



## CLINICAL REPORT

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

## abstract

FREE

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

Hari Cheryl Sachs, MD, FAAP\* and COMMITTEE ON DRUGS

**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

This document is copyrighted and is property of the American Academy of Pediatrics and its Board of Directors. All authors have filed conflict of interest statements with the American Academy of Pediatrics. Any conflicts have been resolved through a process approved by the Board of Directors. The American Academy of Pediatrics has neither solicited nor accepted any commercial involvement in the development of the content of this publication.

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.

[www.pediatrics.org/cgi/doi/10.1542/peds.2013-1985](http://www.pediatrics.org/cgi/doi/10.1542/peds.2013-1985)

doi:10.1542/peds.2013-1985

All clinical reports from the American Academy of Pediatrics automatically expire 5 years after publication unless reaffirmed, revised, or retired at or before that time.

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2013 by the American Academy of Pediatrics

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

Primary Author: Philip O. Anderson, PharmD

Contributor: Jason Sauberan, PharmD

Peer Review Panel:

Cheston M. Berlin, Jr, MD

Shinya Ito, MD

Kathleen Uhl, MD

Sonia Neubauer, MD

\* 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

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

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

### 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> Bogen 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 Microspheres, pertechnetate, WBC Sulfur-colloids, RBC in vivo	Multiple: imaging of kidney, bone, lung, heart, tumors	0 to 4 h, as long as no free pertechnetate 12–24 h 6 h	Consider discarding at least 1 meal after procedure Range depends on dose
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 <sup>57</sup> Co-labeled vitamin B <sub>12</sub> <sup>18</sup> F-FDG  <sup>51</sup> Cr-EDTA <sup>81m</sup> Kr-gas <sup>82</sup> Rb chloride  <sup>111</sup> In-octreotide <sup>111</sup> In -WBC <sup>133</sup> Xe	PET scans Schilling test PET scans  Renal imaging Pulmonary imaging PET scan of myocardium  SPECT, neuroendocrine tumors Cardiac, pulmonary, and cerebral imaging	None 24 h None, first feeding should be expressed breast milk to avoid direct contact <sup>120</sup> None None May resume 1 h after last infusion None 1 wk None	Short physical half-life Pomeroy 2005 <sup>119</sup> Use alternatives for 10 half-lives (10×109 min= 18 h) <sup>a</sup>  No approved US products Half-life 75 s <sup>a</sup>  Depends on dose 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 <sup>131</sup> I-MIBG or -Nal	Imaging of tumors	Greater than 3 wk	Essentially need to stop breastfeeding
Others	<sup>201</sup> Tl-chloride <sup>67</sup> Ga-citrate <sup>22</sup> Na, <sup>75</sup> Se	Cardiac imaging Imaging of tumors	48 h to 2 wk 1 wk to 1 mo Greater than 3 wk	Half-life 73 h <sup>a</sup> Depends on dose 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>

## LEAD AUTHOR

Hari Cheryl Sachs, MD, FAAP

## COMMITTEE ON DRUGS, 2012–2013

Daniel A. C. Frattarelli, MD, FAAP, Chairperson  
 Jeffrey L. Galinkin, MD, FAAP  
 Thomas P. Green, MD, FAAP  
 Timothy Johnson, DO, FAAP  
 Kathleen Neville, MD, FAAP  
 Ian M. Paul, MD, MSc, FAAP  
 John Van den Anker, MD, PhD, FAAP

## FORMER COMMITTEE MEMBERS

Mark L. Hudak, MD, FAAP  
 Matthew E. Knight, MD, FAAP

## LIAISONS

John J. Alexander, MD, FAAP – *Food and Drug Administration*  
 Sarah J. Kilpatrick, MD, PhD – *American College of Obstetricians and Gynecologists*  
 Janet D. Cragan, MD, MPH, FAAP – *Centers for Disease Control and Prevention*  
 Michael J. Rieder, MD, FAAP – *Canadian Pediatric Society*  
 Adelaide Robb, MD – *American Academy of Child and Adolescent Psychiatry*  
 Hari Cheryl Sachs, MD, FAAP – *Food and Drug Administration*  
 Anne Zajicek, MD, PharmD, FAAP – *National Institutes of Health*

