 most extensive studies warrant further examination.[59,62] Von Unruh et al.[62] studied 16 patients treated with valproate, 7 of whom were on monotherapy. Fourteen women and 5 infants gave blood samples; maternal serum levels were reported for 11 of the women (see Table 2). The authors analyzed a total of 36 breast milk samples and found valproate levels to range from 0.4 to 3.9 μg/mL with a mean of 1.9 μg/mL. The mean valproate concentration in milk was 5.1% of the maternal serum concentration on days 3 to 6 postpartum, with a range of 1.3% to 9.6%. The infants' serum samples showed a range from less than 1 to 13.4 μg/mL. In all but one case, the infants' serum concentrations were higher than the milk concentrations. The difference between milk and infant serum concentrations may reflect in utero valproate exposure or decreased ability of the infant to metabolize and excrete the drug.

Nau et al.[59] found that milk concentrations averaged 3% of the mothers' serum concentrations in 6 subjects

Table 2. Valproate Use in Women Who Breast-Feed[a]

Study	Number of Cases	Maternal Serum Level	Milk Level	Milk/Maternal Serum Level, %	Infant Serum Level	Infant Serum/ Maternal Serum Level, %	Infant Age	Infant Complications
Alexander[61] (1979)	1	480 mmol/L	50 mmol/L	10.5	60 mmol/L	10.5	Day 2	No
		580 mmol/L	21 mmol/L	3.6	Undetectable	0	Day 29	No
Dickinson et al[66] (1979)	1	9.9	0.17 (r)	1.7	…	…	Day 3	No
			0.19 (l)	1.9				
		34.3	0.47 (r)	1.4	…	…	Day 6	No
			0.45 (l)	1.3				
Froescher et al[65] (1981)	5 total							
	1	38.9	1.9	4.9	…	…	…	No
	1[b]	30.5	0.4	1.3	…	…	…	No
	1[b]	43.8	1.2	2.8	…	…	…	No
	1[c]	55.3	3.9	7.1	…	…	…	No
	1[d]	31.3	0.5	1.6	…	…	…	No
Nau et al[59] (1981)	6 total							
	1	96.1	2.2	2.2	…	…	Day 4	No
		83.3	2.2	2.6	…	…	Day 12	No
		102.2	5.4	5.2	…	…	Day 20	No
	1	4.74	0.034	0.71	…	…	Day 5	No
		21.4	0.51	2.3	…	…	Day 15	No
		96.3	4.7	4.8	…	…	Day 29	No
	1	24.2	0.45	1.8	…	…	Day 3	No
		10.2	0.13	1.2	…	…	Day 18	No
		32.8	0.72	2.1	…	…	Day 25	No
	1	7.6	0.12	1.5	…	…	Day 38	No
		26.8	1.05	3.9	…	…	Day 47	No
	1[e]	44.6	1.2	2.6	…	…	Day 4	No
		33.3	1.5	4.5	…	…	Day 12	No
	1[d]	49.3	0.38	0.78	…	…	Day 7	No
		73.8	1.6	2.1	…	…	Day 58	No
		15.2	0.18	5.2	…	…	Day 82	No
Bardy et al[64] (1982)	1[c]							
	8:00 am	103 mmol/L	< 3.0 mmol/L	2.9	…	…	2 months	No
	9:00 am	238 mmol/L	14 mmol/L	5.9	< 3.0 mmol/L	1.3		
	11:00 am	123 mmol/L	< 3.0 mmol/L	2.4	14.0 mmol/L (10:30 am)	11.4		
	12:00 pm	…	< 3.0 mmol/L	…	7.0 mmol/L	…		
von Unruh et al[62] (1984)	16 total							
	1[b]	33.3	3.2	9.6	13.4	40	Day 4	No
	1	…	…	…	…	…	…	No
	1	27.9	1.1	3.9	…	…	Day 3	No
	1	…	…	…	…	…	…	No
	1	…	…	…	…	…	…	No
	1[b]	18.6	1.4	7.5	2.3 (Day 3)	12.4	Day 4	No
	1	…	2.1	…	8.0	…	Day 4	No
	1	29.5	2.2	7.5	…	…	Day 5	No
	1[f]	25.3	1.7	6.7	< 1.0	< 4.0	Day 4	No
	1[f]	…	…	…	…	…	…	No
	1	38.9	1.9	4.9	…	…	Day 5	No
	1[b]	43.8	1.2	2.8	…	…	Day 3	No
	1[c]	55.3	3.9	7.1	…	…	Day 6	No
	1[d]	31.3	0.5	1.6	…	…	Day 3	No
	1[b]	30.5	0.4	1.3	…	…	Day 4	No
	1	66.5	1.8	2.7	4.0	6.0	Day 6	No
Tsuru et al[67] (1988)	1	…	3.0	…	…	…	Day 6	No
		…	2.3	…	…	…	Day 7	No
		…	1.4	…	…	…	Day 17	No
	1	…	2.0	…	…	…	Day 1	No
		…	1.4	…	…	…	Day 3	No
		…	3.5	…	…	…	Day 15	No
		…	2.3	…	…	…	Day 29	No
		108	2.8	2.6	…	…	Day 43	No
Stahl et al[70] (1997)	1	…	…	…	6.6	…	3 months	Thrombocytopenia and anemia
Wisner[63] (1996)	2 total							
	1	67	…	…	1	1.5	3 months	No
	1	65	…	…	4	6.0	1 month	No

