The Use of Mood Stabilizers During Breastfeeding

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The literature and majority of professional organizations endorse breastfeeding as a means to provide a number of health benefits to both mother and child. Notably, the postpartum period heralds an increased vulnerability for both new onset and symptom worsening of neuropsychiatric disorders, particularly bipolar disorder in women. While pharmacologic treatment is important for these patients, many physicians have been hesitant to prescribe medication for women who choose to breastfeed, despite the fact that a variety of medical illnesses are routinely treated in breastfeeding women (e.g., epilepsy, infection, allergies, and migraine) and that nursing infants may also directly receive medications for colic and reflux. To date, all psychotropic medications studied enter human breast milk, and many of these medications have undergone detailed investigations. While breastfeeding may complicate pharmacotherapy, it does not preclude it. There are limited scientifically derived guidelines in the treatment of women who choose to breast-feed. The pharmacokinetic properties and potential impact of infant exposure to mood stabilizers must be considered in the decision to breastfeed infants born to mothers receiving pharmacologic treatment for bipolar disorder. Past practices and methodologies for determining continuation of treatment are discussed in this article, as well as the current data for newer categories of drugs being used to treat bipolar disorder and their indications during pregnancy and breastfeeding. Treating pregnant women with neuropsychiatric illnesses in their childbearing years who are breastfeeding involves a thorough risk:benefit analysis to determine the relative safety of pharmacologic therapy. Familiarity with the extant literature and its limitations and practical considerations will enable optimizing treatment plans that maintain maternal mental health, minimize nursing infant exposures, and provide infant monitoring.

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Breastfeeding has been accepted by the majority of the medical field as the ideal form of nutrition for infants. There is considerable effort to promote breastfeeding and to inform doctors and new mothers about the benefits of breastfeeding throughout the postpartum period.[1] Given the risk of onset and exacerbation of neuropsychiatric illness in the postpartum period,[2] it is important to understand the potential effects of pharmacotherapy on the mother-infant relationship and the mother's overall mental health. By including the potential for breastfeeding during the initial treatment planning for childbearing-age women suffering from psychiatric illness and understanding appropriate approaches to treating women in the prenatal period helps to make the decision for and transition to breastfeeding much smoother for women who are undergoing pharmacotherapy.

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Unfortunately, the current classification systems for the safety of medication use during breastfeeding are limited in their direct clinical utility and there remains a lack of consensus for the best methodology to select individual medications. Over the past decade, the quantitative data on psychotropic medications in breastfeeding have demonstrated considerable growth. Consistent with the goal of minimizing nursing infant exposure to medications is consideration of unique factors such as the rate of excretion of medications into the human breast milk and the potentially immature metabolic systems of infants.

The take-home message for clinicians treating women in the perinatal period is to deliver care within their comfort zone. Clinicians who are uncomfortable with prescribing medication to a breastfeeding woman certainly should not be encouraged to do so. Expanding the clinician's knowledge base by reviewing scientific data may serve to widen this comfort zone.

BREASTFEEDING AND MATERNAL MENTAL ILLNESS

Every professional medical group supports breastfeeding as the primary form of infant nutrition. According to the American Academy of Pediatrics,[3] American College of Obstetricians and Gynecologists,[4] and the American

Dietetic Association,[5] breast milk is the only form of nutrition needed for the first year of the infant's life. The likelihood of encountering the clinical decision regarding treatment during breastfeeding continues to rise given that the annual birth rate is over 4 million births every year in the United States[6] and that the majority of neuropsychiatric illness has onset prior to family planning.[7] Further, more than 60% of women are choosing to breast-feed in the United States.[1,4]

Similarly, there is no evidence that mental illness improves during the postpartum period and the risk of severe illness requiring hospitalization rises. Kendell et al.[7] found that the risk of admission to a psychiatric hospital was extremely high in the first 30 days after childbirth, and women with a history of bipolar disorder had a greater risk of admission than women with unipolar depression or schizophrenia.

The most concise, straightforward approach in designing the initial treatment plan for women with bipolar disorder includes

1. Assume that pregnancy is imminent for all female patients between the ages of 8 and 48 years.
2. Document method of birth control at all visits.
3. Recommend supplemental folic acid (800–1000 μg) for all women and higher doses (2000–4000 μg) for women treated with an antiepileptic drug.
4. Assume that women will want to breast-feed.
5. If pharmacotherapy is the best option, consider the following axiom "new and improved = no data." Newer medications have limited or no data on use during pregnancy, the postpartum period, and breastfeeding. Prescribing the newest medication means that if the patient becomes pregnant and wants to breast-feed, there will be little or no data to assist the clinician and patient in making an informed decision.