## CONTRIBUTOR

Ashley Moss, MD, FAAP

## STAFF

Tamar Haro, JD  
 Raymond J. Koteras, MHA

## REFERENCES

- Berlin CM, Briggs GG. Drugs and chemicals in human milk. *Semin Fetal Neonatal Med.* 2005;10(2):149–159
- Anderson PO, Pochop SL, Manoguerra AS. Adverse drug reactions in breastfed infants: less than imagined. *Clin Pediatr (Phila).* 2003;42(4):325–340
- American Academy of Pediatrics, Committee on Drugs. The transfer of drugs and other chemicals into human breast milk. *Pediatrics.* 1983;72(3):375–383
- American Academy of Pediatrics, Committee on Drugs. The transfer of drugs and other chemicals into human breast milk. *Pediatrics.* 1989;84(5):924–936
- American Academy of Pediatrics, Committee on Drugs. The transfer of drugs and other chemicals into human breast milk. *Pediatrics.* 1994;93(1):137–150

6. American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. *Pediatrics*. 2001;108(3):776–789
7. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245
8. Hale TW. Maternal medications during breastfeeding. *Clin Obstet Gynecol*. 2004;47(3):696–711
9. Berlin CM, Jr, Paul IM, Vesell ES. Safety issues of maternal drug therapy during breastfeeding. *Clin Pharmacol Ther*. 2009;85(1):20–22
10. Food and Drug Administration. Draft guidance for industry: clinical lactation studies—study design, data analysis, and recommendations for labeling. February 2005. Available at: [www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127505.pdf](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127505.pdf). Accessed November 26, 2012
11. Gentile S. SSRIs in pregnancy and lactation: emphasis on neurodevelopmental outcome. *CNS Drugs*. 2005;19(7):623–633
12. Gentile S. The safety of newer antidepressants in pregnancy and breastfeeding. *Drug Saf*. 2005;28(2):137–152
13. Fortinguerra F, Clavenna A, Bonati M. Psychotropic drug use during breastfeeding: a review of the evidence. *Pediatrics*. 2009;124(4). Available at: [www.pediatrics.org/cgi/content/full/124/4/e547](http://www.pediatrics.org/cgi/content/full/124/4/e547)
14. Davis MF, Miller HS, Nolan PE Jr. Bupropion levels in breast milk for 4 mother-infant pairs: more answers to lingering questions. *J Clin Psychiatry*. 2009;70(2):297–298
15. Kristensen JH, Ilett KF, Hackett LP, Yapp P, Paech M, Begg EJ. Distribution and excretion of fluoxetine and norfluoxetine in human milk. *Br J Clin Pharmacol*. 1999;48(4):521–527
16. Moretti ME. Psychotropic drugs in lactation—Motherisk Update 2008. *Can J Clin Pharmacol*. 2009;16(1):e49–e57
17. Ostrea EM, Jr, Mantaring JB, III, Silvestre MA. Drugs that affect the fetus and newborn infant via the placenta or breast milk. *Pediatr Clin North Am*. 2004;51(3):539–579, vii
18. Newport DJ, Pennell PB, Calamaras MR, et al. Lamotrigine in breast milk and nursing infants: determination of exposure. *Pediatrics*. 2008;122(1). Available at: [www.pediatrics.org/cgi/content/full/122/1/e223](http://www.pediatrics.org/cgi/content/full/122/1/e223)
19. Newport DJ, Ritchie JC, Knight BT, Glover BA, Zach EB, Stowe ZN. Venlafaxine in human breast milk and nursing infant plasma: determination of exposure. *J Clin Psychiatry*. 2009;70(9):1304–1310
20. Weissman AM, Levy BT, Hartz AJ, et al. Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants. *Am J Psychiatry*. 2004;161(6):1066–1078
21. Schimmell MS, Katz EZ, Shaag Y, Pastuszak A, Koren G. Toxic neonatal effects following maternal clomipramine therapy. *J Toxicol Clin Toxicol*. 1991;29(4):479–484
22. Wesson DR, Camber S, Harkey M, Smith DE. Diazepam and desmethyldiazepam in breast milk. *J Psychoactive Drugs*. 1985;17(1):55–56
23. Fotopoulou C, Kretz R, Bauer S, et al. Prospectively assessed changes in lamotrigine concentration in women with epilepsy during pregnancy, lactation and the neonatal period. *Epilepsy Res*. 2009;85(1):60–64