[a]Concentrations reported in µg/mL unless otherwise noted. Abbreviations: l = left breast, r = right breast.
[b]Valproate and carbamazepine. [c]Valproate and phenytoin. [d]Valproate and clonazepam. [e]Valproate and primidone. [f]Valproate and phenobarbital.

(see Table 2). With one exception, the milk to maternal serum concentration ratio increased over time.

Because metabolites are often implicated in cytotoxicity, carcinogenicity, and mutagenicity, Nau et al.[59] attempted to quantify the valproate metabolites present in breast milk. The only one consistently found was the 3-keto metabolite. Its concentrations in milk averaged 7% of the maternal 3-keto serum concentration. It is not clear what risk, if any, this metabolite has for a breastfeeding infant.

In brief, studies of women treated with valproate who are breast-feeding are few in number. Limitations of most of these studies can be attributed to small sample size, incomplete data collection, variable sample collection, and lack of generalizability to all ages of breastfeeding infants.

Because of a paucity of adverse effects associated with breastfeeding during treatment with valproate, valproate has been considered compatible with breastfeeding. Some authors, however, recommend against its use during breastfeeding because of the increased risk of fatal hepatotoxicity in children under 2 years of age who are treated with valproate.[71,72] While this remains a risk in breastfed infants, the serum levels of valproate in nursing infants are considerably lower than in infants treated directly with valproate. Whether these levels are low enough to create a no-risk environment is open to question. The recent report of thrombocytopenia and anemia in a breastfeeding infant suggests that exposure to valproate via breast milk may be problematic for some infants. Thus, while valproate appears relatively safe to use during breastfeeding, it is not without risks that require consideration.

Carbamazepine. Although carbamazepine is excreted into human breast milk, it is classified by the American Academy of Pediatrics Committee on Drugs as compatible with breastfeeding.[39] The serum half-life of carbamazepine in infants is equal to or longer than in adults. In adults, the half-life ranges from 12 to 30 hours. In one study,[73] the half-life ranged from 12.9 to 35.8 hours in neonates exposed in utero but not through breast milk. Another study[74] found a range of 15 to 42 hours with a mean half-life of 28 hours in both breastfed and in utero–exposed neonates. As with valproate, the recommendations for breastfeeding while being treated with carbamazepine are derived almost exclusively from case reports and studies in epileptic women. There are only 2 reports of breastfeeding women taking carbamazepine for psychiatric purposes.[63,75]

Carbamazepine is found in breast milk in concentrations between 7% and 95% of the mothers' sera[63,65,73–81] (see Table 3). Very few women were studied and of those who were, many were on anticonvulsant polytherapy. Most reports are individual cases. There is even less information on serum carbamazepine levels in nursing infants. Data from the 8 reports show that infant serum carbamazepine levels ranged from 6% to 65% of maternal serum levels (see Table 3).[63,74,75,77–79,81]

There have been 2 reports of carbamazepine-associated hepatic toxicity in breastfeeding infants.[79,82] The first described a 3-week-old boy with cholestatic hepatitis that was felt to be consistent with drug-induced hepatitis from carbamazepine exposure during pregnancy and breastfeeding.[82] The cholestasis resolved after discontinuation of nursing. No carbamazepine levels were reported.

