Published in final edited form as:
Headache. 2013 April ; 53(4): 614–627. doi:10.1111/head.12064.

Use of Common Migraine Treatments in Breast-Feeding Women: A Summary of Recommendations

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Abstract

Background—Breast-feeding has important health and emotional benefits for both mother and infant, and should be encouraged. While there are some data to suggest migraine may improve during breast-feeding, more than half of women experience migraine recurrence with 1 month of delivery. Thus, a thorough knowledge base of the safety and recommended use of common acute and preventive migraine drugs during breast-feeding is vital to clinicians treating migraine sufferers. Choice of treatment should take into account the balance of benefit and risk of medication. For some of the medications commonly used during breast-feeding, there is not good evidence about benefits.

Methods—A list of commonly used migraine medications was agreed upon by the 6 authors, who treat migraine and other headaches on a regular basis and are members of the Women's Special Interest Section of the American Headache Society. Each medication was researched by the first author utilizing widely accepted data sources, such as the American Academy of Pediatrics publication “The Transfer of Drugs and Other Chemicals Into Human Milk; Thomas Hale's manual *Medications and Mothers Milk*; Briggs, Freeman, and Yaffe's reference book *Drugs in Pregnancy and Lactation*; and the National Library of Medicine's Drugs and Lactation Database (LactMed) – a peer-reviewed and fully referenced database available online.

Results—Many commonly used migraine medications may be compatible with breast-feeding based on expert recommendations. Ibuprofen, diclofenac, and eletriptan are among acute medications with low levels in breast milk, but studies of triptans are limited. Toxicity is a concern with aspirin due to an association with Reye's syndrome; sedation or apnea is a concern with opioids. Finally, preventive medications not recommended include zonisamide, atenolol, and tizanidine.

Conclusions—Several excellent resources are available for clinicians making treatment decisions in breast-feeding women. Clinicians treating migraine should discuss both acute and preventive treatment options shortly before and within a few months after delivery, keeping in mind the clinical features of the individual patient, and in consultation with their obstetrician and pediatrician. An awareness of the pharmacological data that are currently available and how to access that data may be helpful in making treatment decisions in this population.

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Keywords

migraine; lactation; breast-feeding; treatment

The majority of new mothers prefer to breast-feed their infants following delivery. Current standards suggest breast-feeding is the optimal form of infant nutrition, and is recommended by both the American College of Obstetrics and Gynecology and the American Academy of Pediatrics (AAP). Potential beneficial effects of breast-feeding for infants are numerous, and may include decreased risk of gastrointestinal illness,[1] lower rates of atopic disease,[2] and improved cognition.[3] Breast-feeding may also benefit the mother by decreasing the risk of breast and ovarian cancer, and allowing a faster return to normal weight.[4] Just over half of the women with migraine have recurrence of migraine in the first month after childbirth.[5] Post-partum migraine occurrence may be delayed by breast-feeding, with most studies supporting breast-feeding as protective against migraine.[5,6] However, some studies suggest that female migraineurs may not improve and continue to experience migraine attacks during lactation.[7,8] A breast-feeding woman with migraine may forego treatment or even stop breast-feeding due to her fears of exposing her infant to medication. It is important to balance the risk of medication exposure with the benefit of migraine treatment. While many medications are considered to be compatible with breast-feeding, studies on breast-feeding women and their infants are rarely done due to obvious ethical concerns. However, cases of significant infant toxicity do exist, suggesting a careful, individualized risk assessment.

To some extent, most drugs transfer into breast milk. Exceptions include heparin and insulin as their size is too large to cross biological membranes. The transfer of drugs into breast milk is commonly described quantitatively using the milk to plasma (M/P) concentration ratio. The infant dose (mg/kg) can be expressed as a percentage of the maternal dose (mg/kg). A cut-off of 10% has been recommended as a guide for the safe use of most drugs during lactation, with a very low risk of infant effects.[9,10] Multiple factors influence the transfer of drugs into human breast milk and infant exposure to those drugs. Those lipophilic drugs with small molecular size, low maternal plasma protein binding, and weakly basic pH compared with milk are likely to have greater concentrations in breast milk. However, drugs that are hydrophilic, inhaled or topical, or have a high maternal first-pass metabolism are less likely to be in breast milk. Additionally, the age of the infant should be considered: premature infants clear drugs poorly, while by 7 months of age infants clear drugs at a rate similar to adults.[11]

For drugs that appear in breast milk to any significant extent, it may be reasonable to reduce infant exposure by alternating breast and bottle-feeding, or by adjusting the timing of when the medication is taken relative to breast-feeding. This approach may be particularly useful for medications with a short half-life and acute migraine treatments.