24. Viguera AC, Newport DJ, Ritchie J, et al. Lithium in breast milk and nursing infants: clinical implications. *Am J Psychiatry*. 2007;164(2):342–345
25. Grandjean EM, Aubry JM. Lithium: updated human knowledge using an evidence-based approach: part III: clinical safety. *CNS Drugs*. 2009;23(5):397–418
26. Bogen DL, Sit D, Genovese A, Wisner KL. Three cases of lithium exposure and exclusive breastfeeding. *Arch Women Ment Health*. 2012;15(1):69–72
27. Tonn P, Reuter SC, Hiemke C, Dahmen N. High mirtazapine plasma levels in infant after breast feeding: case report and review of the literature. *J Clin Psychopharmacol*. 2009;29(2):191–192
28. Whitworth A, Stuppaec C, Yazdi K, et al. Olanzapine and breast-feeding: changes of plasma concentrations of olanzapine in a breast-fed infant over a period of 5 months. *J Psychopharmacol*. 2010;24(1):121–123
29. Hendrick V, Fukuchi A, Altshuler L, Widawski M, Wertheimer A, Brunhuber MV. Use of sertraline, paroxetine and fluvoxamine by nursing women. *Br J Psychiatry*. 2001;179:163–166
30. Stowe ZN, Hostetter AL, Owens MJ, et al. The pharmacokinetics of sertraline excretion into human breast milk: determinants of infant serum concentrations. *J Clin Psychiatry*. 2003;64(1):73–80
31. Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics*. 2012;129(3). Available at: [www.pediatrics.org/cgi/content/full/129/3/e827](http://www.pediatrics.org/cgi/content/full/129/3/e827)
32. Liebrechts-Akkerman G, Lao O, Liu F, et al. Postnatal parental smoking: an important risk factor for SIDS. *Eur J Pediatr*. 2011;170(10):1281–1291
33. Moon RY; Task Force on Sudden Infant Death Syndrome. SIDS and other sleep-related infant deaths: expansion of recommendations for a safe infant sleeping environment. *Pediatrics*. 2011;128(5):1030–1039
34. Koren G. MotherRisk update: drinking alcohol while breastfeeding. *Can Fam Physician*. 2002;48:29–41
35. Backstrand JR, Goodman AH, Allen LH, Pelto GH. Pulque intake during pregnancy and lactation in rural Mexico: alcohol and child growth from 1 to 57 months. *Eur J Clin Nutr*. 2004;58(12):1626–1634
36. Mennella JA, Yourshaw LM, Morgan LK. Breastfeeding and smoking: short-term effects on infant feeding and sleep. *Pediatrics*. 2007;120(3):497–502
37. Institute of Medicine, Subcommittee on Nutrition During Lactation. *Nutrition During Lactation*. Washington, DC: National Academies Press; 1991
38. Jain AE, Lacy T. Psychotropic drugs in pregnancy and lactation. *J Psychiatr Pract*. 2005;11(3):177–191
39. Malone K, Papagni K, Ramini S, Keltner NL. Antidepressants, antipsychotics, benzodiazepines, and the breastfeeding dyad. *Perspect Psychiatr Care*. 2004;40(2):73–85
40. Chasnoff IJ, Lewis DE, Squires L. Cocaine intoxication in a breast-fed infant. *Pediatrics*. 1987;80(6):836–838
41. Winecker RE, Goldberger BA, Tebbett IR, et al. Detection of cocaine and its metabolites in breast milk. *J Forensic Sci*. 2001;46(5):1221–1223
42. vande Velde S, Verloof P, Van Biervliet S, et al. Heroin withdrawal leads to metabolic alkalosis in an infant with cystic fibrosis. *Eur J Pediatr*. 2007;166(1):75–76
43. Ariagno R, Karch SB, Middleberg R, Stephens BG, Valdès-Dapena M. Methamphetamine ingestion by a breast-feeding mother and her infant's death: People v Henderson. *JAMA*. 1995;274(3):215
44. Bartu A, Dusci LJ, Ilett KF. Transfer of methylamphetamine and amphetamine into breast milk following recreational use of methylamphetamine. *Br J Clin Pharmacol*. 2009;67(4):455–459
45. Djulus J, Moretti M, Koren G. Marijuana use and breastfeeding. *Can Fam Physician*. 2005;51:349–350
46. Campolongo P, Trezza V, Palmery M, Trabace L, Cuomo V. Developmental exposure to cannabinoids causes subtle and enduring neurofunctional alterations. *Int Rev Neurobiol*. 2009;85:117–133