The second report[79] described a newborn who showed jaundice during the first day of life, transient hepatic dysfunction with direct hyperbilirubinemia, and high concentrations of γ-glutamyltransferase. The mother breastfed exclusively for 9 days and then "occasionally" nursed. The hepatic dysfunction resolved despite continued breastfeeding. The milk to maternal serum ratio was 0.51 on day 2 and 0.34 on day 63. The infant serum to maternal serum ratio was 0.33 on day 2 and 0.17 on day 63. In this case, hepatic dysfunction cannot be clearly related to breastfeeding because the infant's problems began within the first day of life. It is more likely that in utero exposure to carbamazepine was the culprit, although breastfeeding could have been a contributing factor. The definition of "occasional" breastfeeding is unclear, and, consequently, how much carbamazepine the infant received under such circumstances is unknown.

Brent and Wisner[75] reported seizure-like activity in a 3-week-old infant exposed to carbamazepine, fluoxetine, and buspirone during pregnancy and postpartum until 21 days of age. All neurologic evaluations of the infant were normal at that time. The mother reported additional episodes at 4 months and 5½ months of age. It is unclear if the mother resumed breastfeeding. None of these episodes were observed by medical personnel, and all neurologic evaluations remained normal. The infant was developing normally without further symptoms at 1 year of age. Due to lack of supporting medical documentation of the episodes, the multiple medications involved, and the uncertainty of exposure via breast milk after 21 days of age, conclusions about the contribution of carbamazepine to these episodes cannot be made.

Drowsiness, irritability, refusal to feed, and a high-pitched cry occurred in a breastfed 10-week-old infant whose mother was being treated with the antihistamine clemastine, carbamazepine, and phenytoin.[81] The infant had been healthy and fully breast-fed without problems until 12 hours after clemastine was added to the regimen of carbamazepine and phenytoin. One day after discontinuation of clemastine, despite continued nursing, the infant's symptoms resolved. Thus, the symptoms seen in this case were most likely due to either clemastine alone or to an interaction of clemastine with the anticonvulsants.

Froescher et al.[65] studied 10 women taking either carbamazepine alone or carbamazepine and valproate (see Table 3). The median concentration of carbamazepine in breast milk for both groups was 35.2% of the maternal blood concentration, with a range of 24.1% to 45.7%. In this study,

Table 3. Carbamazepine Use in Women Who Breast-Feed[a]