While the potential effect of these medications on the nursing infant is the primary focus for the data collected, the primary objectives for this review article are as follows: (1) to summarize the current known data available for commonly used migraine medications used during lactation and (2) to provide a list of resources for clinicians to consult when making migraine treatment decisions in this population. It is hoped that this review article can be a valuable resource for headache clinicians treating lactating migraineurs.

METHODS

A literature search was performed to determine the most highly regarded sources of information about the use of migraine medication during breast-feeding. Four sources of

information were identified, and were agreed upon by all the authors of this article to be the most useful and most reliable source of information. The rationale for selecting these sources will be discussed in the following section.

The first author contacted the AAP to determine if clinical guidelines for migraine medication use during lactation have been established. The AAP does not have established evidence-based guidelines on treating migraine in lactation. However, they have a “retired” policy statement called “The Transfer of Drugs and Other Chemicals Into Human Milk.”[12] This policy statement does not designate drugs as “safe” or “unsafe”; rather, it lists drugs and other agents into tables based on what is known or has been reported about the effect of the drug on the infant or on lactation, if known. The 7 tables are as follows:

- Table 1: Cytotoxic Drugs That May Interfere With Cellular Metabolism of the Nursing Infant
- Table 2: Drugs of Abuse for Which Adverse Effects on the Infant During Breastfeeding Have Been Reported
- Table 3: Radioactive Compounds That Require Temporary Cessation of Breastfeeding
- Table 4: Drugs for Which the Effect on Nursing Infants is Unknown But May Be of Concern
- Table 5: Drugs That Have Been Associated With Significant Effects on Some Nursing Infants and Should Be Given to Nursing Mothers With Caution
- Table 6: Maternal Medications Usually Compatible With Breastfeeding
- Table 7: Food and Environmental Agents: Effects on Breastfeeding.

A drawback of the AAP policy statement is that it was published in 2001 and has now been officially “retired” by the AAP. The designation of “retired” indicates that the 2001 publication no longer represents an official policy of the AAP. The AAP Committee on Drugs is preparing a new clinical report on selected therapeutics in lactation, with a projected completion in 2012. In the meantime, the AAP recommends the National Library of Medicine's Drugs and Lactation database (LactMed) as an excellent source of information concerning drugs to which breast-feeding mothers may be exposed. LactMed is a peer-reviewed and fully referenced database that is part of the National Library of Medicine's TOXNET system. It can be accessed at http://toxnet.nlm.nih.gov.[13] The LactMed database includes information on drugs and lactation, including maternal levels of medications in breast milk, drug levels in infant blood, potential effects in breast-feeding infants, and effects on lactation. It is free and available for both providers and patients. A recent addition is a free downloadable application for handheld devices like iPhone. This database is updated every 1–2 months. LactMed does not assign any rating system to medication for lactation; it simply lists all that is known about a particular medication in regard to lactation.

A third resource is a comprehensive manual entitled *Medications and Mothers Milk* written by Thomas Hale, PhD.[14] In this manual, the author reviews scientific literature and assigns a lactation risk category (LRC) to all listed medications. This manual is updated more frequently than theAAP policy statement. It was last published in 2010 as the 14th edition. It is available as a paperback book and can be ordered online at http://www.iBreastfeeding.com. This current edition is over 1000 pages. Medications are listed alphabetically using generic names. The index includes name brands to help locate the medication entry. Each drug monograph lists the pregnancy risk category as established by the Food and Drug Administration, Hale's LRC, and the AAP recommendations when available. Many medications have not been reviewed by the AAP committee. In this case,

the monograph will state “not reviewed” for a particular drug. In addition, each listing shows the M/P ratio when it is known,potential drug interactions,and both adult and pediatric concerns. Hale's disclaimer in the manual's preface clarifies that he makes no recommendations as to the safety of these medications during lactation but only reviews what is currently published in the scientific literature. He emphasizes that individual use of medications must be left up to the judgment of the physician, the patient, and other health-care consultants. Hale's LRCs are listed in Table 1.

Another highly regarded and comprehensive reference examining the safety of medication in both pregnancy and lactation is *Drugs in Pregnancy and Lactation* by Briggs, Freeman, and Yaffe.[15] The authors provide recommendations for breast-feeding based in large part on human data, such as milk and maternal plasma levels, infant drug levels after exposure, and reported adverse events. Their categories for breast-feeding recommendations are listed in Table 2.

For this paper, once the authors agreed upon the 4 reference sources, data for the use of migraine medication were collected and summarized. Commonly used migraine medications were divided into categories and listed by the generic names. The AAP rating given in the 2001 policy statement “Transfer of Drugs and Other Chemicals Into Human Milk,” as well as Hale's LRC, was listed for each medication. Hale's LRC was designated as L1, L2, L3, L4, or L5, with L1 being the safest and L5 contraindicated. The Briggs breast-feeding category is similarly listed.

