

Stop using codeine, oxycodone, hydrocodone, tramadol, and aspirin in women who are breastfeeding

➡ Use acetaminophen and/or ibuprofen for pain management in women who are breastfeeding. If narcotic treatment is necessary consider using the lowest effective dose of morphine for the shortest time possible.



Robert L. Barbieri, MD

Editor in Chief, OBG MANAGEMENT
Chair, Obstetrics and Gynecology
Brigham and Women's Hospital, Boston, Massachusetts
Kate Macy Ladd Professor of Obstetrics,
Gynecology and Reproductive Biology
Harvard Medical School, Boston

In 2015 more than 30,000 deaths from opioid overdose were reported (FIGURE, page 10).¹ More than 50% of the deaths were due to prescription opioids. The opioid crisis is a public health emergency and clinicians are diligently working to reduce both the number of opioid prescriptions and the doses prescribed per prescription.

In obstetrics, there is growing concern that narcotics used for the

treatment of pain in women who are breastfeeding may increase the risk of adverse effects in newborns, including excessive sedation and respiratory depression. The American Academy of Pediatrics (AAP), the US Food and Drug Administration (FDA) and the American College of Obstetricians and Gynecologists (ACOG) recommend against the use of codeine and tramadol in women who are breastfeeding because their newborns may have adverse reactions, including excessive sleepiness, difficulty breathing, and potentially fatal breathing problems.²⁻⁴ In addition, there is growing concern that the use of oxycodone and hydrocodone should also be limited in women who are breastfeeding. In this article, I discuss the rationale for these recommendations.

Codeine

Codeine is metabolized to morphine by CYP2D6 and CYP2D7. Both codeine and morphine are excreted into breast milk. Some women are ultrarapid metabolizers of codeine

because of high levels of CYP2D6, resulting in higher concentrations of morphine in their breast milk and their breast fed newborn.^{2,5} In many women who are ultrarapid metabolizers of codeine, CYP2D6 gene duplication or multiplication is the cause of the increased enzyme activity.⁶ Genotyping can identify some women who are ultrarapid metabolizers, but it is not currently utilized widely in clinical practice.

In the United States approximately 5% of women express high levels of CYP2D6 and are ultrarapid metabolizers of codeine.⁴ In Ethiopia as many as 29% of women are ultrarapid metabolizers.⁷ Newborn central nervous system (CNS) depression is the most common adverse effect of fetal ingestion of excessive codeine and morphine from breast milk and may present as sedation, apnea, bradycardia, or cyanosis.⁸ Multiple newborn fatalities have been reported in the literature when lactating mothers who were

Instant Poll



Will you prioritize acetaminophen and/or ibuprofen for pain management in women who are breastfeeding?

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CONTINUED ON PAGE 9

ultrarapid metabolizers took codeine. **The FDA and ACOG recommend against the use of codeine in lactating women.**

Hydrocodone

Hydrocodone, a hydrogenated ketone derivative of codeine, is metabolized by CYP2D6 to hydromorphone. Both hydrocodone and hydromorphone are present in breast milk. In lactating mothers taking hydrocodone, up to 9% of the dose may be ingested by the breastfeeding newborn.⁹ There is concern that hydrocodone use by women who are breastfeeding and are ultrarapid metabolizers may cause increased fetal consumption of hydromorphone resulting in adverse outcomes in the newborn. The AAP cautions against the use of hydrocodone.²

Oxycodone

Oxycodone is metabolized by CYP2D6 to oxymorphone and is concentrated into breast milk.¹⁰ Oxymorphone is more than 10 times more potent than oxycodone. In one study of lactating women taking oxycodone, codeine, or acetaminophen, the rates of neonate CNS depression were 20%, 17%, and 0.5%, respectively.¹¹ The authors concluded that for mothers who are breastfeeding oxycodone was no safer than codeine because both medications were associated with a high rate of depression in the neonate. Newborns who develop CNS depression from exposure to oxycodone in breast milk will respond to naloxone treatment.¹² The AAP recommends against prescribing oxycodone for women who are breastfeeding their infants.²

In a recent communication, the Society for Obstetric Anesthesia and Perinatology (SOAP) observed

that in the United States, following cesarean delivery the majority of women receive oxycodone or hydrocodone.¹³ SOAP disagreed with the AAP recommendation against the use of oxycodone or hydrocodone in breastfeeding women. SOAP noted that all narcotics can produce adverse effects in newborns of breastfeeding women and that there are no good data that the prescription of oxycodone or hydrocodone is more risky than morphine or hydromorphone. However, based on their assessment of risk and benefit, pediatricians prioritize the use of acetaminophen and morphine and seldom use oxycodone or hydrocodone to treat moderate to severe pain in babies and children.