Currently, few guidelines exist for determining the risk:benefit assessment for pharmacotherapy during lactation.[8] However, numerous sources discuss this assessment, and it is important to keep in mind that the patient may have access to these sources, as well as colleagues in pediatrics and obstetrics. The most common reference is Hale's book *Medications and Mother's Milk*.[9] This comprehensive source for information about medication indications during lactation is frequently updated. The American Academy of Pediatrics Committee on Drugs[3] meets about once every 4 years to update their recommendations, which are another important source to consider when researching particular medications. Academic Web sites are increasingly available, and there are now several mental health programs focused specifically on women's mental health with information about pharmacotherapy in pregnancy and breastfeeding.[1] Journal articles can also be useful, although methodological differences among individual studies make it difficult to establish scientific guidelines from which to derive definitive decisions on the continuation of pharmacotherapy during breastfeeding.[10] Independent of the extant data, reference material, and "academic opinions," the decision to breast-feed while taking psychotropic medication should be made on an individual basis.[3,11–15]

THE POSTPARTUM ENVIRONMENT AND INFANT EXPOSURE

The course of bipolar illness during the postpartum period has received limited investigation, but shows an overall relapse rate of 40% in a total of 183 women studied to date.[7,16–26] There are several unique features in the breastfeeding patient that warrant attention. First, many women have never experienced an extended low-estrogen environment, with fluctuations of prolactin and oxytocin, which may affect mood. Second, breastfeeding patients typically experience greater sleep disruption, which can be detrimental to the bipolar illness. Third, oral contraceptives[27] and fluctuations in estrogen[28] can affect mood and anxiety as well, and the majority of breastfeeding women who also take oral contraceptives receive progestin-only compounds. Fourth, some women may have difficulty producing enough breast milk, and a common medication to enhance milk production (metoclopramide) has the potential to affect mood as well.[29]

Our group and others[30–33] have demonstrated that all psychotropic medications cross the placenta and are present in amniotic fluid. Overall, the majority of medications demonstrate placental passage > 70% (e.g., umbilical cord blood is > 70% maternal serum concentration at delivery). Many of the mood stabilizers (i.e., lithium, lamotrigine, and valproate) cross the placenta at > 100%.[32,34] In contrast, determining nursing infant exposure is more complex.

All psychotropic medications enter the breast milk as well, although medication exposure for a nursing infant is substantially less than the exposure to a fetus during pregnancy (i.e., blood-to-blood in pregnancy and blood-to-milk-to-gut-to-blood in breastfeeding). The majority of psychotropic medication concentrations in human breast milk are typically micrograms/milliliter for antiepileptic drugs and nanograms/milliliter for antipsychotics and antidepressants. As such, nursing infant exposure relative to pregnancy is magnitudes of order difference[35]; clinical concern or changing medications for breastfeeding once exposure has occurred in pregnancy is not consistent with exposure data.

There remains an international disparity in the methodology for determining infant exposure in utero versus while nursing. Historically, investigators have relied on the milk-to-plasma (M/P) concentration ratio of the drug in the mother's milk and blood to determine the infant daily

dose.[11,36–41] Our group has demonstrated that this is woefully inaccurate and, at best, a coarse estimate.[42,43] Psychotropic medications typically display variable excretion over a 24-hour period that parallels the gastrointestinal absorption and a gradient from foremilk to hindmilk with higher concentrations in the hindmilk. Pharmacokinetic modeling for antidepressants, while complicated, is the best predictor of infant serum concentration. Detailed investigations[42–45] have demonstrated that discarding breast milk during peak medication concentrations may significantly reduce nursing infant exposure.

Another method of determining nursing infant exposure in breastfeeding has been to determine the infant dose by percentage of body weight using the M/P ratio, but this assumes that the volume of distribution for these medications by kilogram would be the same in an infant as in an adult, which is likely to be a false assumption. The standard evaluation for medication safety that seems to employ such methods and be consistent in pediatrics and obstetrics is what has become known as the 10% rule.[46] If the estimated infant daily dose is less than 10% of the maternal dose, physicians tend to be less concerned about medication exposure to the infant; however, this methodology is completely empiric.

More recently, measuring infant serum concentrations has become the more direct, although unsubstantiated, method for ascertaining infant exposure. Notably, there is a tendency to view detectable concentrations in nursing infant sera as an indication that the medication should be avoided. Meta-analysis of data sets has been extremely difficult and most likely inaccurate because of the variation in laboratory assay methodology and lack of consensus on assay techniques.