Study	Number of Cases	Maternal Serum Level	Milk Level	Milk/Maternal Serum Level, %	Infant Serum Level	Infant Serum/ Maternal Serum Level, %	Infant Age	Infant Complications
Pynnonen and Sillanpaa[78] (1975)	1[b]	13.5 µmol/L	7.5 µmol/L	56	4.5 µmol/L	33	Day 2	No
		8.5 µmol/L	5.5 µmol/L	65	5.5 µmol/L	65	Day 3	No
		13.0 µmol/L	7.5 µmol/L	58	7.5 µmol/L	58	Day 30	No
Pynnonen et al[77] (1977)	3 total							
	1[b]	3.2	1.8	56	1.1	34	Day 2	No
		2.0	1.3	65	1.3	65	Day 3	No
		3.1	1.8	58	1.8	58	Week 4	No
	1[b]	2.6	1.5	58	…	…	Week 3	No
		2.6	1.8	69	0.5	19	Week 5	No
	1[b]	2.4	1.5	63	…	…	Week 3	No
Niebyl et al[76] (1979)	1[c]	5.8	2.3 (skim fraction)	40	…	…	Week 5	No
		5.8	1.4 (lipid fraction)	24				
Froescher et al[65] (1981)	10 total							
	1	4.6	2.1	45.7	…	…	…	No
	1	5.9	2.5	42.4	…	…	…	No
	1[d]	5.9	2.0	33.9	…	…	…	No
	1	6.3	2.1	33.3	…	…	…	No
	1	6.9	2.6	37.7	…	…	…	No
	1	7.4	2.7	36.5	…	…	…	No
	1	8.7	2.1	24.1	…	…	…	No
	1	8.9	3.6	40.4	…	…	…	No
	1[d]	10.0	2.7	27	…	…	…	No
	1	11.0	2.9	24.6	…	…	…	No
Kok et al[81] (1982)	1[e]	4.0	1.0	25	< 1.0	< 25	10 weeks	Drowsiness, irritability, refusal to feed, high-pitched cry
Kaneko et al[73] (1982)	25 total	…	1.1 mean	…	…	…	Days 1–5	No
		4.1 ± 1.6 (range of 0.2–7.3)	1.8 ± 0.9 (range of 0.5–3.8)	41.0 ± 16.8	…	…	…	
	1[f]	…	0.3				Day 30	Drowsiness, poor sucking, poor weight gain
Kuhnz et al[74] (1983)	5 total							
	1	6.9	1.4	20	…	…	Day 3	Hyperexcitability 2nd, 3rd week
		8.8	3.0	34	0.5	6	Day 5	
	1	9.7	2.3	24	…	…	Day 5	Poor feeding/partially breastfed; sedation 1st, 2nd week
		6.7	2.5	37	…	…	Day 6	
		5.3	3.0	57	…	…	Day 15	
		…	…	…	1.0	…	Day 28	
	1[g]	…	…	…	4.7	…	Day 28	Feeding modality not indicated; hyperexcitability 3rd day–4 weeks
	1	1.1	1.05	95	…	…	Day 19	Poor feeding/partially breastfed; sedation 1st, 2nd week
		1.9	1.05	55	…	…	Day 28	
	1	6.6	1.6	24	…	…	Day 5	Feeding modality not indicated; normal neonatal behavior
		5.9	1.5	25	…	…	Day 14	
		2.9	0.85	29	…	…	Day 20	
		4.9	1.4	29	…	…	Day 27	
Frey et al[82] (1990)	1	…	…	…	…	…	Week 3	Cholestatic hepatitis
Merlob et al[79] (1992)	1	5.5	2.8	51	1.8	33	Day 2	Direct hyperbilirubinemia; increased GGT
		6.5	2.2	34	1.1	17	Day 63	No
Wisner[63] (1996)	1	4.7 (total CBZ)	…	…	0.7	15	3 months	No
		1.15 (free CBZ)	…	…	0.22	20		
Brent and Wisner[75] (1998)	1[h]	6.3 ng/mL	< 0.5	< 8	0.5	8	Day 13	No
		7.1	0.5	7	< 0.5	< 7	Day 21	At 3 weeks and 4 months seizure-like episodes reported; all evaluations were normal

[a]Abbreviation: CBZ = carbamazepine, GGT = γ-glutamyltransferase. Concentrations are reported as µg/mL unless otherwise noted.
[b]CBZ and phenytoin.
[c]CBZ and primidone.
[d]CBZ and valproate.
[e]CBZ, phenytoin, and clemastine (antihistamine).
[f]CBZ, phenytoin, phenobarbital, and primidone.
[g]CBZ and clonazepam.
[h]CBZ, fluoxetine, and buspirone.

as the maternal serum levels increased, the percentage of carbamazepine in the breast milk decreased. Thus, the concentrations of carbamazepine in the milk remained relatively constant despite increasing maternal serum concentrations. The range in the milk was 2.0 to 3.6 μg/mL, whereas the maternal serum range was 4.6 to 11.0 μg/mL.

Pynnonen et al.[77] obtained breast milk and colostrum from 3 women on chronic carbamazepine and phenytoin therapy. The mean concentration ratio of milk to mothers' sera was 0.6, with ranges reported from 0.24 to 0.69 (see Table 3). Kuhnz et al.[74] obtained 11 breast milk samples from 4 women and found a mean concentration ratio of milk to mothers' sera of 0.39 ± 0.22 (see Table 3).

Because of concerns that some intermediates have mutagenic, cytotoxic, and carcinogenic properties, Pynonnen et al.[77] and Kuhnz et al.[74] measured the carbamazepine epoxide intermediate as well. Pynonnen and colleagues[77] found the milk to maternal serum ratio for carbamazepine 10,11-epoxide to be 1.05. Kuhnz et al.[74] found the mean ± SD ratio to be 0.49 ± 2.8 in 6 breast milk samples of 3 women. The clinical implications of these findings are unclear.