Tramadol

Tramadol is metabolized by CYP2D6 to O-desmethyltramadol. Both tramadol and O-desmethyltramadol are excreted into breast milk. In ultrarapid metabolizers, a greater concentration of O-desmethyltramadol is excreted into breast milk. The FDA reported that they identified no serious neonatal adverse events in the literature due to the use of tramadol by women who are breastfeeding. However, given that tramadol and its CYP2D6 metabolite enter breast milk and the potential for life-threatening respiratory depression in the infant, the FDA included tramadol in its warning about codeine.³

Codeine, hydrocodone, oxycodone, and tramadol are all metabolized to more potent metabolites by the CYP2D6 enzyme. Individuals with low CYP2D6 activity, representing about 5% of the US population, cannot fully activate these narcotics. Hence they may not get adequate pain relief when treated with codeine, oxycodone, hydrocodone,

or tramadol. Given their resistance to these medications they may first be placed on a higher dose of the narcotic and then switched from a high ineffective dose of one of the agents activated by CYP2D6 to a high dose of morphine or hydromorphone. This can be dangerous because they may then receive an excessive dose of narcotic and develop respiratory depression.¹⁴

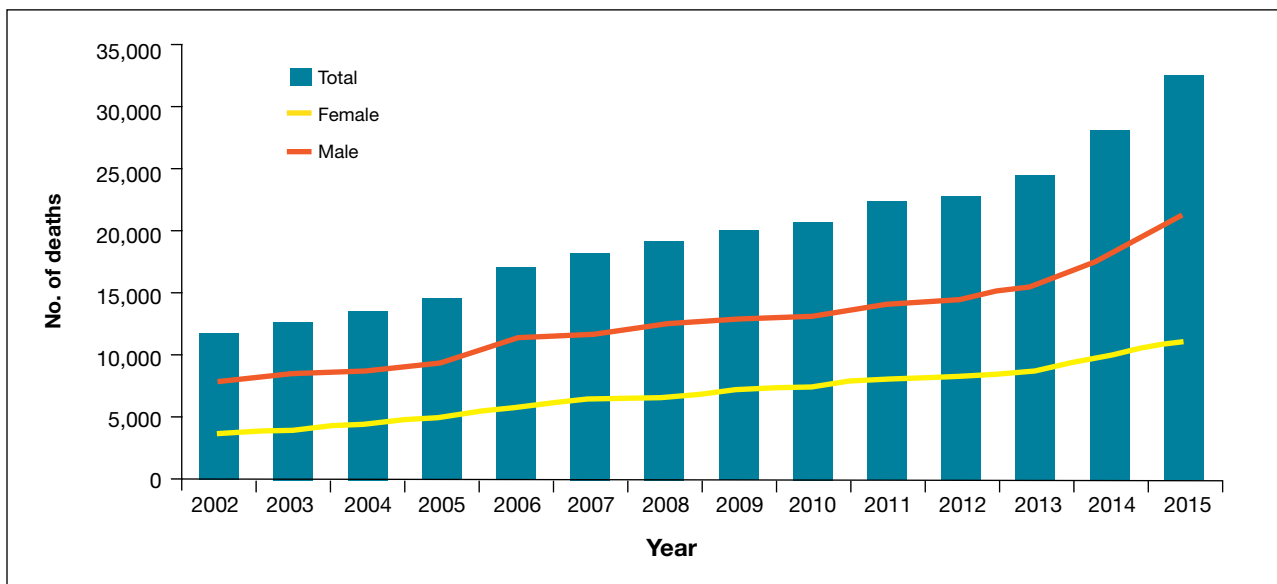
Aspirin

There are very little high quality data about the use of aspirin in women breastfeeding and the effect on the neonate. If a mother takes aspirin, the drug will enter breast milk. It is estimated that the nursing baby receives about 4% to 8% of the mother's dose. The World Health Organization recommends that aspirin is compatible with breastfeeding in occasional small doses, but repeated administration of aspirin in normal doses should be avoided in women who are breastfeeding. If chronic or high-dose aspirin therapy is recommended, the infant should be monitored for side effects including metabolic acidosis¹⁵ and coagulation disorders.¹⁶ The National Reye's Syndrome Foundation recommends against the use of aspirin in women who are breastfeeding because of the theoretical risk of triggering Reye syndrome.¹⁷ Acetaminophen and ibuprofen are recommended by the WHO for chronic treatment of pain during breastfeeding.¹⁶

