



## CLINICAL REPORT

# The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on Selected Topics

## abstract

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Many mothers are inappropriately advised to discontinue breastfeeding or avoid taking essential medications because of fears of adverse effects on their infants. This cautious approach may be unnecessary in many cases, because only a small proportion of medications are contraindicated in breastfeeding mothers or associated with adverse effects on their infants. Information to inform physicians about the extent of excretion for a particular drug into human milk is needed but may not be available. Previous statements on this topic from the American Academy of Pediatrics provided physicians with data concerning the known excretion of specific medications into breast milk. More current and comprehensive information is now available on the Internet, as well as an application for mobile devices, at LactMed (<http://toxnet.nlm.nih.gov>). Therefore, with the exception of radioactive compounds requiring temporary cessation of breastfeeding, the reader will be referred to LactMed to obtain the most current data on an individual medication. This report discusses several topics of interest surrounding lactation, such as the use of psychotropic therapies, drugs to treat substance abuse, narcotics, galactagogues, and herbal products, as well as immunization of breastfeeding women. A discussion regarding the global implications of maternal medications and lactation in the developing world is beyond the scope of this report. The World Health Organization offers several programs and resources that address the importance of breastfeeding (see <http://www.who.int/topics/breastfeeding/en/>). *Pediatrics* 2013;132:e796–e809

## INTRODUCTION

Lactating women can be exposed to medications or other therapeutics, either on a limited or long-term basis, depending on the need to treat acute or chronic conditions. Many women are advised to discontinue nursing or avoid taking necessary medications because of concerns about possible adverse effects in their infants.<sup>1</sup> Such advice is often not based on evidence, because information about the extent of drug excretion into human milk may be unavailable, and for many drugs, information is limited to data from animal studies, which may not correlate with human experience. In addition, not all drugs are excreted in clinically significant amounts into human milk, and the presence of a drug in human milk may not pose a risk for the infant. To weigh the risks and benefits of breastfeeding, physicians need to consider multiple factors. These factors include the need for the drug by the mother, the potential effects of

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**KEY WORD**

human milk

**ABBREVIATIONS**

AAP—American Academy of Pediatrics

FDA—Food and Drug Administration

HBV—hepatitis B vaccine

HPV—human papillomavirus vaccine

NSAID—nonsteroidal antiinflammatory drug

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

\*The recommendations in this review are those of the authors and do not represent the views of the US Food and Drug Administration.

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the drug on milk production, the amount of the drug excreted into human milk, the extent of oral absorption by the breastfeeding infant, and potential adverse effects on the breastfeeding infant. The age of the infant is also an important factor in the decision-making process, because adverse events associated with drug exposure via lactation occur most often in neonates younger than 2 months and rarely in infants older than 6 months.<sup>2</sup> In the near future, pharmacogenetics may also provide important guidance for individualized decisions.

In large part because of efforts by Cheston Berlin, Jr, MD, a statement by the American Academy of Pediatrics

(AAP) on the transfer of drugs and chemicals into human milk was first published in 1983<sup>3</sup> and underwent several subsequent revisions,<sup>4,5</sup> the most recent of which was published in 2001.<sup>6</sup> Previous editions were intended to list drugs potentially used during lactation and to describe possible effects on the infant and/or on lactation. Revisions for the statement can no longer keep pace with the rapidly changing information available via the Internet, published studies, and new drug approvals. A more comprehensive and current database is available at LactMed (<http://toxnet.nlm.nih.gov>). LactMed includes up-to-date information on drug levels in

human milk and infant serum, possible adverse effects on breastfeeding infants, potential effects on lactation, and recommendations for possible alternative drugs to consider. Common herbal products are also included. For this reason, with the exception of radioactive compounds that require temporary or permanent cessation of breastfeeding, the reader will be referred to LactMed to obtain the most current data on an individual medication.

This statement reviews proposed changes in US Food and Drug Administration (FDA) labeling that are designed to provide useful information to the physician and to outline general

LactMed is part of the National Library of Medicine's Toxicology Data Network (TOXNET)

Each record includes the following information:

- Generic name: refers to US-adopted name of active portion of the drug
- Scientific name: genus and species of botanical products (when applicable)
- Summary of use during lactation (includes discussion of conflicting recommendations and citations)
- Drug levels
  - Maternal levels: based on studies that measure concentration in breast milk; includes relative infant dose (weight-adjusted percentage of maternal dose) when possible
  - Infant levels: serum or urine concentrations from the literature
- Effects in breastfed infants: adverse events with Naranjo\* assessment of causality (definite, probably, possibly, unlikely)
- Possible effects on lactation: if known, including effects on infants that may interfere with nursing (eg, sedation)
- Alternative drugs to consider: may not be comprehensive
- References
- Chemical Abstracts Service Registry Number
- Drug class
- LactMed record number
- Last revision date

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\* The Naranjo probability scale is a method used to estimate the probability that an adverse event is caused by a drug.<sup>7</sup>

considerations for individual risk/benefit counseling. An update regarding the use of antidepressants, anxiolytics, and antipsychotics in the lactating woman is also provided, because the use of psychotropic agents during lactation is still debated. Since publication of the last statement, numerous questions have been raised regarding the use of methadone in the lactating woman. For this reason, therapies for substance abuse and smoking cessation are discussed. Given the finding that codeine use may be associated with toxicity in patients, including neonates with ultrarapid metabolism, a brief review of alternative agents to treat pain in the lactating woman is provided. The use of galactagogues is also reviewed because more women now endeavor to breastfeed adopted infants or preterm neonates. The increasing use of herbal products has invited a discussion of the merits of these alternative therapies in the nursing woman. Finally, immunization of breastfeeding women and their infants will be reviewed to assist pediatricians in encouraging immunization when needed in lactating women and addressing parental reluctance to immunize breastfed infants.