In addition, the authors summarized the listings into tables for reference. Table 3 lists recommendations for commonly used acute migraine treatments, and Table 4 recommendations for commonly used migraine preventive drugs. In addition, each medication was researched by the first author of this review, utilizing LactMed for any additional up-to-date information. For details of the pharmacokinetics of each medication, including M/P ratio and maternal protein binding percentages, Hale's comprehensive manual and the Briggs/Freeman/Yaffe reference were used.

The AAP policy statement and the LRC as assigned by the Hale or the Briggs manual of a drug will often be different than what is found in the Physicians Desk Reference (PDR). This is because the PDR is a compendium of pharmaceutical manufacturers' package inserts. Most package inserts will designate drugs not to be used during breast-feeding due to lack of clinical studies done in breast-feeding mothers.

RESULTS

Acute Migraine Medications in Lactation

Simple Analgesics

1. Acetaminophen: Compatible with breast-feeding by AAP. LRC L1. Briggs category: compatible.
2. Aspirin: Associated with Reye's syndrome in infants. In infants of breast-feeding mothers taking aspirin, the potential adverse effects on platelet function is unclear. Peak milk levels occur at about 3 hours after ingestion and are eliminated more slowly from milk than plasma.[16] Should be given to nursing mothers with caution by AAP. LRC L3. Briggs category: potential toxicity.

Non-Steroidal Anti-Inflammatory Drugs

1. Diclofenac: Not reviewed by the AAP. Milk levels are low, and no pediatric adverse events have been noted. LRC L2. Briggs category: probablyc compatible.

2. Ibuprofen: Compatible with breast-feeding by AAP. LRC L1. Briggs category: compatible.
3. Indomethacin: Compatible with breast-feeding by AAP. One seizure reported in a 7-day-old.[17] LRC L3. Briggs category: probably compatible.
4. Ketorolac: Compatible with breast-feeding by AAP. No pediatric adverse events in 1 published study of 10 lactating women taking ketorolac 10 mg 4 times a day.[18] LRC L2. Briggs category: probably compatible.
5. Naproxen: Compatible with breast-feeding by AAP. One case of prolonged bleeding, hemorrhage, and anemia in a 7-day-old infant.[19] LRC L3 in episodic use; LRC L4 in chronic use. Briggs category: probably compatible.

Triptans

1. Almotriptan: Not reviewed by the AAP. No published evidence. LRC L3. Briggs category: probably compatible.
2. Eletriptan: Not reviewed by the AAP. One published study of 8 women given 80 mg of eletriptan showed no pediatric adverse events. Only 0.02% of the dose is present in breast milk at 24 hours.[20] LRC L2. Briggs category: compatible.
3. Frovatriptan: Not reviewed by the AAP. No published evidence. LRC L3. Briggs category: probably compatible.
4. Naratriptan: Not reviewed by the AAP. No published evidence. LRC L3. Briggs category: probably compatible.
5. Rizatriptan: Not reviewed by the AAP. No data are available for transfer into human milk, but it is concentrated in rodent milk with an M/P ratio of 5; therefore, caution is recommended in Hale's reference book.[14] LRC L3. Briggs category: probably compatible.
6. Sumatriptan: Compatible with breast-feeding by the AAP. A published study of 5 lactating women showed no adverse pediatric events.[21] LRC L3. Briggs category: probably compatible.
7. Zolmitriptan: Not reviewed by the AAP. No published evidence. LRC L3. Briggs category: probably compatible.

Ergots and Ergot Alkaloids

1. Dihydroergotamine: Not specifically addressed by AAP. DHE has significantly lower oral bioavailability and higher protein binding than ergotamine. Nevertheless, it is grouped with ergotamine in Hale's LRC L4. Briggs category: contraindicated.
2. Ergotamine: Can decrease prolactin and decrease milk production. In one 1934 study, it was noted to cause vomiting, diarrhea, and convulsions in infants when doses used for migraine are taken by the nursing mother.[22] Use caution if given to nursing mothers by AAP. LRC L4. Briggs category: contraindicated.

Antiemetics and Neuroleptics

1. Metoclopramide: Effect on infant is unknown by AAP. May increase breast milk production, although less potent than domperidone.[23] LRC L2. Briggs category: potential toxicity.

