



Drug Principles in Lactation

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LEARNING OBJECTIVES

1. Evaluate relative infant doses to determine preferable agents in breastfeeding infants.
2. Classify potentially hazardous agents as relatively or completely contraindicated in breastfeeding.
3. Estimate the lactation safety of a new drug with no human data.
4. Devise a safe medication plan for treating breastfeeding women with an acute disease state.
5. Develop a medication regimen for women with a chronic medical condition.
6. Synthesize strategies for breastfeeding women to minimize the quantity of drug their infant consumes.

ABBREVIATIONS IN THIS CHAPTER

M/P	Milk/plasma ratio
NAS	Neonatal abstinence syndrome
RID	Relative infant dose
SSRI	Selective serotonin reuptake inhibitor
VZV	varicella-zoster virus

[Table of other common abbreviations.](#)

INTRODUCTION

Breastfeeding provides the perfect nutrition to newborns and infants: not only is it readily available and always at the right temperature, it helps promote bonding between mother and child and positively influences the infant's mental development. Current recommendations include exclusively breastfeeding through 6 months of age and then continuing to predominantly breastfeed (supplementing with water or water-based liquids) or partly breastfeed (adding in other liquids and solids) through 1 year or older (CDC 2014).

Breastfeeding rates across the United States have increased in recent years. For children born in 2011, 79% of newborns were breastfed (exclusively, predominantly, or partly). This number drops to 49% at 6 months and to 27% at 1 year. Exclusive breastfeeding was considerably lower (i.e., 40.7% at 3 months, 18.8% at 6 months). Rates of breastfeeding vary in the United States; southern states tend to have lower rates of overall breastfeeding, whereas western and northeastern states have higher rates of exclusive breastfeeding for at least 6 months (CDC 2014).

Benefits of Breastfeeding for the Infant

Breastfed infants have many advantages, both immediate and long term, over formula-fed infants. Beyond reduced infections and decreased risk of childhood and adult obesity, exclusive breastfeeding for a longer duration is associated with advantages in premature infants such as promoting intestinal cell maturation and reducing the risk of developing necrotizing enterocolitis (Reisinger 2014; Herrmann 2014). In addition, breast milk reduces the incidence of sepsis and lowers the cost of neonatal ICU stays (Chapman 2013).

Breast milk is the main source of the infant's intestinal flora. Bacterial content in human milk increases throughout the lactation process, with the lowest concentration in colostrum and the highest

in mature milk. Women delivering preterm infants have lower concentrations of *Bifidobacterium* and *Lactobacillus* spp. with higher concentrations of *Enterococcus* spp. in their colostrum than do women delivering at term. Women who deliver by cesarean section have higher levels of bacteria in colostrum and transitional milk than do women who deliver vaginally (Khodayar-Pardo 2014). It is unknown how or why this occurs, although newborns delivered by cesarean section bypass the normal acquisition of vaginal flora during the birth process. The increased bacterial count in breast milk does not compensate for this lack of bacterial colonization. Further data suggest that breast milk also contains stem cells that can integrate and repair or replace neural cells in the infant (Twigger 2013). Because of this possibility, these cells may provide a biologic mechanism for higher IQs in breastfed infants.

In term newborns and infants, exclusive breastfeeding has been associated with a lower risk of sudden infant death syndrome (Hauck 2011) and a decrease in morbidity and mortality related to pneumonia in children younger than 2 years (Lamberti 2013). Exclusive breastfeeding for 3 months reduces attention-deficit/hyperactivity disorder rates, and a duration of any breastfeeding beyond 3 months may reduce the risk of developing the disorder (Mimouni-Bloch 2013; Shamberger 2012). In one study, children given a diagnosis of pediatric cancer of the blood, lymphatic system, or CNS had considerably shorter mean and median durations of exclusive breastfeeding than did controls (Ortega-Garcia 2008).