When considering the risk:benefit assessment, it is important to consider the risks of nontreatment. The child is potentially exposed to either the mother's untreated illness or a psychotropic medication. Nonexposure only exists when the mother has nonpharmacologic treatment and/or remains well in the absence of treatment. Maternal mental illness, when untreated, can expose the infant to adverse effects.[47–50] Hendrick et al.[47] found that infants who were exposed to antidepressants through breast milk did not have low weight at 6 months; however, infants who were exposed to maternal depression 2 months or more postpartum weighed significantly less at 6 months than infants whose mother's depression lasted less than 2 months or infants of euthymic mothers. Exposure to maternal psychiatric illness has been demonstrated to have adverse effects on children later in life.[49,50] For example, one study[49] found that infant exposure to maternal depression was the most significant predictor of high cortisol levels in children who were exposed to higher levels of maternal stress compared with children who were exposed to moderate or low levels of maternal stress. Another study[50] suggested that exposure to maternal depression is also associated with criminality in male offspring. More recently, a study[51] derived from the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) program found that maternal depression was associated with much higher rates of psychiatric illnesses in the children.

Bottle feeding is a viable alternative to breastfeeding with certain advantages for women undergoing pharmacotherapy. First, the infant would not be exposed to the medications, and second, some women might be relieved to have permission not to breast-feed. Bottle feeding could also be helpful in reducing sleep pattern disruptions for patients who are able to obtain additional support for help with night feedings. Of course there are downsides, including maternal guilt over not breast-feeding and the loss of potential benefits to both mother and infant. Also, if a woman has been informed that breastfeeding is the right thing to do, and then her physician suggests that she forgo breastfeeding during treatment, that may encourage her to stop her medication without the physician's knowledge and lead to risks of the untreated illness.

MEDICATION RATINGS SYSTEMS

The current medication ratings systems regarding the safety of medications during breastfeeding send mixed messages that fail to inform the decision-making process. Hale's book *Medications and Mother's Milk*[9] provides the most commonly used rating system of L1 through L5, with L1 being considered the safest medication to use during nursing. For a medication to obtain a rating of L1 requires a large number of women and/or a controlled study with a large data set. Notably, the term "large" is poorly defined. That type of information is unavailable for most drugs, though some drugs have earned L1 ratings in Hale's book despite the lack of controlled data, which suggests that the ratings are inconsistent. The American Academy of Pediatrics ratings scale[3] consists of 4 ratings: (1) usually compatible with breastfeeding, (2) unknown but of concern, (3) associated with significant side effects and should be used with caution, and (4) requires cessation of breastfeeding. Table 1 compares the Hale and the American Academy of Pediatrics ratings for several medications typically utilized in patients with bipolar disorder. As shown in the table, the ratings do not consistently reflect the data. For example, fluoxetine has a total of 202 infant blood samples and a Hale rating of L3/L2 (the L3 rating is for premature infants). However, despite the relatively substantial group of 202 blood samples from infants exposed to fluoxetine, the American Academy of Pediatrics has rated fluoxetine as unknown but of concern. Citalopram, as another example, is listed by Hale as an L3. This rating, compared with the other antidepressants that are rated L2, is based on its relatively small sample size compared with the others. These inconsistencies in ratings can be confusing, so it is important to understand

Table 1. Breastfeeding and Psychotropic Medications Commonly Utilized in Bipolar Patients: Comparing the Safety and Organization Ratings

Drug	Exposed Infants (N)[a]	Hale Rating[b]	American Academy of Pediatrics Rating[c]
Bupropion	17	L3	Unknown but may be of concern
Citalopram	69	L3	Not rated
Fluoxetine	202	L3/L2	Unknown but may be of concern
Sertraline	180	L2	Unknown but may be of concern
Paroxetine	105	L2	Unknown but may be of concern
Carbamazepine	51	L2	Usually compatible with breastfeeding
Valproate (valproic acid)	38	L2	Usually compatible with breastfeeding
Lamotrigine	16	L3	Unknown but may be of concern
Lithium	32	L4	Significant side effects; should be given with caution
Olanzapine	16	L2	Not rated
Risperidone	3	L3	Not rated
Quetiapine	7	L4	Not rated