47. Garry A, Rigourd V, Amirouche A, et al. Cannabis and breastfeeding. *J Toxicol*. 2009;2009:596149
48. Jansson LM; Academy of Breastfeeding Medicine Protocol Committee. ABM clinical protocol #21: guidelines for breastfeeding and the drug-dependent woman. *Breastfeed Med*. 2009;4(4):225–228
49. Jones HE, Martin PR, Heil SH, et al. Treatment of opioid-dependent pregnant women: clinical and research issues. *J Subst Abuse Treat*. 2008;35(3):245–259
50. Centers for Disease Control and Prevention. Human immunodeficiency virus (HIV), and acquired immunodeficiency syndrome (AIDS). Available at: [www.cdc.gov/breastfeeding/disease/hiv.htm](http://www.cdc.gov/breastfeeding/disease/hiv.htm). Accessed November 3, 2012
51. Jansson LM, Velez M, Harrow C. Methadone maintenance and lactation: a review of the literature and current management guidelines. *J Hum Lact*. 2004;20(1):62–71
52. Hirose M, Hosokawa T, Tanaka Y. Extradural buprenorphine suppresses breast feeding after caesarean section. *Br J Anaesth*. 1997;79(1):120–121
53. Glatstein MM, Garcia-Bourmissen F, Finkelstein Y, Koren G. Methadone exposure during lactation. *Can Fam Physician*. 2008;54(12):1689–1690
54. Farid WO, Dunlop SA, Tait RJ, Hulse GK. The effects of maternally administered methadone, buprenorphine and naltrexone on offspring: review of human and animal data. *Curr Neuropharmacol*. 2008;6(2):125–150
55. Jansson LM, Choo R, Velez ML, Lowe R, Huestis MA. Methadone maintenance and long-term lactation. *Breastfeed Med*. 2008;3(1):34–37
56. Jansson LM, Choo R, Velez ML, et al. Methadone maintenance and breastfeeding in the neonatal period. *Pediatrics*. 2008;121(1):106–114
57. Johnson RE, Jones HE, Jasinski DR, et al. Buprenorphine treatment of pregnant opioid-dependent women: maternal and neonatal outcomes. *Drug Alcohol Depend*. 2001;63(1):97–103
58. Lindemalm S, Nydert P, Svensson JO, Stahle L, Sarman I. Transfer of buprenorphine into breast milk and calculation of infant drug dose. *J Hum Lact*. 2009;25(2):199–205
59. Chan CF, Page-Sharp M, Kristensen JH, O'Neil G, Ilett KF. Transfer of naltrexone and its metabolite 6,beta-naltrexol into human milk. *J Hum Lact*. 2004;20(3):322–326
60. Abdel-Latif ME, Pinner J, Clews S, Cooke F, Lui K, Oei J. Effects of breast milk on the severity and outcome of neonatal abstinence syndrome among infants of drug-dependent mothers. *Pediatrics*. 2006;117(6). Available at: [www.pediatrics.org/cgi/content/full/117/6/e1163](http://www.pediatrics.org/cgi/content/full/117/6/e1163)
61. Malpas TJ, Darlow BA. Neonatal abstinence syndrome following abrupt cessation of breastfeeding. *N Z Med J*. 1999;112(1080):12–13
62. Molyneux A. Nicotine replacement therapy. *BMJ*. 2004;328(7437):454–456
63. Ilett KF, Hale TW, Page-Sharp M, Kristensen JH, Kohan R, Hackett LP. Use of nicotine patches in breast-feeding mothers: transfer of nicotine and cotinine into human milk. *Clin Pharmacol Ther*. 2003;74(6):516–524
64. Chaudron LH, Schoenecker CJ. Bupropion and breastfeeding: a case of a possible infant seizure. *J Clin Psychiatry*. 2004;65(6):881–882
65. Madadi P, Shirazi F, Walter FG, Koren G. Establishing causality of CNS depression in breastfed infants following maternal codeine use. *Paediatr Drugs*. 2008;10(6):399–404
66. Madadi P, Koren G, Cairns JU, et al. Safety of codeine during breastfeeding: fatal morphine poisoning in the breastfed neonate of a mother prescribed codeine. *Can Fam Physician*. 2007;53(1):33–35
67. Sauberan JB, Anderson PO, Lane JR, et al. Breast milk hydrocodone and hydro-morphone levels in mothers using hydrocodone for postpartum pain. *Obstet Gynecol*. 2011;117(3):611–617
68. Food and Drug Administration. FDA Alert. Information for healthcare professionals: use of codeine products in nursing mothers. August 17, 2007. Available at: [www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm124889.htm](http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm124889.htm). Accessed November 26, 2012
69. Robieux I, Koren G, Vandenberg H, Schneiderman J. Morphine excretion in breast milk and resultant exposure of a nursing infant. *J Toxicol Clin Toxicol*. 1990;28(3):365–370
70. Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. *Br J Anaesth*. 2004;92(2):208–217
71. Bar-Oz B, Bulkowstein M, Benyamini L, et al. Use of antibiotic and analgesic drugs during lactation. *Drug Saf*. 2003;26(13):925–935
72. Spigset O, Hägg S. Analgesics and breastfeeding: safety considerations. *Paediatr Drugs*. 2000;2(3):223–238
73. Seaton S, Reeves M, McLean S. Oxycodone as a component of multimodal analgesia for lactating mothers after Caesarean section: relationships between maternal plasma, breast milk and neonatal plasma levels. *Aust N Z J Obstet Gynaecol*. 2007;47(3):181–185
74. Lam J, Kelly L, Ciszakowski C, et al. Central nervous system depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. *J Pediatr*. 2011;160(1):33.e2–37.e2
75. Rigourd V, Amirouche A, Tasseau A, Kintz P, Serreau R. Retrospective diagnosis of an adverse drug reaction in a breastfed neonate: liquid chromatography-tandem mass spectrometry quantification of dextropropoxyphene and norpropoxyphene in newborn and maternal hair. *J Anal Toxicol*. 2008;32(9):787–789
76. Naumburg EG, Meny RG. Breast milk opioids and neonatal apnea. *Am J Dis Child*. 1988;142(1):11–12
77. Food and Drug Administration. Medwatch Safety Information. Propoxyphene: withdrawal – risk of cardiac toxicity. November 19, 2010. Available at: [www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm234389.htm](http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm234389.htm). Accessed November 26, 2012
78. Spencer J, Gonzalez L, Barnhart D. Medications in the breastfeeding mother. *Am Fam Physician*. 2001;64(1):119–126
79. Jacqz-Aigrain E, Serreau R, Boissinot C, et al. Excretion of ketoprofen and nalbuphine in human milk during treatment of maternal pain after delivery. *Ther Drug Monit*. 2007;29(6):815–818
80. van der Marel CD, Anderson BJ, van Lingen RA, et al. Paracetamol and metabolite pharmacokinetics in infants. *Eur J Clin Pharmacol*. 2003;59(3):243–251
81. Gardiner SJ, Doogue MP, Zhang M, Begg EJ. Quantification of infant exposure to celecoxib through breast milk. *Br J Clin Pharmacol*. 2006;61(1):101–104
82. Bell AD, Roussin A, Cartier R, et al; Canadian Cardiovascular Society. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society guidelines. *Can J Cardiol*. 2011;27(suppl A):S1–S59
83. Academy of Breastfeeding Medicine Protocol Committee. ABM Clinical Protocol #9: use of galactagogues in initiating or augmenting the rate of maternal secretion. *Breastfeed Med*. 2011;6(1):41–49
84. Campbell-Yeo ML, Allen AC, Joseph KS, et al. Effect of domperidone on the composition of preterm human breast milk. *Pediatrics*. 2010;125(1). Available at: [www.pediatrics.org/cgi/content/full/125/1/e107](http://www.pediatrics.org/cgi/content/full/125/1/e107)