Kaneko et al.[73] studied the "clinical characteristics of possible side effects related to maternal antiepileptic drug use and drug disposition, including the level of antiepileptic drugs in breast milk."(p343) With regard to carbamazepine, they analyzed 25 breast milk samples. In addition to the findings in Table 3, the authors reported that the initial mean milk to maternal serum ratio was 0.616, but decreased over the next 3 days to a mean of 0.382. Despite the use of a control group of 50 infants of healthy women, results from this study are inconclusive because the authors did not distinguish between women on carbamazepine monotherapy and those on anticonvulsant polytherapy.

The generalizability of the data to all carbamazepine-exposed nursing infants is very limited owing to the small number of cases and because the information does not adequately address infants' serum levels. Furthermore, most of the levels that were obtained were taken within the first few days of life and quite likely reflect a combination of the residual exposure during pregnancy and exposure from breast milk. Previously, no adverse effects had been attributed to breastfeeding during treatment with carbamazepine, but in view of the 4 reports of poor feeding[73,74,81] and the 2 recent reports of hepatic dysfunction in breastfeeding infants,[79,82] its safety needs to be reassessed.

Gabapentin. No reports of breastfeeding infants exposed to gabapentin or of the amount of gabapentin in breast milk have been published. An unpublished research report conducted by the manufacturer analyzed the blood, urine, and breast milk of 6 healthy women treated with 400 mg of gabapentin (data on file, Parke-Davis). One woman was unable to produce breast milk. In the other 5 women, the amount of gabapentin in breast milk was about equal to that in the women's plasma. The manufacturer had no spontaneous reports of gabapentin levels in breast milk and no reports of levels in nursing infants.

Lamotrigine. There are 3 reports of lamotrigine concentrations in breastfeeding infants.[83–85] The manufacturer had no further unpublished data (E.P. Goodale, Pharm.D., written communication, Nov. 1999). The milk to maternal serum ratio was approximately 0.6 in all of the cases, with a range of 0.35 to 0.65 in the first. The first infant, followed for 5 months postpartum, had an estimated daily intake of 2 to 5 mg of lamotrigine, with serum levels ranging from 2.8 μg/mL (at 2 days after birth and exclusively breastfed) to less than 0.2 μg/mL (when feedings were supplemented with formula in a 3:1 ratio).[83] The second case described a 2-week-old infant whose serum levels were 25% of the mother's levels.[84] The third report measured serum lamotrigine levels in 3 women and their infants. The infants' serum levels were 23% to 33% of the maternal serum concentrations.[85] None of the infants experienced adverse effects. Nonetheless, exposure of breastfeeding infants to lamotrigine is of some potential concern because of the increased risk of severe life-threatening rashes in children with epilepsy who are treated with the drug.

CONCLUSIONS

After detailed review of the literature on breastfeeding while the mother is being treated with lithium, valproate, carbamazepine, gabapentin, or lamotrigine, we reached the following general conclusions. The recommendations of physicians and the American Academy of Pediatrics Committee on Drugs are based on very limited data, most derived from case reports. The recommendations for valproate and carbamazepine are based primarily on women treated for epilepsy, many of whom also received other anticonvulsants, thus limiting the generalizability to women treated with those medications for psychiatric purposes. Most of the reports of infants' serum levels were based on newborn data, thus limiting generalizability to older infants who may metabolize and excrete the medications more easily. Similarly, we are unable to reach conclusions about possible effects on premature infants since there are no reports describing this cohort. Furthermore, in newborns, the relationship between the amount of medication in milk and in infant serum is confounded by medication exposure in utero. In at least 2 cases, the combination of breastfeeding and in utero exposure may have contributed to adverse events.

In summary, nursing infants exposed to valproate receive the lowest concentration of medication with a mean infant serum to maternal serum ratio of 0.09. The mean infant serum to maternal serum ratios of carbamazepine and lithium are 0.31 and 0.43, respectively. At least one adverse event in a breastfed infant has been reported

with lithium, valproate, and carbamazepine. In each case the infant recovered without sequelae.

Recommendations regarding the compatibility of each of the medications with breastfeeding should be reevaluated, as these drugs may be more similar than different in their potential risks than is currently indicated. Lithium may not have as much propensity for toxicity as was once thought. Valproate and carbamazepine may not be as benign as they appeared initially. Insufficient information exists to suggest recommendations for gabapentin or lamotrigine except to reinforce the concern about exposing infants to lamotrigine given the increased risk of life-threatening rashes in children under 16. Finally, more data must be collected and reported on psychiatric patients who breast-feed while taking mood stabilizers so that more informed decisions can be made about the use of these medications in this population.