## GENERAL CONSIDERATIONS

Several factors should be considered when advising a woman regarding a decision to breastfeed her infant while she is on drug therapy. The benefits of breastfeeding for both the infant and mother need to be weighed against the risks of drug exposure to the infant (or to the mother, in the case of agents intended to induce lactation). Many factors affect the individual risk/benefit decision, including specific information about chemical and pharmacologic properties of the drug, which may be available from resources such as LactMed and in product labeling. In

general, chemical properties of a drug, such as lack of ionization, small molecular weight, low volume of distribution, low maternal serum protein binding, and high lipid solubility, facilitate drug excretion into human milk. Drugs with long half-lives are more likely to accumulate in human milk, and drugs with high oral bioavailability are more easily absorbed by the infant.<sup>8</sup> The adverse event profile of the drug is another property that affects the individual risk/benefit ratio. Use of a drug with a significant adverse effect in a lactating woman (such as an arrhythmia) may be acceptable to treat a serious illness in the mother; however, use of the same drug to increase milk production would not be acceptable. For drugs with an adverse event profile that correlates with increasing dosage, higher maternal doses may be associated with greater neonatal toxicity. In addition, the timing of exposure and the duration of therapy are other important considerations. A decision to breastfeed when continuing treatment with an agent for which in utero exposure also has occurred differs from a decision to initiate a novel therapy in the early postpartum period. Similarly, the risks of a single-dose therapy or short-term treatment may differ from those of a chronic therapy.

In addition to pharmacokinetic or chemical properties of the drug, the infant's expected drug exposure is influenced by infant and maternal factors beyond basic known pharmacokinetic and chemical properties of the drug itself. For example, the risk of adverse reactions in a preterm infant or an infant with underlying chronic medical conditions may be higher than that for a more mature or healthier infant. Certain drugs may accumulate in the breastfed infant because of reduced clearance or immaturity of metabolic pathways. However, for other

drugs (eg, acetaminophen), the immaturity of these same pathways may protect an infant from toxic drug metabolites. Similarly, patients with specific genotypes may experience drug toxicity, as evidenced by fatalities observed in individuals who demonstrate ultrarapid metabolism of codeine.<sup>9</sup> Finally, certain infant conditions, such as metabolic diseases, and maternal health conditions may preclude nursing (eg, HIV) or require multiple therapies that are particularly toxic (eg, cancer treatment).

## CHANGES IN DRUG LABELING

In the past, the lactation section in FDA-approved labeling was often limited to statements that advise caution or contain an admonition to discontinue breastfeeding or discontinue therapy, depending on the importance to the mother. In 2008, the FDA published a proposed revision to the regulations, which affects the pregnancy and lactation sections of labeling. The agency is currently working on the final rule, which is intended to provide a clinically oriented framework for placement of pregnancy and lactation information into drug labeling and to permit the patient and physician to explore the risk/benefit on the basis of the best available data. Under the proposed rule, the current Nursing Mothers section is replaced by a section called Lactation. The Lactation section of labeling will contain 3 subsections: Risk Summary, Clinical Considerations, and Data. The Risk Summary section will include a summary of what is known about the excretion of the drug into human milk and potential effects on the breastfed infant, as well as maternal milk production. The Clinical Considerations section will include methods to minimize exposure of the breastfed infant to the drug when applicable, as well as information about monitoring for

expected adverse drug effects on the infant. The Data component will provide a detailed overview of the existing data that forms the evidence base for the other 2 sections.

In addition to the proposed rule, the FDA published "Guidance for Industry: Clinical Lactation Studies: Study Design, Data Analysis, and Recommendations for Labeling."<sup>10</sup>

Along with outlining recommendations regarding lactation study design as well as the timing and indications for these studies, this draft guidance includes advice on parameters (several of which are used in LactMed) that can be used to inform physicians about the extent of drug exposure. Using these parameters, drug exposure to the infant may be measured directly in infant serum or estimated on the basis of pharmacokinetic parameters. These estimates of infant exposure (for example, relative infant dose) can be expressed as a percent of weight-adjusted maternal or, when known, weight-adjusted pediatric dose.

### ESTIMATES OF DRUG EXPOSURE

Daily Infant Dosage (mg/day)=

$$\sum (\text{drug concentration in each milk collection} \times \text{expressed volume in each milk collection})$$

OR

$$C_{\text{milk}} [\text{average drug concentration in milk (mg/mL)}] \times V_{\text{milk}} (\text{volume in mL of milk ingested in 24 hours})$$

Note:  $V_{\text{milk}}$  is typically estimated to be 150 mL/kg/day

Relative Infant Dose

$$\% \text{ Maternal Dose} = [\text{Daily Infant Dosage (mg/kg/day)} \div \text{Maternal Dose (mg/kg/day)}] \times 100$$

$$\% \text{ Infant or Pediatric Dose} = [\text{Daily Infant Dosage (mg/kg/day)} \div \text{Infant or Pediatric dose (mg/kg/day)}] \times 100$$