85. Collins KK, Sondheimer JM. Domperidone-induced QT prolongation: add another drug to the list. *J Pediatr*. 2008;153(5):596–598
86. Djeddi D, Kongolo G, Lefaix C, Mounard J, Léké A. Effect of domperidone on QT interval in neonates. *J Pediatr*. 2008;153(5):663–666
87. Zuppa AA, Sindico P, Orchi C, Carducci C, Cardiello V, Romagnoli C. Safety and efficacy of galactogogues: substances that induce, maintain and increase breast milk production. *J Pharm Pharm Sci*. 2010;13(2):162–174
88. Hansen WF, McAndrew S, Harris K, Zimmerman MB. Metoclopramide effect on breastfeeding the preterm infant: a randomized trial. *Obstet Gynecol*. 2005;105(2):383–389
89. Fife S, Gill P, Hopkins M, Angello C, Boswell S, Nelson KM. Metoclopramide to augment lactation, does it work? A randomized trial. *J Matern Fetal Neonatal Med*. 2011;24(11):1317–1320
90. Kauppila A, Arvela P, Koivisto M, Kivinen S, Ylikorkkala O, Pelkonen O. Metoclopramide and breast feeding: transfer into milk and the newborn. *Eur J Clin Pharmacol*. 1983;25(6):819–823
91. Fewtrell MS, Loh KL, Blake A, Ridout DA, Hawdon J. Randomised, double blind trial of oxytocin nasal spray in mothers expressing breast milk for preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2006;91(3):F169–F174
92. Betzold CM. Galactogogues. *J Midwifery Womens Health*. 2004;49(2):151–154
93. Ulbricht C, Basch E, Burke D, et al. Fenugreek (*Trigonella foenum-graecum* L. Leguminosae): an evidence-based systematic review by the natural standard research collaboration. *J Herb Pharmacother*. 2007;7(3-4):143–177
94. Abebe W. Herbal medication: potential for adverse interactions with analgesic drugs. *J Clin Pharm Ther*. 2002;27(6):391–401
95. Korman SH, Cohen E, Preminger A. Pseudo-maple syrup urine disease due to maternal prenatal ingestion of fenugreek. *J Paediatr Child Health*. 2001;37(4):403–404
96. Jackson PC. Complementary and alternative methods of increasing breast milk supply for lactating mothers of infants in the NICU. *Neonatal Netw*. 2010;29(4):225–230
97. Nordeng H, Havnen GC. Use of herbal drugs in pregnancy: a survey among 400 Norwegian women. *Pharmacoepidemiol Drug Saf*. 2004;13(6):371–380
98. Denham BE. Dietary supplements—regulatory issues and implications for public health. *JAMA*. 2011;306(4):428–429
99. Food and Drug Administration. Consumer advisory: kava-containing dietary supplements may be associated with severe liver injury. March 25, 2002. Available at: [www.fda.gov/Food/ResourcesForYou/Consumers/ucm085482.htm](http://www.fda.gov/Food/ResourcesForYou/Consumers/ucm085482.htm). Accessed November 26, 2012
100. Medline Plus. Yohimbe. Available at: [www.nlm.nih.gov/medlineplus/druginfo/natural/759.html](http://www.nlm.nih.gov/medlineplus/druginfo/natural/759.html). Accessed November 26, 2012
101. Food and Drug Administration. Safety alerts for human medical products 2008–2010. Available at: [www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm](http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm). Accessed November 26, 2012
102. US Government Accountability Office. Herbal dietary supplements: examples of deceptive or questionable marketing practices and potentially dangerous advice. May 26, 2010. Available at: [www.gao.gov/products/GAO-10-662T](http://www.gao.gov/products/GAO-10-662T). Accessed November 26, 2012
103. Gardiner P. Complementary, holistic, and integrative medicine: chamomile. *Pediatr Rev*. 2007;28(4):e16–e18