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Normal infant feeding schedules from birth through 6 months of age
- Standard treatments for common medical conditions
- FDA-required changes to product labeling requirements
- Baby-Friendly Hospital Initiative guidelines and requirements

[Table of common laboratory reference values](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- CDC. [Breastfeeding](#) [homepage on the Internet]
- WHO. [10 Facts on Breastfeeding](#) [homepage on the Internet]

Benefits of Breastfeeding for the Mother

Breastfeeding is a calorie-intense endeavor that promotes postpartum weight loss and has many other benefits to the mother. Studies have shown a reduced risk of non-insulin-dependent diabetes and metabolic syndrome in women who breastfeed. In addition, evidence shows a decreased risk of hypertension in women who breastfed compared with women who never or only briefly breastfed (Stuebe 2011) and a lower risk of developing atherosclerosis, as determined by carotid artery intima-media thickness (Gunderson 2015). Women who breastfed for at least 10 months had the most benefit in early subclinical markers for atherosclerotic disease.

Meta-analyses have shown that longer durations of breastfeeding decrease the risk of both breast and ovarian cancers (Zhou 2015; Feng 2014). Suppression of ovulatory cycles and lower hormonal levels associated with breastfeeding are protective against both cancers. Breastfeeding facilitates mammary cell differentiation, reduces toxic accumulation of organochlorines in the breast, and leads to expression of a negative growth factor in cancerous mammary cells. Women who breastfed have lower recurrences of breast cancer than those who did not, with breastfeeding for at least 6 months offering greater protection (Mayor 2015). Breastfeeding for at least 8–10 months provides the most benefit against ovarian cancer.

Stages of Lactation

The process of breastfeeding can be divided into three stages, with the fourth representing discontinuation. Stage I lactogenesis begins during mid-pregnancy and prepares the breast for milk production. Casein and lactose are secreted into the alveoli, which comprise the milk ducts. These components remain in the breast until colostrum is produced, at which time they are ejected with new milk. Colostrum is a thick yellow liquid containing beta-carotene and many other important nutrients, antioxidants, cytokines, and immunologic components. Colostrum has relatively little fat and caloric value compared with milk produced later, but it is much higher in fat-soluble vitamins, protein, and immunoglobulin (Ig)A. Colostrum is produced in low quantities during the first days after birth, with 2–20 mL per feeding session. A newborn's stomach can hold about 5–7 mL on the first day, increasing to around 20 mL by day 3. Although women may feel like their colostrum is inadequate, this is the perfect volume for a newborn stomach. Multiparous women produce colostrum sooner and in higher volume than primiparous women. Newborns feed at least 8–12 times daily. They may cluster feedings within a relatively short period or sleep for a longer duration after a larger volume intake (Lawrence 2016).

During the initial stage of breastfeeding, large gaps between lactocytes exist, allowing large molecules to enter breast milk. These gaps are essential for transmission of many of the important components of breast milk: immunologic cells such as macrophages, neutrophils, lymphocytes,

and immunoglobulins. However, these large gaps also allow higher-molecular-weight drugs to enter breast milk. Fortunately, the volume of milk consumed is low, and the quantity of drug consumed is usually minimal.

The volume of milk produced dramatically increases days 2–5 after childbirth, which is the start of stage II lactogenesis. The drop in progesterone after delivery stimulates significantly larger volumes of milk production. Prolactin concentrations are elevated with reduced progesterone concentrations, and oxytocin is secreted for milk letdown. Maternal sensory input from her newborn increases oxytocin concentrations, promoting the bond between mother and child. However, oxytocin release is inhibited by maternal stress and pain. Educating new mothers and their providers on the importance of managing pain with nonpharmacologic and drug therapy will promote better breastfeeding. Milk “coming in” may be delayed by maternal obesity, increased maternal age, gestational diabetes requiring insulin for treatment, and a low LATCH score in the first 24 hours (Chapman 2014). The LATCH score evaluates five characteristics of a breastfeeding session: the infant’s latch, audible swallowing, type of nipple, maternal comfort, and need for assistance with positioning the newborn during feeding (hold), with higher scores associated with improved success and continued breastfeeding at 6 weeks postpartum (Kumar 2006).