### ANTIDEPRESSANTS, ANXIOLYTICS, AND ANTIPSYCHOTICS

Previous statements from the AAP categorized the effect of psychoactive drugs on the nursing infant as "unknown but may be of concern." Although new data have been published since 2001, information on the long-term effects of these compounds is still limited. Most publications regarding psychoactive drugs describe the pharmacokinetics in small numbers of lactating women with short-term observational studies of their infants. In addition, interpretation of the effects on the infant from the small number of longer-term studies is confounded by prenatal treatment or exposure to multiple therapies. For these reasons, the long-term effect on the developing infant is still largely unknown.<sup>11,12</sup>

Many antianxiety drugs, antidepressants, and mood stabilizers appear in low concentrations in human milk, with estimated relative infant doses less than 2% of weight-adjusted maternal dose and/or milk-plasma ratios less than 1.<sup>13</sup> However, the percentage of maternal doses that approach clinically significant levels (10% or more) have been reported for bupropion,<sup>14</sup> diazepam,<sup>13</sup> fluoxetine,<sup>15</sup> citalopram,<sup>16</sup> lithium,<sup>17</sup> lamotrigine,<sup>18</sup> and venlafaxine.<sup>19</sup> Data on drug excretion in human milk are not available for up to one-third of psychoactive therapies.<sup>13</sup>

Because of the long half-life of some of these compounds and/or their metabolites, coupled with an infant's immature hepatic and renal function, nursing infants may have measurable amounts of the drug or its metabolites in plasma and potentially in neural tissue. Infant plasma concentrations that exceed 10% of therapeutic maternal plasma concentrations have been reported for a number of selective serotonin reuptake inhibitors,

**TABLE 1** Psychoactive Drugs With Infant Serum Concentrations Exceeding 10% of Maternal Plasma Concentrations<sup>a</sup>

Agent	Reference
Citalopram	Weissman 2004 <sup>20</sup>
Clomipramine	Schimmell 1991 <sup>21</sup>
Diazepam	Wesson 1985 <sup>22</sup>
Doxepin	Moretti 2009 <sup>16</sup>
Fluoxetine	Weissman 2004, <sup>20</sup> product labeling
Fluvoxamine	Weissman 2004 <sup>20</sup>
Lamotrigine	Newport 2008, <sup>18</sup> Fotopoulou 2009 <sup>23</sup>
Lithium	Viguerra 2007, <sup>24</sup> Grandjean 2009, <sup>25</sup> Boğen 2012 <sup>26</sup>
Mirtazapine	Tonn 2009 <sup>27</sup>
Nortriptyline	Weissman 2004 <sup>20</sup>
Olanzapine	Whitworth 2008 <sup>28</sup>
Sertraline	Hendrick 2001, <sup>29</sup> Stowe 2003 <sup>30</sup>
Venlafaxine	Newport 2009 <sup>19</sup>

<sup>a</sup> Based on individual maternal-infant pair(s); may include active metabolites.

antipsychotics, anxiolytics, and mood stabilizers (see Table 1).

Mothers who desire to breastfeed their infant(s) while taking these agents should be counseled about the benefits of breastfeeding as well as the potential risk that the infant may be exposed to clinically significant levels and that the long-term effects of this exposure are unknown. Consideration should be given to monitoring growth and neurodevelopment of the infant.

### DRUGS FOR SMOKING CESSATION OR TO TREAT SUBSTANCE ABUSE/ALCOHOL DEPENDENCE

Although many women are appropriately advised to refrain from smoking, drinking, and using recreational drugs during and after pregnancy, in part because of adverse effects on their infants (see Table 2), some are unable to do so and may seek assistance after delivery. Maternal smoking is not an absolute contraindication to breastfeeding.<sup>31</sup> Nonetheless, for multiple reasons, including the association of sudden infant death syndrome with

**TABLE 2** Drugs of Abuse for Which Adverse Effects on the Breastfeeding Infant Have Been Reported<sup>a</sup>

Drug	Reported Effect or Reason for Concern	Reference
Alcohol	Impaired motor development or postnatal growth, decreased milk consumption, sleep disturbances. Note: Although binge drinking should be avoided, occasional, limited ingestion (0.5 g of alcohol/kg/d; equivalent to 8 oz wine or 2 cans of beer per day) may be acceptable.	Koren 2002, <sup>34</sup> Backstrand 2004, <sup>35</sup> Mennella 2007 <sup>36</sup> National Academy of Sciences 1991 <sup>37</sup>
Amphetamines	Hypertension, tachycardia, and seizures. In animal studies of postnatal exposure, long-term behavioral effects, including learning and memory deficits and altered locomotor activity, were observed.	Product labeling
Benzodiazepines	Accumulation of metabolite, prolonged half-life in neonate or preterm infant is noted; chronic use not recommended.	Jain 2005, <sup>38</sup> Malone 2004 <sup>39</sup>
Cocaine	Apnea, cyanosis, withdrawal, sedation, cyanosis, and seizures. Intoxication, seizures, irritability, vomiting, diarrhea, tremulousness.	Chasnoff 1987, <sup>40</sup> Winecker 2001 <sup>41</sup>
Heroin	Withdrawal symptoms, tremors, restlessness, vomiting, poor feeding.	vandeVelde 2007 <sup>42</sup>
LSD	Potent hallucinogen.	
Methamphetamine	Fatality, persists in breast milk for 48 h.	Ariagno 1995, <sup>43</sup> Bartu 2009 <sup>44</sup>
Methylene dioxy-methamphetamine (ecstasy)	Closely related products (amphetamines) are concentrated in human milk.	
Marijuana (cannabis)	Neurodevelopmental effects, delayed motor development at 1 y, lethargy, less frequent and shorter feedings, high milk-plasma ratios in heavy users.	Djulus 2005, <sup>45</sup> Campolongo 2009, <sup>46</sup> Garry 2010 <sup>47</sup>
Phencyclidine	Potent hallucinogen, infant intoxication.	AAP 2001, <sup>6</sup> Academy of Breastfeeding Medicine <sup>48</sup>