104. Dugoua JJ, Seely D, Perri D, Koren G, Mills E. Safety and efficacy of black cohosh (*Cimicifuga racemosa*) during pregnancy and lactation. *Can J Clin Pharmacol*. 2006;13(3):e257–e261
105. Dugoua JJ, Perri D, Seely D, Mills E, Koren G. Safety and efficacy of blue cohosh (*Caulophyllum thalictroides*) during pregnancy and lactation. *Can J Clin Pharmacol*. 2008;15(1):e66–e73
106. Dugoua JJ, Seely D, Perri D, Koren G, Mills E. Safety and efficacy of chastetree (*Vitex agnus-castus*) during pregnancy and lactation. *Can J Clin Pharmacol*. 2008;15(1):e74–e79
107. Perri D, Dugoua JJ, Mills E, Koren G. Safety and efficacy of echinacea (*Echinacea angustifolia*, *E. purpurea* and *E. pallida*) during pregnancy and lactation. *Can J Clin Pharmacol*. 2006;13(3):e262–e267
108. Seely D, Dugoua JJ, Perri D, Mills E, Koren G. Safety and efficacy of panax ginseng during pregnancy and lactation. *Can J Clin Pharmacol*. 2008;15(1):e87–e94
109. Dugoua JJ, Mills E, Perri D, Koren G. Safety and efficacy of ginkgo (*Ginkgo biloba*) during pregnancy and lactation. *Can J Clin Pharmacol*. 2006;13(3):e277–e284
110. Dugoua JJ, Mills E, Perri D, Koren G. Safety and efficacy of St. John's wort (hypericum) during pregnancy and lactation. *Can J Clin Pharmacol*. 2006;13(3):e268–e276
111. Budzynska K, Gardner ZE, Dugoua JJ, Low Dog T, Gardiner P. Systematic review of breastfeeding and herbs. *Breastfeed Med*. 2012;7(6):489–503
112. Drugs and Lactation Database (LactMed). Available at: <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. Accessed May 8, 2013
113. Klier CM, Schmid-Siegel B, Schäfer MR, et al. St. John's wort (*Hypericum perforatum*) and breastfeeding: plasma and breast milk concentrations of hyperforin for 5 mothers and 2 infants. *J Clin Psychiatry*. 2006;67(2):305–309
114. Tiran D. The use of fenugreek for breastfeeding women. *Complement Ther Nurs Midwifery*. 2003;9(3):155–156
115. Dourmishev LA, Dourmishev AL. Activity of certain drugs in inducing of inflammatory myopathies with cutaneous manifestations. *Expert Opin Drug Saf*. 2008;7(4):421–433
116. ICRP. Radiation dose to patients from radiopharmaceuticals. Addendum 3 to ICRP Publication 53. ICRP Publication 106. Approved by the Commission in October 2007. *Ann ICRP*. 2008;38(1-2):1–197
117. Stabin MG, Breitz HB. Breast milk excretion of radiopharmaceuticals: mechanisms, findings, and radiation dosimetry. *J Nucl Med*. 2000;41(5):863–873
118. Chen MM, Coakley FV, Kaimal A, Laros RK Jr. Guidelines for computed tomography and magnetic resonance imaging use during pregnancy and lactation. *Obstet Gynecol*. 2008;112(2 pt 1):333–340
119. Pomeroy KM, Sawyer LJ, Evans MJ. Estimated radiation dose to breast feeding infant following maternal administration of <sup>57</sup>Co labelled to vitamin B12. *Nucl Med Commun*. 2005;26(9):839–841
120. Devine CE, Mawlawi O. Radiation safety with positron emission tomography and computed tomography. *Semin Ultrasound CT MR*. 2010;31(1):39–45
121. Atkinson WL, Pickering LK, Schwartz B, Weniger BG, Iskander JK, Watson JC; Centers for Disease Control and Prevention. General recommendations on immunization. Recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR Recomm Rep*. 2002;51(RR-2):1–35
122. Vesikari T, Prymula R, Schuster V, et al. Efficacy and immunogenicity of live-attenuated human rotavirus vaccine in breast-fed and formula-fed European infants. *Pediatr Infect Dis J*. 2012;31(5):509–513
123. Silfverdal SA, Ekholm L, Bodin L. Breast-feeding enhances the antibody response