2. Ondansetron: No data available in infants. LRC L2. Briggs category: probably compatible.
3. Prochlorperazine: Caution suggested; increased risk of apnea. Not reviewed by the AAP. LRC L3. Briggs category: potential toxicity.
4. Promethazine: Sedation and apnea in younger infants; do not use if high risk apnea. Not reviewed by the AAP. LRC L2. Briggs category: probably compatible.
5. Chlorpromazine: Excreted in breast milk, and occasionally found in low concentrations in infant plasma and urine. Although no adverse events were noted with monotherapy, dual therapy with haloperidol was associated with decline in developmental scores between the 12 and 18 assessments.[24] Effect on nursing infants is unknown but may be of concern by the AAP. LRC L3. Briggs category: potential toxicity.
6. Haloperidol: Found in breast milk at concentrations about one-half of maternal. No known adverse events noted.[25] Effect on nursing infants is unknown but may be of concern by the AAP. LRC L2. Briggs category: potential toxicity.
7. Olanzapine: In 1 study, mean infant plasma levels were undetectable with no adverse effects on infants;[26] however, another study showed higher rates of breast-feeding discontinuation in subjects taking olanzapine compared with controls.[27] Not reviewed by the AAP. LRC L2. Briggs category: potential toxicity.

Opioids

1. Butorphanol: Compatible with breast-feeding by the AAP. Possible sedation in infant. LRC L2. Briggs category: probably compatible.
2. Codeine: Compatible with breast-feeding by the AAP. Four cases of neonatal apnea have been reported following administration of 60 mg codeine every 4–6 hours to breast-feeding mothers; apnea resolved after discontinuation of maternal codeine.[28] LRC L3. (Note: Although in the majority of women codeine is LRC L3, in rare conditions when a mother is a rapid metabolizer [a rare condition that leads to increased formation of morphine from codeine], codeine may be considered LRC L5; an infant death was reported in a case published in *Lancet*). Briggs category: potential toxicity.
3. Hydrocodone: Not reviewed by the AAP. No data on hydrocodone levels in milk are available. Potentially could cause sedation, constipation, or apnea especially in neonates. LRC L3. Briggs category: potential toxicity.
4. Hydromorphone: Not reviewed by the AAP. Milk levels reported to be low but caution recommended in weak or premature infants, or after prolonged use. LRC L3. Briggs category: probably compatible.
5. Meperidine: Compatible with breast-feeding by the AAP. A published study showed neurobehavioral depression after 3 days in mothers treated with meperidine post-Cesarean section.[29] Potential pediatric concerns also include sedation and poor suckling reflex. LRC L2 in older infants; LRC L3 if used post-partum. Briggs category: compatible.
6. Oxycodone: Not reviewed by the AAP. No adverse pediatric concerns have been noted, but sedation is possible. LRC L3. Briggs category: probably compatible.

Miscellaneous

1. Butalbital: Not reviewed by the AAP. No published evidence, but sedation is a concern. LRC L3. Briggs category: potential toxicity.
2. Caffeine: Compatible with breast-feeding by the AAP with moderate intake (2–3 cups per day) of caffeinated beverages. Caution is urged when interpreting caffeine quantities; a “cup” of coffee traditionally references a 150-mL or 5-oz. serving - meaning that 2–3 times this quantity may be compatible with breast-feeding. This is roughly the capacity of a single “cup” at a coffee shop. LRC L2. Briggs category: compatible.
3. Diphenhydramine: Not reviewed by the AAP. Sedation of infant is a concern. Manufacturer considers the drug contraindicated due to increased sensitivity of newborns to antihistamines.[30] LRC L2. Briggs category: probably compatible.
4. Isometheptene: Not reviewed by the AAP. No published evidence, but infant stimulation a potential concern. LRC L3. Briggs category: probably compatible.
5. Lidocaine: Compatible with breast-feeding by the AAP. Several studies have been done and show no pediatric concerns. LRC L2. Briggs category: probably compatible.
6. Magnesium sulfate: Compatible with breast-feeding by the AAP. LRC L1. Briggs category: compatible.
7. Prednisone and prednisolone: Compatible with breast-feeding by the AAP. No pediatric concerns have been reported, but infant growth and development could potentially be affected by prolonged high-dose therapy. LRC L2. Briggs category: compatible.
8. Dexamethasone: A long-acting corticosteroid, similar in effect to prednisone, although more potent. No data are available on the transfer of dexamethasone into human milk. LRC L3. Not reviewed by the AAP. Briggs category: probably compatible.

Preventive Migraine Medications in Lactation

In this section, commonly used migraine preventive medications will be divided into categories and listed alphabetically. Hale's LRC, Briggs category, and the AAP rating will be listed. For medications not listed, clinicians are encouraged to use the resources listed in this article to get information about use during lactation.