<sup>a</sup> Effect on maternal judgment or mood may affect ability to care for infant.

tobacco exposure,<sup>32,33</sup> lactating women should be strongly encouraged to stop smoking and to minimize secondhand exposure. Exposure to alcohol or recreational drugs may impair a mother's judgment and interfere with her care of the infant and can cause toxicity to the breastfeeding infant (see Table 2).

Limited information is available regarding the use of medications in lactating women to treat substance abuse or alcohol dependence or for smoking cessation. However, the presence of behaviors, such as continued ingestion of illicit drugs or alcohol, and underlying conditions, such as HIV infection, are not compatible with breastfeeding.<sup>49,50</sup> Patients also require ongoing psychosocial support to maintain abstinence.<sup>48</sup>

Methadone, buprenorphine, and naltrexone are 3 agents approved by the FDA for use in the treatment of opioid dependence. Continued breastfeeding by women undergoing such treatment presumes that the patient remains abstinent, is HIV negative, and is en-

rolled in and closely monitored by an appropriate drug treatment program with significant social support.<sup>48,51</sup>

Potential adverse effects on breastfeeding infants from methadone (according to product labeling) and buprenorphine include lethargy, respiratory difficulty, and poor weight gain.<sup>52</sup> The long-term effects of methadone in humans are unknown. Nonetheless, methadone levels in human milk are low, with calculated infant exposures less than 3% of the maternal weight-adjusted dose.<sup>53,54</sup> Plasma concentrations in infants are also low (less than 3% of maternal trough concentrations) during the neonatal period and up to 6 months postpartum.<sup>55,56</sup> For these reasons, guidelines from the Academy of Breastfeeding Medicine encourage breastfeeding for women treated with methadone who are enrolled in methadone-maintenance programs.<sup>48</sup>

Buprenorphine is excreted into human milk and achieves a level similar to that in maternal plasma.<sup>57</sup> Infant exposure

appears to be up to 2.4% of the maternal weight-adjusted dose.<sup>55,56,58</sup> However, buprenorphine can be abused, and although the significance in humans is unknown, labeling for buprenorphine and buprenorphine/naloxone combinations states that use is not advised by lactating women, because animal lactation studies have shown decreased milk production and viability of the offspring. FDA labeling also advises caution for use of naltrexone in nursing infants of opioid-dependent women. Of note, published information on naltrexone is limited to 1 case report that estimates infant exposure to be low (7 µg/kg/d, or 0.86% of the maternal weight-adjusted dose).<sup>59</sup>

Transferred amounts of methadone or buprenorphine are insufficient to prevent symptoms of neonatal abstinence syndrome.<sup>49,60</sup> Neonatal abstinence syndrome can occur after abrupt discontinuation of methadone.<sup>51,61</sup> Thus, breastfeeding should not be stopped abruptly, and gradual



weaning is advised if a decision is made to discontinue breastfeeding.

Limited information is available for disulfiram and naltrexone, agents that are used to treat alcohol dependence. As noted previously, a low relative infant dose (<1%) was observed in a single case report of naltrexone exposure in a 6-week-old breastfed infant.<sup>59</sup> FDA labeling discourages use of disulfiram and both the injectable and oral form of naltrexone in lactating women.

Only one-third of women successfully discontinue smoking without pharmacologic aids.<sup>62</sup> Nicotine replacement therapy, bupropion, and varenicline are agents indicated for use as aids to smoking cessation treatment. Nicotine replacement therapy is compatible with breastfeeding as long as the dose (assuming a cigarette delivers ~1 mg of nicotine) is less than the number of cigarettes typically smoked, because nicotine passes freely into human milk and is orally absorbed as nicotine. Cotinine concentrations are lower than those related to tobacco use. Short-acting products (eg, gum or lozenges) are recommended.<sup>62</sup> Infant exposure decreases proportionally with maternal patch doses.<sup>65</sup>

In contrast, bupropion is excreted into human milk with exposures that may exceed 10% (range, 1.4%–10.6%) of the maternal dose.<sup>14</sup> Although infant levels were not measured, there is a case report of a seizure in a 6-month-old breastfed infant potentially related to bupropion.<sup>64</sup> Limited published information is available for varenicline, but the varenicline label includes a boxed warning for serious neuropsychiatric adverse events, including suicidal ideation or behavior. FDA labeling discourages use of both these agents in lactating women.