- to Hib and Pneumococcal serotype 6B and 14 after vaccination with conjugate vaccines. *Vaccine*. 2007;25(8):1497–1502
124. Pisacane A, Continisio P, Palma O, Cataldo S, De Michele F, Vairo U. Breastfeeding and risk for fever after immunization. *Pediatrics*. 2010;125(6). Available at: [www.pediatrics.org/cgi/content/full/125/6/e1448](http://www.pediatrics.org/cgi/content/full/125/6/e1448)
  125. Bohlke K, Galil K, Jackson LA, et al. Postpartum varicella vaccination: is the vaccine virus excreted in breast milk? *Obstet Gynecol*. 2003;102(5 pt 1):970–977
  126. Kroger AT, Atkinson WL, Marcuse EK, Pickering LK; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-15):1–48
  127. Centers for Disease Control and Prevention (CDC). Transmission of yellow fever vaccine virus through breast-feeding - Brazil, 2009. *MMWR Morb Mortal Wkly Rep*. 2010;59(5):130–132
  128. Traiber C, Coelho-Amaral P, Ritter VR, Winge A. Infant meningoencephalitis caused by yellow fever vaccine virus transmitted via breastmilk. *J Pediatr (Rio J)*. 2011;87(3):269–272
  129. American Academy of Pediatrics, Council on Environmental Health. In: Etzel RA, Balk SJ, eds. *Pediatric Environmental Health*. 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012