Acetaminophen and ibuprofen

For the medication treatment of pain in women who are breastfeeding, the WHO recommends the use of acetaminophen and ibuprofen.¹⁶ Acetaminophen is transferred from the maternal circulation into breast milk, but it is estimated that the dose to the nursing neonate is <0.3%

FIGURE Number of opioid deaths in the United States¹



of the maternal dose.¹⁸ In mothers taking ibuprofen 1600 mg daily, the concentration of ibuprofen in breast milk was below the level of laboratory detection (<1 mg/L).¹⁹ Ibuprofen treatment is thought to be safe for women who are breastfeeding because of its short half-life (2 hours), low excretion into milk, and few reported adverse effects in infants.

Morphine

Morphine is not metabolized by CYP2D6 and is excreted into breast milk. Many experts believe that women who are breastfeeding may take standard doses of oral morphine with few adverse effects in the newborn.^{20,21} For the treatment of moderate to severe pain in opioid-naïve adults, morphine doses in the range of 10 mg orally every 4 hours up to 30 mg orally every 4 hours are prescribed. When using a solution of morphine, standard doses are 10 mg to 20 mg every 4 hours, as needed to treat pain. When using morphine tablets, standard doses are 15 mg to 30 mg every 4 hours.

The WHO states that occasional doses of morphine are usually safe for women breastfeeding their newborn.¹⁶ The AAP recommends the use of morphine and hydromorphone when narcotic agents are needed to treat pain in breastfeeding women.²

Hydromorphone

Hydromorphone, a hydrogenated ketone derivative of morphine, is not metabolized by CYP2D6 and is excreted into breast milk. There are limited data on the safety of hydromorphone during breastfeeding. Breast milk concentrations of hydromorphone are low, and an occasional dose is likely associated with few adverse effects in the breastfeeding newborn.²² For the treatment of moderate to severe pain in opioid-naïve adults, hydromorphone doses in the range of 2 mg orally every 4 hours up to 4 mg orally every 4 hours are prescribed. Like all narcotics, hydromorphone can result in central nervous system depression. If a mother ingests sufficient quantities of hydromorphone, respiratory depression in the breastfeeding

newborn can occur. In one case report, a nursing mother was taking hydromorphone 4 mg every 4 hours for pain following a cesarean delivery. On day 6 following birth, her newborn was lethargic and she brought the infant to an emergency room. In the emergency room the infant became apneic and was successfully treated with naloxone, suggesting a narcotic overdose due to the presence of hydromorphone in breast milk.²³ Hydromorphone should only be used at the lowest effective dose and for the shortest time possible.

The bottom line


Pediatricians seldom prescribe codeine, oxycodone, hydrocodone, or tramadol for the treatment of pain in newborns or children. Pediatricians generally use acetaminophen and morphine for the treatment of pain in newborns. Although data from large, high quality clinical trials are not available, expert opinion recommends that acetaminophen and ibuprofen should be prescribed as first-line medications for the

CONTINUED ON PAGE 12

treatment of pain in women who are breastfeeding. Use of narcotics that are metabolized by CYP2D6 should be minimized or avoided in women who are breastfeeding. If narcotic medication is necessary, the lowest effective dose of morphine or hydromorphone should be prescribed for the shortest time possible. If morphine is prescribed to women who are breastfeeding, they

should be advised to observe their baby for signs of narcotic excess, including drowsiness, poor nursing, slow breathing, or low heart rate.

The goal of reducing morbidity and mortality from opioid use is a top public health priority. Obstetrician-gynecologists can contribute through the optimal use of opioid analgesics. Reducing the number of opioid prescriptions

and the quantity of medication prescribed per prescription is an important first step in our effort to reduce opioid-related deaths. 