Antidepressants: Tricyclic Antidepressants

1. Amitriptyline: Drug concentrations of tricyclic antidepressants in breast milk are similar to plasma levels,[31] but these drugs and their metabolites do not appear to accumulate in infants.[32] Effect on nursing infants is unknown but may be of concern by the AAP. No pediatric adverse effects in several studies. LRC L2. Briggs category: potential toxicity.
2. Nortriptyline: There are no detectable plasma drug levels in infants of mothers on chronic nortriptyline.[33] Effect on nursing infants is unknown but may be of concern by the AAP. No pediatric adverse effects in several studies. LRC L2. Briggs category: potential toxicity.
3. Doxepin: Its long-lasting metabolite N-desmethyldoxepin may accumulate, and there is a case report of a near fatality in an 8-week-old infant.[34] Effect on nursing

infants is unknown but may be of concern by the AAP. LRC L5. Briggs category: potential toxicity.

4. Imipramine: There are relatively longer term studies in infants up to 2 years old with no detectable infant plasma levels and no adverse events.[35] Effect on nursing infants is unknown but may be of concern by the AAP. LRC L2. Briggs category: potential toxicity.

5. Protriptyline: No known reports or effects, but its low molecular weight suggests that it would be excreted into breast milk. Not reviewed by the AAP and no LRC rating. Briggs category: potential toxicity.

Antidepressants: Others

1. Bupropion: Effect on nursing infants is unknown but may be of concern by the AAP. One case of seizure in a 6-month-old.[36] LRC L3. Briggs category: potential toxicity.

2. Citalopram: Not reviewed by the AAP. Two cases of excessive somnolence, decreased feeding, and weight loss have been reported.[37] However, the majority of studies show no or limited side effects in breast-fed infants. LRC L2. Briggs category: potential toxicity.

3. Duloxetine: Not reviewed by the AAP. Milk levels in 1 study of 6 mothers were low, and no adverse pediatric effects have been reported.[38] LRC L3. Briggs category: potential toxicity.

4. Escitalopram: Not reviewed by the AAP. Reported data show relatively low infant dose in breast-fed infants and no adverse effects. LRC L2. Briggs category: potential toxicity.

5. Fluoxetine: Effect on nursing infants is unknown but may be of concern by the AAP. Severe colic, fussiness, and crying reported in 1 case study.[39] LRC L2. Briggs category: potential toxicity.

6. Paroxetine: Effect on nursing infants is unknown but may be of concern by the AAP. A neonatal withdrawal effect may follow in utero exposure but no adverse effect noted in breast-fed infants. LRC L2. Briggs category: potential toxicity.

7. Sertraline: Effect on nursing infants is unknown but may be of concern by the AAP. A published study of 11 mother/infant pairs suggests minimal transfer of sertraline into human milk.[40] LRC L2. Briggs category: potential toxicity.

8. Venlafaxine: Not reviewed by the AAP. Pediatric adverse effects have been reported upon delivery if exposed in utero to various serotonin–norepinephrine reuptake inhibitors, such as venlafaxine. A prospective investigation of perinatal pharmacology from January 2001 through July 2006 included 13 women and their nursing infants who chose to continue venlafaxine during lactation. The mean M/P ratio was 275.3%, with the highest venlafaxine and desvenlafaxine (an active venlafaxine metabolite, in addition to being the primary component of the drug, Pristiq® [Pfizer Pharmaceuticals, New York, NY, USA]) concentrations in breast milk 8 hours after maternal ingestion. No adverse events were observed or reported in the nursing infants. LRC L3.[41] Briggs category: potential toxicity.

Antiepileptics

1. Topiramate: Not reviewed by the AAP. No pediatric concerns reported in a group of 2 women receiving 150–200 mg/day at 3 weeks post-partum.[42] Observation for sedation is advised. LRC L3. Briggs category: potential toxicity.
2. Valproic acid: Compatible with breast-feeding by the AAP. Several studies show low milk levels, but monitoring for liver and platelet changes may be necessary. LRC L2. Briggs category: potential toxicity.
3. Gabapentin: Not reviewed by the AAP. No pediatric concerns have been reported. LRC L2. Briggs category: probably compatible.
4. Lamotrigine: Effect on nursing infants is unknown but may be of concern by the AAP. A study of 30 women on lamotrigine for seizure disorders reported infant plasma levels to be 18.3% of maternal plasma levels.[43] One case of severe apnea in a 16-day-old, breast-fed infant.[44] May produce significant plasma levels in some breast-fed infants, and monitoring of infant's plasma levels closely is recommended. LRC L3. Briggs category: potential toxicity.
5. Zonisamide: Not reviewed by the AAP. A published study showed high milk levels with the relative infant dose 33% of the maternal dose.[45] This is quite high. No reported adverse effects have been reported.LRC L5. Briggs category:potential toxicity.