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

Hari Cheryl Sachs and COMMITTEE ON DRUGS

*Pediatrics* 2013;132:e796

DOI: 10.1542/peds.2013-1985 originally published online August 26, 2013;

<b>Updated Information &amp; Services</b>	including high resolution figures, can be found at: <a href="http://pediatrics.aappublications.org/content/132/3/e796">http://pediatrics.aappublications.org/content/132/3/e796</a>
<b>References</b>	This article cites 115 articles, 23 of which you can access for free at: <a href="http://pediatrics.aappublications.org/content/132/3/e796#BIBL">http://pediatrics.aappublications.org/content/132/3/e796#BIBL</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>Current Policy</b> <a href="http://www.aappublications.org/cgi/collection/current_policy">http://www.aappublications.org/cgi/collection/current_policy</a> <b>Committee on Drugs</b> <a href="http://www.aappublications.org/cgi/collection/committee_on_drugs">http://www.aappublications.org/cgi/collection/committee_on_drugs</a> <b>Nutrition</b> <a href="http://www.aappublications.org/cgi/collection/nutrition_sub">http://www.aappublications.org/cgi/collection/nutrition_sub</a> <b>Breastfeeding</b> <a href="http://www.aappublications.org/cgi/collection/breastfeeding_sub">http://www.aappublications.org/cgi/collection/breastfeeding_sub</a> <b>Pharmacology</b> <a href="http://www.aappublications.org/cgi/collection/pharmacology_sub">http://www.aappublications.org/cgi/collection/pharmacology_sub</a> <b>Therapeutics</b> <a href="http://www.aappublications.org/cgi/collection/therapeutics_sub">http://www.aappublications.org/cgi/collection/therapeutics_sub</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.aappublications.org/site/misc/Permissions.xhtml">http://www.aappublications.org/site/misc/Permissions.xhtml</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://www.aappublications.org/site/misc/reprints.xhtml">http://www.aappublications.org/site/misc/reprints.xhtml</a>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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

Hari Cheryl Sachs and COMMITTEE ON DRUGS

*Pediatrics* 2013;132:e796

DOI: 10.1542/peds.2013-1985 originally published online August 26, 2013;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/132/3/e796>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2013 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