## PAIN MEDICATIONS

Rarely, normal doses of codeine given to lactating women may result in

dangerously high levels of its active metabolite morphine in breastfeeding infants. A fatality has been noted in an infant of a mother with ultrarapid metabolism.<sup>65</sup> In this infant, the post-mortem level of morphine (87 ng/mL) greatly exceeded a typical level in a breastfeeding infant (2.2 ng/mL), as well as the therapeutic range for neonates (10–12 ng/mL). In addition, unexplained apnea, bradycardia, cyanosis, and sedation have been reported in nursing infants of mothers receiving codeine.<sup>2,66</sup> Hydrocodone is also metabolized via the CYP2D6 pathway. On the basis of pharmacokinetic data, infants exposed to hydrocodone through human milk may receive up to 9% of the relative maternal dose.<sup>67</sup> Given the reduced clearance of hydrocodone in neonates and the adverse events observed in ultrarapid metabolizers of codeine, caution is advised for use of codeine and hydrocodone in both the mother and nursing infant. Close monitoring for signs and symptoms of neonatal as well as maternal toxicity is recommended. A commercial test to identify ultrarapid metabolizers is not yet widely available. The incidence of this specific CYP2D6 genotype varies with racial and ethnic group as follows: Chinese, Japanese, or Hispanic, 0.5% to 1.0%; Caucasian, 1.0% to 10.0%; African American, 3.0%; and North African, Ethiopian, and Saudi Arabian, 16.0% to 28.0%.<sup>68</sup>

For these reasons, when narcotic agents are needed to treat pain in the breastfeeding woman, agents other than codeine (eg, butorphanol, morphine, or hydromorphone) are preferred. Clinically insignificant levels of butorphanol are excreted into human milk. Morphine appears to be tolerated by the breastfeeding infant, although there is 1 case report of an infant with plasma concentrations within the therapeutic range.<sup>69</sup> Clear-

ance of morphine is decreased in infants younger than 1 month and approaches 80% of adult values by 6 months of age.<sup>70</sup> Limited data suggest that use of hydromorphone for brief periods may be compatible with breastfeeding<sup>71,72</sup>; however, FDA labeling discourages use. Regardless of the choice of therapy, to minimize adverse events for both the mother and her nursing infant, the lowest dose and shortest duration of therapy should be prescribed. Drug delivery via patient-controlled anesthesia or administration by the epidural route may also minimize infant exposure.

Other narcotic agents, such as oxycodone, pentazocine, propoxyphene, and meperidine, are not recommended in the lactating mother. Relatively high amounts of oxycodone are excreted into human milk, and therapeutic concentrations have been detected in the plasma of a nursing infant.<sup>73</sup> Central nervous system depression was noted in 20% of infants exposed to oxycodone during breastfeeding.<sup>74</sup> Thus, use of oxycodone should be discouraged. Limited published data are available about pentazocine. However, respiratory depression and apnea occur frequently in infants, particularly in neonates or in preterm infants, who are treated with pentazocine. Propoxyphene has been associated with unexplained apnea, bradycardia, and cyanosis, as well as hypotonia in nursing infants.<sup>75,76</sup> Moreover, propoxyphene was withdrawn from the market because significant QT prolongation occurred at therapeutic doses.<sup>77</sup> Meperidine use is associated with decreased alertness of the infant and is likely to interfere with breastfeeding.<sup>71</sup> Although estimates of meperidine exposure are low (approximately 2% to 3% of the maternal weight-adjusted dose), the half-life of the active metabolite for meperidine is prolonged, and it may accumulate in infant blood or tissue.<sup>71,72</sup>

When narcotics are not required to relieve mild to moderate pain, other analgesic agents can be used. Presuming that pain relief is adequate, short-acting agents, such as ibuprofen and acetaminophen, are acceptable.<sup>78</sup> Although the half-life of ibuprofen may be prolonged in neonates, particularly in preterm infants (according to product labeling), minimal amounts of ibuprofen are excreted into human milk.<sup>72</sup> Despite reduced clearance of acetaminophen,<sup>79</sup> hepatotoxicity is less common in neonates than in older infants, in part because of low levels of certain cytochrome P-450 enzymes, which convert acetaminophen into toxic metabolites.<sup>80</sup> Acetaminophen is available for both oral and intravenous administration.

Although all nonsteroidal antiinflammatory drugs (NSAIDs) carry a boxed warning regarding gastrointestinal bleeding and potential long-term cardiac toxicity, according to their product labeling and Gardiner et al,<sup>81</sup> celecoxib, flurbiprofen, and naproxen are considered to be compatible with breastfeeding, because less than 1% is excreted into human milk. In addition, a breastfeeding infant would receive less than 1% of the relative pediatric dose of celecoxib prescribed for a 2-year-old (according to product labeling). However, long-term use of naproxen is not recommended because of the drug's long half-life and case reports of gastrointestinal tract bleeding and emesis. Avoiding NSAIDs in breastfeeding infants with ductal-dependent cardiac lesions may be prudent.

Limited published data on other NSAIDs (etodolac, fenoprofen, meloxicam, oxaprozin, piroxicam, sulindac, and tolmetin) are available, and FDA labeling discourages their use for a variety of reasons. Although the implications for humans are unknown, meloxicam concentrations in milk of lactating animals exceed plasma con-

centrations. Diflunisal has a long half-life and is not recommended because of potential adverse events, including cataracts and fatality, in neonatal animals. Similarly, mefenamic acid has a prolonged half-life in preterm infants. Injectable and oral forms of ketorolac are contraindicated in nursing women, according to product labeling, because of potential adverse effects related to closure of the ductus arteriosus in neonates. Less than 1% of ketorolac nasal spray is excreted into human milk, and unlike the oral and intravenous forms of ketorolac, use is not contraindicated (product labeling).