Antihypertensives

1. Propranolol: Compatible with breast-feeding by the AAP. Studies show low M/P ratios of .33–1.65. No adverse pediatric events have been reported, but caution is recommended in infants or mothers with asthma. LRC L2. Briggs category: potential toxicity.
2. Timolol: Compatible with breast-feeding by the AAP. No pediatric adverse events have been noted. LRC L2. Briggs category: probably compatible.
3. Atenolol: Associated with significant effects on some nursing infants and should be given to nursing mothers with caution by the AAP. One report of hypotension, bradycardia, and cyanosis in a breast-fed infant of a mother taking 100 mg daily.[46] LRC L3. Briggs category: potential toxicity.
4. Candesartan: Not reviewed by the AAP. No pediatric concerns reported but caution is recommended as it may adversely affect the development of immature kidneys due to its action as an angiotensin receptor blocker on the renin–angiotensin system. LRC L3. Briggs category: probably compatible.
5. Labetalol: Compatible with breast-feeding by the AAP. Only small amounts secreted into human milk in 1 study of 3 women receiving 600–1200 mg a day of labetalol.[47] No pediatric adverse events reported. LRC L2. Briggs category: probably compatible.
6. Lisinopril: Not reviewed by the AAP. No breast-feeding data available on this product. Angiotensin converting enzyme (ACE) inhibitors, such as lisinopril, are contraindicated in the third trimester, but other ACE inhibitors, such as captopril or enalapril, may be used in term infants several weeks post-partum.[48] LRC L3. Briggs category: probably compatible.
7. Metoprolol: Compatible with breast-feeding by the AAP. No pediatric concerns have been reported. However, observation for hypotension, weakness, and bradycardia is advised. LRC L3. Briggs category: potential toxicity.

8. Nadolol: Compatible with breast-feeding by the AAP. No pediatric concerns have been reported, but it has a high M/P ratio of 4.6 and a relatively long half-life of 20–24 hours. LRC L4. Briggs category: potential toxicity.
9. Verapamil: Compatible with breast-feeding by the AAP. Three studies show low concentrations in milk. No adverse pediatric events have been reported. LRC L2. Briggs category: probably compatible.

Miscellaneous

1. Onabotulinumtoxin A: Not reviewed by the AAP. Botulinum is not secreted into breast milk as long as it is injected properly into the muscle. LRC L3. Briggs category: probably compatible.
2. Alprazolam: Effect in infants is unknown but may be of concern by the AAP. A neonatal withdrawal syndrome was evident in a breast-fed infant first week post-partum; the mother took 0.5 mg 2–3 times daily during pregnancy and post-partum.[49] This data suggest that the amount of alprazolam in breast milk was insufficient to prevent a withdrawal syndrome. LRC L3. Briggs category: potential toxicity.
3. Clonazepam: Not reviewed by the AAP. In a group of women receiving 2 mg or less per day, with or without quetiapine or paroxetine, no drug was detected in breast milk.[50] Low incidence of toxicity is suggested by available data. LRC L3. Briggs category: potential toxicity.
4. Combined hormonal contraceptives: Compatible with breast-feeding by the AAP. Very little information is available on today's low-dose formulations. High-dose pills may suppress milk production and lower protein content in breast milk. Not recommended for the first 4–8 weeks of lactation. LRC L3. Briggs category: probably compatible.
5. Estrogen–estradiol: Compatible with breast-feeding by the AAP. Possible suppression of milk production. LRC L3. Briggs category: compatible.
6. Melatonin: Not reviewed by the AAP. No pediatric concerns have been reported. LRC L3. Briggs category: probably compatible in low doses.
7. Riboflavin: Compatible with breast-feeding by the AAP. No pediatric adverse events have been reported. LRC L1. Briggs category: compatible.
8. Magnesium sulfate: Compatible with breast-feeding by the AAP. LRC L1. Briggs category: compatible.
9. Tizanidine: Not reviewed by the AAP. No pediatric adverse events have been reported, but caution is advised since this product has a long half-life, high lipid solubility, and significant central nervous system (CNS) penetration. LRC L4. Briggs category: potential toxicity.
10. Quetiapine: One study of quetiapine in breast milk suggested that the levels are too low to affect infants.[51] Not reviewed by the AAP LRC L2. Briggs category: potential toxicity.
11. Cyproheptadine: Not reviewed by the AAP. Can lower prolactin levels with chronic use and affect lactation.[52] Contraindicated by manufacturer because of increased sensitivity of newborns to antihistamines.[30] LRC L3. Briggs category: probably compatible.