RECOMMENDATIONS

Given the paucity of information on all mood stabilizers and the reports of adverse events with lithium, valproate, and carbamazepine, our recommendations are as follows. If a woman requires pharmacologic treatment during the postpartum period, the choice of mood stabilizer should be based on the clinical status of the patient and the patient's historical response to medication regardless of breastfeeding status. All new mothers should be given the available information about the risks of nursing while taking medication. This discussion should include the known risks of potential toxicity and adverse events, as well as unknown hypothetical risks including behavioral teratogenicity and future psychiatric disorders in the child. Furthermore, mothers should be made aware of the risks and benefits of breastfeeding and the risks of not taking medication.

If a mother has received medication during the final weeks of her pregnancy, we recommend a 1- or 2-day washout period for the infant. During these first few days, the mother may "pump and dump" to assure the beginning of her milk supply while avoiding the potential additive exposure of medication via colostrum to the transplacental load. While this is a reasonable approach, some babies may have difficulty accepting the breast after having been exposed to a bottle nipple. However, with the assistance of lactation consultants and/or a supportive pediatrician, this obstacle can usually be overcome.

The psychiatrist should inform the mother of potential signs of toxicity so that she can monitor the infant carefully. In the case of lithium, symptoms of toxicity should be described and a detailed explanation provided of the risks of infant dehydration and its effect on lithium levels. We recommend using formula supplements either partially or totally during episodes of an infant's illness or dehydration to limit the lithium exposure and risk for toxicity. If, at any time, toxicity is suspected, infant and maternal serum levels should be obtained, and breastfeeding should be suspended, at least temporarily.

For valproate, the mother should be informed of signs of hepatic dysfunction or hematologic abnormalities. If an adverse reaction is suspected, nursing should be discontinued, at least temporarily, and infant serum and maternal serum should be obtained to measure valproate and 3-keto metabolite levels.

For carbamazepine, the mother should be informed of signs of hepatic dysfunction and central nervous system effects such as sedation and poor feeding. If the infant develops any of these signs or symptoms, carbamazepine and carbamazepine 10,11-epoxide levels in the infant serum and maternal serum should be obtained and breastfeeding should be discontinued, at least temporarily.

For data collection and research, it is important to obtain periodic milk and maternal and infant serum concentrations. However, for clinical purposes, periodic collection of milk and infant serum levels is not indicated in the absence of clinical manifestations. The psychiatrist should try to avoid polypharmacy and should keep the mother on the lowest effective dose to minimize infant exposure.

Further research would be welcome in this area. Because of the small sample size that would occur at any one institution, it is essential that collaboration occurs between treatment sites. A protocol could be instituted at each site to obtain consistent data regarding medication levels in the milk, maternal serum, and infant serum as well as evaluations of infant behavior and development. In this way, the variability of the data, such as the age of the infant or the time of the serum sample relative to medication dosing, would be controlled and more informed judgments regarding these medications could be made. In addition, long-term prospective studies of breastfed infants are needed to monitor the children's neurodevelopment following exposure. This type of information would help address concerns about behavioral teratogenicity and risk for future development of psychiatric disorders. For the anticonvulsants, these studies need to include women with psychiatric disorders.

Finally, a breastfeeding registry should be established to allow reports of cases with both positive and negative outcomes. In this way, a database could be established that would allow patients and physicians to make more fully informed decisions about breastfeeding.

Currently, the University of Rochester Medical Center's Lactation Study Center (phone: 716-275-0088) maintains a database of more than 1000 medications and drugs and provides free information to physicians regarding their use and effects during breastfeeding. There is also a registry for pregnant women who are using antiepileptic drugs: the AED (Antiepileptic Drug) Pregnancy Registry, Genetics & Teratology Unit, 149 CNY-MGH East - Room 5022A, Charlestown, MA 02129-2000, 1-888-233-2334 or 1-888-AED-AED4.

Drug names: buspirone (BuSpar), carbamazepine (Tegretol and others), clonazepam (Klonopin and others), divalproex sodium (Depakote), fluoxetine (Prozac), gabapentin (Neurontin), lamotrigine (Lamictal), phenobarbital (Donnatal and others), phenytoin (Dilantin and others), primidone (Mysoline), valproic acid (Depakene).

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