[a]Data from Ragan et al.[52]
[b]Ratings from Hale.[9] Definitions: LI = safest, L2 = safer, L3 = moderately safe, L4 = possibly hazardous, L5 = contraindicated.
[c]Ratings from the American Academy of Pediatrics Committee on Drugs.[3]

Table 2. Mood Stabilizers and Atypical Antipsychotics in Breastfeeding

Medication Studied	Mother/Infant Pairs (N)	Adverse Events
Mood stabilizers: newer anticonvulsants		
Lamotrigine		
Tomson et al[57]	1	None
Rambeck et al[58]	1	None
Öhman et al[38]	10	None
Liporace et al[59]	4	None
Oxcarbazepine		
Bulau et al[60]	1	None
Topiramate		
Öhman et al[61]	3	None
Atypical antipsychotics[a]		
Clozapine		
Barnas et al[62]	0	N/A
Olanzapine		
Goldstein et al[63]	2	None
Kirchheiner et al[64]	1	None
Croke et al[65]	5	None
Friedman and Rosenthal[66]	1	None
Gardiner et al[39]	7[b]	None
Ambresin et al[67]	0	N/A
Quetiapine		
Lee et al[68]	1	None
Misri et al[69]	6	None
Risperidone		
Hill et al[56]	0	N/A
Ratnayake and Libretto[70]	2	None
Ilett et al[71]	2	None

[a]No published data available for aripiprazole or ziprasidone.
[b]Only 6 infant serum samples were obtained in this study (N = 6), although all 7 maternal serum samples were obtained.
Abbreviation: N/A = no available data.

that the guidelines set forth for prescribing medications in nursing women are primarily derived from small samples and case studies.

There are obvious discrepancies with ratings of mood stabilizers as well. For example, carbamazepine has a cumulative sample size of > 50 nursing infant serum collections, has a Hale rating of L2, and is considered compatible with breastfeeding. This rating is not driven by the data, because there are several reports of elevated liver enzymes in nursing infants. Valproate has far fewer cases and is given the same ratings both by Hale and the American Academy of Pediatrics. In the case of lithium, the rating also seems unrelated to the data. Lithium received a Hale rating of L4 based on several cases in which mothers took lithium during pregnancy and the infants were evaluated soon after delivery and described to have tremor and shakes within the first week of life.[13,53,54] However, this effect may have had nothing to do with breastfeeding, but rather was a result of lithium ingestion during pregnancy, demonstrated by a recent article by Newport et al.[32] When lithium is compared with valproate, there is an imbalance in the ratings. Valproate received an L2 rating and is considered compatible with breastfeeding, even though it has an only slightly larger sample size than lithium and one of the 38 cases reported a drop in infant platelet levels.[55]

For Hale, the ratings for the atypical antipsychotics are ranked by which have the most information relative to other medications in that class. However, this method assumes that the medicines are clinically equivalent, which is certainly not the case. Some patients, as we know, respond better to some medications than others. Also, some of the data can be problematic. For example, the sample data for risperidone are misleading because one infant did not actually nurse[56]; the measures were purely from breast milk, but the mother was bottle-feeding.

Although new data are continuously becoming available, 2 drug classes that still have little information regarding safety during breastfeeding are the newer antiepileptic drugs and the atypical antipsychotics. Table 2 shows available information on adverse events with frequently prescribed newer anticonvulsants and atypical antipsychotics available for use in women with neuropsychiatric illnesses. No adverse effects have been found in any of the studies so far. However, the sample sizes are low, and only a total of 8 blood samples have been taken to measure infant serum drug concentrations. Several of the atypical antipsychotic studies[39,56,63–68] either did not discuss infant serum drug concentrations or obtained infant daily dose based on maternal serum concentration and milk concentrations. On the other hand, the data for the newer anticonvulsants are rapidly accumulating. Data for lamotrigine in nursing are on the rise because of its expanding use in pregnancy.[72] Infants studied have had higher-than-expected concentration levels after breast-feeding exposure even though only 60% of the drug is transferred to the breast milk[59] accounting for the ratings. However, as with the antipsychotics, the cumulative sample sizes for

Table 3. Recommendations for Infant Monitoring

Drug	Index
Lithium	Lithium level
	Complete blood count
	Blood urea nitrogen/chromium (BUN/Cr) levels
	Thyroid-stimulating hormone (TSH)
Valproate	Valproate level (free and total)
	Platelets
	Liver enzymes
Carbamazepine	Carbamazepine (free and total)
	Complete blood count
	Liver enzymes
Lamotrigine	Rash
	Liver enzymes
Atypical antipsychotics	Weight
	Blood sugar
Typical antipsychotics	Stiffness
	Creatine phosphokinase, if indicated