There is little known information about the safety of many nutraceutical products in breast-feeding.This includes preventive treatments for migraine, such as coenzyme Q10 and petasites (butterbur), although coenzyme Q10 is present in breast milk normally.[53]

DISCUSSION

There are no evidence-based guidelines for the treatment of migraine during breast-feeding. Current data and recommendations are limited by the lack of clinical studies done in breast-feeding women and the very small numbers reported in case reports or small published studies. However, despite these limitations, there are many treatment options for migraine that are compatible with breast-feeding. Excellent resources are available to help clinicians in making treatment decisions in the breast-feeding female migraine patient. Suggested resources include the following:

1. *Medications and Mothers' Milk* by Thomas Hale, PhD (14th edition, 2010);
2. AAP policy statement: The Transfer of Drugs and Other Chemicals Into Human Milk. Look for a new updated policy statement in 2013; it will be posted on the official AAP website at http://www.aap.org;
3. Access to LactMed by computer or electronic device (http://toxnet.nlm.nih.gov/cgi-bin); and
4. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk by Gerald Briggs et al (9th edition).

An open discussion with our patients about available resources, and the risks and benefits of various medications while nursing, can foster a collaborative approach to migraine treatment during breast-feeding. Consideration of potential efficacy should be taken into account when making treatment decisions. Updated guidelines for the prevention of episodic migraine were completed in 2012 by the American Headache Society and the American Academy of Neurology.[54] Awareness of these guidelines, including the level of evidence for a particular medication being considered, should be considered when making treatment decisions in breast-feeding women. For acute migraine treatment, the United States Headache Consortium Guidelines can be helpful in balancing safety with efficacy of a particular treatment.[55] The best approach is often to see the patient in the third trimester before giving birth to discuss if the mother will breast-feed after giving birth, and the potential risks of acute and preventive migraine medication. For acute migraine, medications with very low absorption into breast milk may be appropriate, with no need to discontinue breast-feeding. As examples, ibuprofen and eletriptan have very low levels in breast milk, and many acute medications have short half-lives, making it fairly easy to briefly discontinue breast-feeding. The decision to use preventive medication while breast-feeding is more complicated. For women with a history of refractory migraine, long-lasting or especially disabling migraine, or history of migraine worsening soon after a previous pregnancy, it may be reasonable to start preventive medication immediately after giving birth and bottle feeding, or to only use preventive medication with very low concentrations in breast milk. For women previously treated successfully with a particular preventive, it may be worth restarting that same medication soon after delivery. For women with episodic migraine for whom acute medications are effective and in those doing well during pregnancy, it may be reasonable to delay preventive medication to allow women to breast-feed. Breast-feeding while taking medications may be higher risk to preterm infants in their first month or two as their ability to metabolize drugs is lower.

A follow-up visit after giving birth should address migraine frequency and severity if the mother is breast-feeding, and if so how long she plans to do so. The majority of women

breast-feed in the early post-partum period, but less than half of women continue to breast-feed at 6 months and only about 30% of women exclusively breast-feed at 3 months.[56] A few medications that are considered high risk in pregnancy may be relatively safer for breast-feeding due to low concentrations in breast milk, such as valproate. Starting at lower doses and titrating up more slowly than usual is 1 strategy. For example, when starting topiramate, this might mean starting at 15 mg instead of 25 mg, or increasing the dose every 2–3 weeks instead of weekly. For tricyclic antidepressants, such as amitriptyline or nortriptyline, this may mean starting at 10 mg rather than 25 mg. Starting at low doses allows the ability to assess for any adverse effects on the infant, such as sedation, and within the first months of life infant metabolism rapidly increases.

In the absence of controlled clinical trials and evidence-based guidelines, health care providers can strive to make good treatment decisions based on the pharmacological data that are currently available. Our migraine patients desirous of breast-feeding will benefit from our awareness of what is known about medication use during breast-feeding.

Acknowledgments

Source of Funding: None.

Conflict of Interest: S.H., M.M., A.C., S.L., and S.S. have no conflicts of interest relevant to this paper. B.L.P. receives salary support through the National Institute of Neurological Disorders and Stroke (K2310896737).

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Table 1

Hale's Lactation Risk Categories

L1 SAFEST: Drugs have been taken by a large number of breast-feeding women without any observed increase in adverse effects in the infant. Controlled studies in breast-feeding women fail to demonstrate risk to the infant, and the possibility of harm to the breast-feeding infant is remote, or the product is not orally bioavailable in an infant.
L2 SAFER: Drugs that have been studied in a limited number of breast-feeding women without an increase in adverse effects in the infant. And/or the evidence of a demonstrated risk that is likely to follow use of this medication in a breast-feeding woman is remote.
L3 MODERATELY SAFE: Drugs for which there are no controlled studies in breast-feeding women; however, the risk of untoward effects to a breast-fed infant is possible, or controlled studies show only minimal nonthreatening adverse effects. Drugs should only be given if the potential benefit justifies the potential risk to the infant. (New medications that have no published data are automatically put into this category, regardless of how safe they may be.)
L4 POSSIBLY HAZARDOUS: Positive evidence of risk to a breast-fed infant or to breast milk production, but the benefits from use in breast-feeding mothers may be acceptable despite the risk to the infant (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
L5 CONTRAINDICATED: Significant and documented risk to the infant. Drug should not be used as the risk outweighs any possible benefit.