Carisoprodol and its active metabolite, meprobamate, are concentrated in human milk (2–4 times maternal plasma concentrations). Impaired milk production has been observed, and animal studies suggest maternal use may lead to less effective infant feeding (because of sedation) and/or decreased milk production (according to product labeling).

Low doses (75–162 mg/d) of aspirin may be acceptable<sup>82</sup>; however, use of high-dose aspirin therapy during breastfeeding is not advised, because the serum concentration of salicylate in breastfeeding infants has been reported to reach approximately 40% of therapeutic concentrations. Adverse events, such as rash, platelet abnormalities, bleeding, and metabolic acidosis have also been reported.<sup>71</sup>

## **GALACTAGOGUES**

Galactagogues, or agents to stimulate lactation, are often used to facilitate lactation, particularly for mothers of preterm infants. They also may be used to induce lactation in an adoptive mother. However, evidence to support these agents, including use of dopamine antagonists, such as domperidone and metoclopramide; herbal treatments; and hormonal manipulation, is lacking.<sup>83</sup>

Although a placebo-controlled study ( $n = 42$ ) suggested that domperidone may increase milk volume in mothers of preterm infants,<sup>84</sup> maternal safety has not been established. The FDA issued a warning in June 2004 regarding use of domperidone in breastfeeding women because of safety concerns based on published reports of arrhythmia, cardiac arrest, and sudden death associated with intravenous therapy. Furthermore, treatment with oral domperidone is associated with QT prolongation in children and infants.<sup>85,86</sup> Domperidone is not an approved product in the United States, and labeling for oral formulations marketed outside the United States do not recommend use during lactation.

Several small trials (each with fewer than 25 subjects) published before 1990 suggested that metoclopramide increases prolactin concentrations and/or milk production in mothers of both term and preterm infants.<sup>87</sup> However, more recent controlled studies do not replicate this finding.<sup>88,89</sup> Human milk concentrations of metoclopramide are similar to therapeutic concentrations in adult plasma,<sup>88</sup> and measurable amounts can be detected in breastfeeding infants.<sup>90</sup> Clearance of metoclopramide in neonates is prolonged, which may result in excessive serum concentrations and the risk of conditions associated with overdose, such as methemoglobinemia. Of concern, prolactin concentrations were increased in 4 of 7 infants exposed to metoclopramide via human milk.<sup>90</sup> The safety profile for metoclopramide includes adverse reactions, such as dystonia, depression, suicidal ideation, and gastrointestinal tract disturbances, as well as a boxed warning about the risk of tardive dyskinesia. These risks to the mother limit the usefulness of this therapy.

Although a pilot study in 8 lactating women performed decades ago suggested that oxytocin nasal spray

increased human milk production, a larger placebo-controlled trial in 51 women has not confirmed that observation.<sup>91</sup> Oxytocin nasal spray is no longer marketed in the United States. Similarly, anecdotal reports supporting the use of the herb fenugreek to facilitate lactation have not been confirmed by controlled studies.<sup>92,93</sup> Fenugreek contains coumarin, which may interact with NSAIDs.<sup>94</sup> Use of fenugreek in lactating women also is associated with maple-syrup odor in infants.<sup>95</sup> Available data do not support the routine use of other herbal products, such as fennel, to facilitate lactation.<sup>96</sup>

In summary, galactagogues have a limited role in facilitating lactation and have not been subject to full assessments of safety for the nursing infant. Nursing mothers should seek consultation with a lactation specialist and use non-pharmacologic measures to increase milk supply, such as ensuring proper technique, using massage therapy, increasing the frequency of milk expression, prolonging the duration of pumping, and maximizing emotional support.

## COMMONLY USED HERBAL PRODUCTS

Despite the frequent use of herbal products in breastfeeding women (up to 43% of lactating mothers in a 2004 survey),<sup>97</sup> reliable information on the safety of many herbal products is lacking. Herbal products are not subject to the same standards for manufacturing and proven effectiveness and safety as are drug products before they are marketed.<sup>98</sup> In fact, the use of several herbal products may be harmful, including kava and yohimbe. For example, the FDA has issued a warning that links kava supplementation to severe liver damage.<sup>99</sup> Breastfeeding mothers should not use yohimbe because of reports of associated fatalities in children.<sup>100</sup> In addition, from 2008 through 2010, the

FDA recalled 10 or more dietary supplements each year because of the presence of potentially toxic undeclared ingredients in the supplement.<sup>101</sup> Similarly, the US Government Accountability Office found that 16 of 40 common herbal dietary supplements obtained from retail stores contained pesticide residues.<sup>102</sup>

Safety data are lacking for many herbs commonly used during breastfeeding, such as chamomile,<sup>103</sup> black cohosh,<sup>104</sup> blue cohosh,<sup>105</sup> chastetree,<sup>106</sup> echinacea,<sup>107</sup> ginseng,<sup>108</sup> ginkgo,<sup>109</sup> *Hypericum* (St John's wort),<sup>110,111</sup> and valerian.<sup>112</sup> Adverse events have been reported in both breastfeeding infants and mothers. For example, St John's wort may cause colic, drowsiness, or lethargy in the breastfed infant even though milk production and infant weight do not appear to be adversely affected<sup>110</sup> and relative maternal dose and infant plasma concentrations are low.<sup>113</sup> Prolonged use of fenugreek may require monitoring of coagulation status and serum glucose concentrations.<sup>114</sup> For these reasons, these aforementioned herbal products are not recommended for use by nursing women. Although supplementation of nursing mothers with iron and vitamins is safe as long as recommended daily allowances are not exceeded, the use of other nutritional supplements may not be. For instance, L-tryptophan has been associated with eosinophilic myositis.<sup>115</sup> Therefore, physicians should inquire about the use of herbal products and dietary supplements in lactating women and discuss the need for caution because of the paucity of data available.