During stage II, additional blood and fluid enter the breast, causing fullness, heaviness, and warmth; the fluid is necessary to increase milk production, and the body adapts within 2 days to relieve the associated discomfort. Transitional milk spans the gap between colostrum and mature milk, which is produced around 14 days after delivery. The hallmark of stage III lactogenesis is the maintenance of milk supply. Mature milk is higher in caloric value and fat concentrations than previous forms of milk.

As a breastfeeding session begins, the milk (foremilk) is lower in fat concentration and higher in water and protein (Lawrence 2016). As the session continues, the fat concentration increases to 3.6%; when the breast is almost empty, the milk is known as hindmilk. This process is a continuum rather than two different types of milk. As milk is produced and remains in the breast, fat globules tend to conglomerate and adhere to alveolar walls. When suckling is initiated, the newest milk is released first, followed by the higher-fat content milk, which is forced down ducts to be ejected. Hence, if breastfeeding is frequently occurring, there is less time for lipids to become stuck in the alveoli, and the period of foremilk is considerably shorter.

The volume of milk produced varies from day to day and from breast to breast. Primiparous women produce mature milk with higher fat content than multiparous women. Milk supply depends on the demand, so women who breastfeed less often produce less milk. Hence, full breasts inhibit further milk production. In general, infants older than 1 month consume 3–5 oz of milk per feeding session.

Barriers to Successful Breastfeeding

Lack of emotional support is a common reason women discontinue breastfeeding, especially early on. Breastfeeding can be difficult during the first days after delivery. Without appropriate social support, women may feel they need to supplement their breast milk with formula. Supplementation can lead to overfeeding; this is not possible with breastfeeding alone. Women and their support system may have a preconceived notion of how much an infant should consume, thus offering more formula than the infant desires. Breastfed infants feed more often than formula-fed infants. This concerns some mothers and more often their uninformed support, leading to women questioning whether they are producing enough milk. Fussy infants are not always hungry, but this behavior may be interpreted as such. Newborns displaying rooting behavior (turning the head towards the breast and positioning the mouth to suckle) soon after a previous feeding session may generate the same concern, but this can be normal behavior. Infants supplemented with formula may sleep more, hindering appropriate breastfeeding frequency and leading to decreased milk production.

Women may stop breastfeeding for a variety of reasons (e.g., a need to return to work, competing family responsibilities). These women may be uncomfortable breastfeeding in public, have inadequate space (e.g., a public restroom), or have insufficient time or breaks in their workday to pump milk. Other women stop breastfeeding secondarily to their infants seeming uninterested in breastfeeding. Minimizing distractions and assessing any changes that were made to normal routines for the mother (e.g., different foods or a new fragrance) may help the infant return to attentive feeding.

Many women find breastfeeding too painful to continue, from either cracked nipples or poor latching by her infant. An experienced consultant can assist with these problems. The application of cool packs or chilled cabbage leaves may soothe breasts after breastfeeding or pumping. Lanolin often helps with injured or painful nipples and is available OTC.

Resources for women include the [Baby-Friendly Hospital Initiative guidelines](#), which provide lactation support in the hospital and after discharge, as well as [La Leche League](#), [Nursing Mothers Advisory Council](#), [Breastfeeding USA](#), the [Office on Women’s Health](#), and [CDC](#). The Affordable Care Act requires insurers to cover the cost of a breast pump and support and counseling visits with a lactation consultant.