Table 2

Drugs in Pregnancy and Lactation: Briggs Breast-Feeding Recommendation Categories

Category	Description
Compatible	Drug has no or limited excretion into breast milk or does not cause toxicity.
Hold breast-feeding	Maternal benefit of therapy outweighs the benefits of breast milk to an infant. Hold breast-feeding until therapy is completed.
No (limited) human data – probably compatible	Available data suggest that the drug does not represent a significant risk to a nursing infant.
No (limited) human data – potential toxicity	Characteristics of the drug suggest that breast-feeding could represent a clinically significant risk to the infant.
No (limited) human data – potential toxicity (mother)	Breast-feeding could represent a clinically significant risk to the mother (ie, loss of essential vitamins or nutrients).
Contraindicated	Drug may cause severe toxicity, or breast-feeding is contraindicated due to the condition for which the drug is indicated.

Table 3

Breast-Feeding Recommendations for Acute Migraine Treatment

Drug	Hale Lactation Rating	Drugs in Pregnancy and Lactation Briggs Category
Simple analgesics and non-steroidal anti-inflammatory drugs		
Acetaminophen	L1	Compatible
Aspirin	L3	Potential toxicity
Diclofenac	L2	Probably compatible
Ibuprofen	L1	Compatible
Indomethacin	L3	Probably compatible
Ketorolac	L2	Probably compatible
Naproxen	L3 or L4	Probably compatible
Migraine-specific medications		
Almotriptan	L3	Probably compatible
Eletriptan	L2	Compatible
Frovatriptan	L3	Probably compatible
Naratriptan	L3	Probably compatible
Rizatriptan	L3	Probably compatible
Sumatriptan	L3	Probably compatible
Zolmitriptan	L3	Probably compatible
Dihydroergotamine	L4	Contraindicated
Ergotamine	L4	Contraindicated
Antiemetics and neuroleptics		
Metoclopramide	L2	Potential toxicity
Ondansetron	L2	Probably compatible
Prochlorperazine	L3	Potential toxicity
Promethazine	L2	Probably compatible
Chlorpromazine	L3	Potential toxicity
Haloperidol	L2	Potential toxicity
Olanzapine	L2	Potential toxicity
Opioids		
Butorphanol	L2	Probably compatible
Codeine	L3	Potential toxicity
Hydrocodone	L3	Potential toxicity
Hydromorphone	L3	Probably compatible
Meperidine	L2	Compatible
Oxycodone	L3	Probably compatible
Others		
Butalbital	L3	Potential toxicity
Caffeine	L2	Compatible
Isometheptene	L3	Probably compatible
Lidocaine	L2	Probably compatible
Dexamethasone	L3	Probably compatible

Drug	Hale Lactation Rating	Drugs in Pregnancy and Lactation Briggs Category
Prednisone	L2	Compatible
Diphenhydramine	L2	Probably compatible

Table 4

Breast-Feeding Recommendations for Commonly Used Migraine Prophylactic Medications

Drug	Hale Lactation Rating	Drugs in Pregnancy and Lactation Briggs Category
Antidepressants		
Amitriptyline	L2	Potential toxicity
Nortriptyline	L2	Potential toxicity
Doxepin	L5	Potential toxicity
Imipramine	L2	Potential toxicity
Protriptyline	–	Potential toxicity
Bupropion	L3	Potential toxicity
Citalopram	L2	Potential toxicity
Duloxetine	L3	Potential toxicity
Escitalopram	L2	Potential toxicity
Fluoxetine	L2	Potential toxicity
Paroxetine	L2	Potential toxicity
Sertraline	L2	Potential toxicity
Venlafaxine	L3	Potential toxicity
Antiepileptics		
Topiramate	L3	Potential toxicity
Valproic Acid	L2	Potential toxicity
Gabapentin	L2	Probably compatible
Lamotrigine	L3	Potential toxicity
Zonisamide	L5	Potential toxicity
Antihypertensives		
Propranolol	L2	Potential toxicity
Timolol	L2	Probably compatible
Atenolol	L3	Potential toxicity
Candesartan	L3	Probably compatible
Labetalol	L2	Probably compatible
Lisinopril	L3	Probably compatible
Metoprolol	L3	Potential toxicity
Nadolol	L4	Potential toxicity
Verapamil	L2	Probably compatible
Others		
Onabotulinumtoxin A	L3	Probably compatible
Magnesium	L1	Compatible
Riboflavin	L1	Compatible
Cyproheptadine	L3	Probably compatible