## DIAGNOSTIC IMAGING

When feasible, elective imaging procedures should be delayed until a woman is no longer breastfeeding. For most radiopharmaceuticals, breastfeeding should be interrupted for a time period based on the rate of de-

cline of the agent and dosimetry to avoid infant exposures greater than 1 mSv (100 mrem). For agents that may be concentrated in breast tissue, close contact of the mother with the infant and, consequently, nursing may need to be avoided for a period of time, although expressed milk that has been refrigerated until the radioactivity has decayed may be safe. General guidelines based on Nuclear Regulatory Commission regulations and International Commission on Radiologic Protection guidelines<sup>116</sup> are cited in Tables 3 and 4. However, because there is considerable variability in milk radioactivity, and close contact with an infant may result in additional exposure, consultation with a radiologist should be sought. If deemed necessary, individualized testing of expressed milk may be performed to ensure that radioactivity has reached background levels before breastfeeding is resumed.<sup>117</sup>

Notably, because radiolabeled iodinated products are concentrated in the developing thyroid and radioactivity persists after imaging with most <sup>131</sup>I and <sup>125</sup>I radiopharmaceuticals (with the exception of <sup>125</sup>I-hippurate), breastfeeding should be interrupted for a minimum of 3 weeks. Similarly, <sup>22</sup>Na and <sup>67</sup>Ga (gallium) administration also require a prolonged (3-week) interruption in breastfeeding. Because the lactating breast has a greater <sup>131</sup>I affinity than does the nonlactating breast, women should cease breastfeeding at least 4 weeks before whole-body procedures with <sup>131</sup>I and should discontinue breastfeeding thereafter. Doing so will reduce the radiation dose and potential cancer risk to maternal breast tissue.

Traditionally, lactating women receiving intravascular gadolinium or iodinated contrast (as opposed to radiolabeled iodine) are advised to discontinue nursing for 24 hours. However, a minimal amount (0.04%) of the intravenous dose reaches human milk, and, of that, less than 1% to



**TABLE 3** Radioactive Compounds That May Require Temporary Cessation of Breastfeeding: Recommendations of the International Commission on Radiologic Protection

Compound	Examples	Example of Procedures	Recommended Time for Cessation of Breastfeeding	Comments
<sup>14</sup> C-labeled	Triolein, glycocholic acid, urea	<i>Helicobacter pylori</i> breath test	None	No approved US products
<sup>99m</sup> Tc-labeled	DMSA, DTPA, phosphonates (MDP), PYP, tetrofosmin	Multiple: imaging of kidney, bone, lung, heart, tumors	0 to 4 h, as long as no free pertechnetate	Consider discarding at least 1 meal after procedure
	Microspheres, pertechnetate, WBC		12–24 h	Range depends on dose
	Sulfur-colloids, RBC in vivo		6 h	
I-labeled	<sup>123</sup> I, <sup>125</sup> I or <sup>131</sup> I-iodo hippurate	Thyroid imaging	12 h	Note: whole-body irradiation with <sup>131</sup> I requires prolonged cessation
Others	<sup>11</sup> C- <sup>11</sup> N or <sup>11</sup> O-labeled	PET scans	None	Short physical half-life
	<sup>57</sup> Co-labeled vitamin B <sub>12</sub>	Schilling test	24 h	Pomeroy 2005 <sup>119</sup>
	<sup>18</sup> F-FDG	PET scans	None, first feeding should be expressed breast milk to avoid direct contact <sup>120</sup>	Use alternatives for 10 half-lives (10×109 min= 18 h) <sup>a</sup>
	<sup>51</sup> Cr-EDTA	Renal imaging	None	
	<sup>81m</sup> Kr-gas	Pulmonary imaging	None	No approved US products
	<sup>82</sup> Rb chloride	PET scan of myocardium	May resume 1 h after last infusion	Half-life 75 s <sup>a</sup>
	<sup>111</sup> In-octreotide	SPECT, neuroendocrine tumors	None	
	<sup>111</sup> In -WBC		1 wk	Depends on dose
	<sup>133</sup> Xe	Cardiac, pulmonary, and cerebral imaging	None	Half-life 5 d <sup>a</sup>

DMSA, dimercaptosuccinic acid; DTPA, diethylenetriaminepentaacetate; EDTA, ethylenediaminetetraacetic acid; FDG, fludeoxyglucose; PET, positron emission tomography; PYP, pyrophosphate; RBC, red blood cell; SPECT, single-photon emission computed tomography; WBC, white blood cell.

<sup>a</sup> FDA-approved drug labeling.