Table 4. Conservative Approach to Treating Women With Neuropsychiatric Disorders During Lactation

All women of the reproductive years should be treated as if they are pregnant or breast-feeding from the very first visit
Bottle-feeding is a viable option
Document the method of birth control and remind breast-feeding women that they can get pregnant
If a medication was effective during pregnancy, medication should not be switched after birth as this exposes the infant to a second medication and there is virtually no data on 2 medication exposures. Similarly, the clinician cannot apply the majority of breast-feeding data to support this approach because these breast-feeding studies did not have women taking different medications in pregnancy
Use medications that have previously been efficacious for the individual. Trying new medication because it has more data in breastfeeding risks medication exposure and continued maternal illness
Infant monitoring should be consistent with the impact of medications in adults. Routine nursing infant serum monitoring for antidepressants is not recommended
The current classification systems do not reliably reflect the available data and are typically both class- and illness-specific, though they fail to inform the clinician of this specificity
Academic Web sites with peer-reviewed information provide the most accurate information

the newer anticonvulsants are still considerably small.[38] The pharmacologic armamentarium for the treatment of many neuropsychiatric illnesses, especially bipolar disorder, has been expanding and will continue to expand partly because these disorders typically require more complex pharmacologic interventions. As the armamentarium expands, it will be necessary to learn more about the drugs, not just in treatment, but in pregnancy and breastfeeding as well.

INFANT MONITORING

Currently, there are no established guidelines for nursing-infant monitoring, and developing guidelines will require all groups—pediatrics, psychiatry, neurology—to come together for multidisciplinary action. In the meantime, there are certainly several take-home points to remember. First, monitoring of breastfed infants whose mothers take psychotropic medications is extremely important and not often discussed. After childbirth, the infant loses maternal metabolic supports, and the rate of maturation of the various infant metabolic systems is variable. Premature infants raise additional concerns because metabolic maturation takes place at an even slower rate than in full-term infants. Infant monitoring should be consistent with the side-effect profile of the individual medication and the indices potentially affected by that medicine. From a medicolegal standpoint, all indices that can be affected by mood stabilizers or antipsychotics medication should be checked in an infant as often or more often as an adult is monitored. Recommendations for serum monitoring indices for frequently prescribed medications in bipolar disorder are listed in Table 3. We acknowledge that these are currently empiric and derived from the conservative approach of reducing both risk to the infant and medicolegal consequences.

Second, if an adverse event is suspected, breastfeeding should be suspended immediately. Simply suspending breastfeeding will provide a good indication of whether or not the adverse event was caused by the medication.

Third, it is important not to load the infant's metabolic system with more than one medication, unless there is clear evidence that the mother's first medication is not working. It is also important to avoid medications that increase infant exposure. For example, if a nursing woman is taking an antiepileptic drug, she should refrain from giving the baby children's acetaminophen very often. Similarly, breastfeeding mothers taking lithium should be advised to practice caution when taking nonsteroidal anti-inflammatory drugs and avoid becoming dehydrated,[12] just as any patient taking lithium should be cautious in these circumstances. Recent advances in pharmacogenetics have provided theoretical concerns for coprescribing medications that inhibit the multidrug resistant proteins both in pregnancy and breastfeeding, which could potentially result in increased fetal/infant exposure.[73]

RECOMMENDATIONS

The lack of available data and the controversy surrounding psychotropic medications in nursing require a complex clinical decision and a thorough risk:benefit assessment. Achieving the goal of treatment during lactation requires minimizing infant exposure and adverse effects while maintaining maternal mental health.[12] There are numerous opinions and recommendations for the treatment of nursing women for neuropsychiatric illness, and no one source should be considered the absolute. A conservative approach to treating women with neuropsychiatric illness during lactation is shown in Table 4.

Clearly, clinical treatment decisions should not be guided solely by case reports or small case series. Maternal mental illness can have significant adverse effects on both the mother and the infant. Breastfeeding complicates treatment but certainly does not preclude it.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin and others), carbamazepine (Tegretol and others), citalopram (Celexa and others), clozapine (Clozaril and others), fluoxetine (Prozac and others), lamotrigine (Lamictal and others), lithium (Eskalith, Lithobid, and others), metoclopramide (Reglan and others), olanzapine (Zyprexa), oxcarbazepine (Trileptal), paroxetine (Paxil and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), topiramate (Topamax), valproic acid (Depakene and others), ziprasidone (Geodon).

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