RBARBIERI@FRONTLINEMEDCOM.COM

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References

- National Overdose Deaths—Number of Deaths from Opioid Drugs. National Institute on Drug Abuse website. <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>. Update January 2017. Accessed September 14, 2017.
- Sachs HC; Committee on Drugs. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. *Pediatrics*. 2013;132(3):e796–e809.
- US Food and Drug Administration. FDA Drug Safety Communication. FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. Silver Spring, MD: US Food and Drug Administration. <https://www.fda.gov/Drugs/DrugSafety/ucm118113.htm>. Published April 2017. Accessed September 12, 2017.
- Practice advisory on codeine and tramadol for breast feeding women. American College of Obstetricians and Gynecologists website. <https://www.acog.org/About-ACOG/News-Room/Practice-Advisories/Practice-Advisory-on-Codeine-and-Tramadol-for-Breastfeeding-Women>. Published April 27, 2017. Accessed September 12, 2017.
- 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.
- Langaee T, Hamadeh I, Chapman AB, Gums JG, Johnson JA. A novel simple method for determining CYP2D6 gene copy number and identifying allele(s) with duplication/multiplication. *PLoS One*. 2015;10(1):e0113808.
- Cascorbi I. Pharmacogenetics of cytochrome p4502D6: genetic background and clinical implication. *Eur J Clin Invest*. 2003;33(suppl 2):17–22.
- Naumburg EG, Meny RG. Breast milk opioids and neonatal apnea. *Am J Dis Child*. 1988;142(1):11–12.
- Sauberan JB, Anderson PO, Lane JR, et al. Breast milk hydrocodone and hydromorphone levels in mothers using hydrocodone for postpartum pain. *Obstet Gynecol*. 2011;117(3):611–617.
- Seaton S, Reeves M, McLean S. Oxycodone as a component of multimodal analgesia for lactating mothers after Cesarean section: relationships between maternal plasma, breast milk and neonatal plasma levels. *Aust N Z J Obstet Gynaecol*. 2007;47(3):181–185.
- Lam J, Kelly L, Ciszkowski C, et al. Central nervous system depression of neonates breastfed by mothers receiving oxycodone for postpartum analgesia. *J Pediatr*. 2012;160(1):33–37.e2.
- Timm NL. Maternal use of oxycodone resulting in opioid intoxication in her breastfed neonate. *J Pediatr*. 2013;162(2):421–422.
- The Society for Obstetric Anesthesia and Perinatology. Comments in response to the ACOG/SMFM Practice Advisory on Codeine and Tramadol for Breastfeeding Women. The Society for Obstetric Anesthesia and Perinatology website. <https://soap.org/soap-response-acog-smfm-advisory.pdf>. Published June 10, 2017. Accessed August 28, 2017.
- Banning AM. Respiratory depression following medication change from tramadol to morphine [article in Danish]. *Ugeskr Laeger*. 1999;161(47):6500–6501.
- Clark JH, Wilson WG. A 16-day old breast-fed infant with metabolic acidosis caused by salicylate. *Clin Pediatr (Phila)*. 1981;20(1):53–54.
- World Health Organization. Breastfeeding and maternal medication. Recommendations for drugs in the 11th WHO model list of essential drugs. <http://apps.who.int/iris/bitstream/10665/62435/1/55732.pdf>. Published 2002. Accessed September 12, 2017.
- Reye's syndrome. National Reye's Syndrome Foundation website. <http://www.reyessyndrome.org>. Accessed September 12, 2017.
- Berline CM Jr, Yaffe SJ, Ragni M. Disposition of acetaminophen in milk, saliva, and plasma of lactating women. *Pediatr Pharmacol (New York)*. 1980;1(2):135–141.
- Townsend RJ, Benedetti TJ, Erickson SH, et al. Excretion of ibuprofen into breast milk. *Am J Obstet Gynecol*. 1984;149(2):184–186.
- Spigset O, Hägg S. Analgesics and breastfeeding: safety considerations. *Paediatr Drugs*. 2000;2(3):223–238.
- Bar-OZ B, Bulkowstein M, Benyamini L, et al. Use of antibiotic and analgesic drugs during lactation. *Drug Saf*. 2003;26(13):925–935.
- Edwards JE, Rudy AC, Wermeling DP, Desai N, McNamara PJ. Hydromorphone transfer into breast milk after intranasal administration. *Pharmacotherapy*. 2003;23(2):153–158.
- Schultz ML, Kostic M, Kharasch S. A case of toxic breast-feeding [published online ahead of print January 6, 2017]. *Pediatr Emerg Care*. doi:10.1097/PEC.0000000000001009.