**TABLE 4** Radioactive Compounds Requiring Prolonged Cessation of Breastfeeding

Compound	Examples	Example of Procedures	Recommended Time for Cessation of Breastfeeding	Comments
I-labeled	<sup>125</sup> I- BMIPP, -HSA, -IPPA, -MIBG, -Nal, or -HSA	Imaging of tumors	Greater than 3 wk	Essentially need to stop breastfeeding
	<sup>131</sup> I-MIBG or -Nal			
Others	<sup>201</sup> Tl-chloride	Cardiac imaging	48 h to 2 wk	Half-life 73 h <sup>a</sup>
	<sup>67</sup> Ga-citrate	Imaging of tumors	1 wk to 1 mo	Depends on dose
	<sup>22</sup> Na, <sup>75</sup> Se		Greater than 3 wk	Essentially need to stop breastfeeding

Use of expressed human milk recommended because of exposure via direct contact.<sup>120</sup> BMIPP, β-methyl-p-iodophenyl-pentadecanoic acid; HSA, human serum albumin; IPPA, iodophenylpentadecanoic; MIBG, metaiodobenzylguanidine; Nal, sodium iodide.

<sup>a</sup> FDA-approved drug labeling.

2% is absorbed by the infant. Therefore, breastfeeding can be continued without interruption after the use of iodinated contrast or gadolinium.<sup>118</sup>

## BREASTFEEDING AND VACCINES

With rare exceptions, maternal immunization does not create any problems for breastfeeding infants, although questions concerning 2 topics often arise regarding lactation and immunization: the effect of lactation on the infant's immune response to a vaccine and a potential adverse effect on the infant from maternal immunization. Breastfeeding does not interfere with

the infant's immune response to most routine immunizations (eg, diphtheria and tetanus toxoids and acellular pertussis vaccine, inactivated poliovirus vaccine, and hepatitis B vaccine [HBV]),<sup>121</sup> despite the presence of maternal antibodies in human milk. Seroconversion rates are also similar between breastfed and formula-fed infants receiving rotavirus vaccine; however, vaccine efficacy for severe rotavirus gastroenteritis appears to be higher in formula-fed infants compared with exclusively breastfed infants, particularly during the second season (98% vs 88%) when breastfeeding has been discontinued.<sup>122</sup> Nonetheless, protection

during the first year is similar. Moreover, breastfeeding enhances the antibody response to pneumococcal and *Haemophilus influenzae* type b vaccines.<sup>123</sup> Breastfeeding may also decrease the incidence of fever after infant immunization.<sup>124</sup> Therefore, the timing of infant feeding (including human milk) relative to immunization is not restricted, even for live vaccines, such as rotavirus.

Lactating women may need to be immunized. Inactivated vaccines (such as tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine; inactivated poliovirus vaccine; influenza; hepatitis A vaccine; HBV; or human papillomavirus vaccine [HPV]) given to

a nursing mother do not pose a risk to the breastfeeding infant. Several vaccines, such as tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine and influenza vaccine, are recommended for the mother during the postpartum period to protect the infant as well as the mother. Other routine or catch-up vaccines, such as HPV, hepatitis A vaccine, and HBV, can be given to the lactating mother. HPV immunization is recommended for women younger than 27 years. The incidence of adverse reactions in nursing infants within 30 days of maternal immunization with HPV was similar to nursing infants of women receiving the control except for acute respiratory illness (according to Gardasil labeling). Hence, caution is warranted when immunizing mothers of infants who are vulnerable to respiratory illnesses (eg, preterm infants, infants with congenital heart disease or chronic respiratory problems).

Most live vaccines are not associated with virus secretion in human milk. For example, despite maternal seroconversion, neither the varicella virus nor antibody to varicella DNA has been detected in breastfeeding infants.<sup>125</sup> Although attenuated rubella can be secreted into human milk and transmitted to breastfed infants, infections are usually asymptomatic or mild. Consequently, postpartum immunization with measles-mumps-rubella vaccine is recommended for women who lack immunity, especially to rubella.<sup>126</sup> In contrast, infants are considered to be at high risk of developing vaccinia

after exposure to smallpox vaccine or encephalitis after yellow fever vaccine. Two cases of meningoencephalitis in nursing infants whose mothers had been immunized against yellow fever are documented in the literature.<sup>127,128</sup> Therefore, most vaccines, with the exception of smallpox or yellow-fever vaccine, which are contraindicated in nonemergency situations, may be administered during lactation.

## SUMMARY

The benefits of breastfeeding outweigh the risk of exposure to most therapeutic agents via human milk. Although most drugs and therapeutic agents do not pose a risk to the mother or nursing infant, careful consideration of the individual risk/benefit ratio is necessary for certain agents, particularly those that are concentrated in human milk or result in exposures in the infant that may be clinically significant on the basis of relative infant dose or detectable serum concentrations. Caution is also advised for drugs and agents with unproven benefits, with long half-lives that may lead to drug accumulation, or with known toxicity to the mother or infant. In addition, specific infants may be more vulnerable to adverse events because of immature organ function (eg, preterm infants or neonates) or underlying medical conditions. Several excellent resources are available for the pediatrician, including product labeling and the peer-reviewed database, LactMed. Consultation with a specialist may be indicated, particularly when the

use of radiopharmaceuticals, oncologic drugs, or other therapies not addressed by LactMed is contemplated. Additional information about topics outside the scope of this report, such as environmental agents, can be obtained from the third edition of the AAP textbook *Pediatric Environmental Health*.<sup>129</sup>

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