Interruptions to breastfeeding that occur before milk production is well established (around 3–4 weeks after birth) can be detrimental to milk production. The need to pump breast milk to either discard or store for later use requires a woman to work harder to maintain her supply. Pumping does not remove milk as effectively as an infant, so it is important for the mother to pump as often as the infant normally feeds (for 10–15 minutes per breast). Breast pumping that occurs too infrequently or for shorter than recommended times may have lower output, although short-duration pumpings (e.g., 5 minutes) can

help supplement the amount obtained during other sessions. The cumulative time spent pumping is in fact more important than the volume pumped at each session. Women may produce only 2 oz per pumping session, which may not provide enough milk for the infant's intake. Extra sessions can help increase milk production and collection.

Many factors can affect a woman's milk supply, including inadequate fluid intake, emotional or physical stress, and some drugs. If women are stressed during interruptions to breastfeeding or become dehydrated, their milk supply will also likely be reduced. Treatment of maternal conditions may be essential, even though the therapy may be contraindicated in lactating women. Sympathomimetic drugs can lead to vasoconstriction of blood vessels in the breast and inhibit prolactin. Ergot agents inhibit prolactin secretion by increasing dopamine concentrations, and certain hormonal agents can decrease estrogen concentrations, all of which lead to reduced milk production. The use of estrogen-containing birth control early after delivery is not recommended. The use of sedating antihistamines can also reduce breast milk production and may cause infant sedation.

DETERMINING INFANT DRUG EXPOSURE

Drug passage into mature milk depends on several factors, including the molecular weight, lipid solubility, protein binding, degree of ionization, volume of distribution, half-life, and pKa of the drug. Agents that easily cross the blood-brain barrier usually enter breast milk more readily. The mammary epithelium is a lipid membrane, making lipid-soluble drugs more likely to penetrate into milk. Water-soluble agents weighing less than 200 Da cross into milk readily, passing through aqueous pores surrounding alveoli in the breast. Drugs up to 800–1000 Da can cross into milk; however, larger molecules enter milk in lower quantities. High protein binding, ionization, and low serum concentrations decrease the likelihood of the drug entering the milk. Most drugs enter milk by simple diffusion; some pass by carrier-mediated diffusion; and some agents (e.g., nitrofurantoin, cimetidine, ranitidine, acyclovir, iodides) are actively transported.

Equilibrium may be established between the maternal plasma and the breast milk. As drug concentrations in the mother decrease, a higher drug concentration in the milk will promote transfer back into the maternal circulation. This occurs if the half-life of the drug is very short, breastfeeding intervals are longer, and the drug is a weak acid or pH neutral. Breast milk is slightly more acidic than maternal plasma, so weakly basic drugs (pKa greater than 7 but less than 10) become ionized and “trapped” in the milk compartment, unable to cross the lipid membrane (D'Apolito 2013). These drugs may still have low relative infant doses compared with more acidic agents in the same pharmacologic class.

Pharmacists can help determine whether a medication is safe for an infant by assessing factors such as milk concentrations from tertiary references specific for lactation and pregnancy and pediatric drug references. Often, these data will help reassure women that it is safe to continue breastfeeding even while taking medications. A milk/plasma ratio (M/P) is often listed in drug references; this is the average milk concentration (or more often a single milk concentration) compared with the average maternal plasma concentration. A value greater than 1 indicates that the drug concentrates in milk, but it does not communicate safety of the medication in breastfeeding. When the M/P is well over 1 but the maternal concentration is almost negligible, the quantity of drug intake by the infant is still minute.

The peak milk concentration can determine maximum infant exposure; however, this value may not be available. For a given drug, the milk concentration in milligrams per milliliter multiplied by the quantity of milk consumed daily (the standard assumption is 150 mL/kg/day) divided by the infant's weight will determine the dose per kilogram per day. This amount can be compared with the maternal dose (milligram per kilogram) resulting in the relative infant dose, expressed as a percentage. Relative infant doses less than 10% are considered safer and are preferred. Most drugs have a relative infant dose less than 1%.

Another way to determine drug safety during lactation is to compare the infant dose from pediatric drug references with the amount the infant consumes through breastfeeding. Often, the total amount an infant receives per day is lower than a single dose given directly to the infant. Pediatric references can also be used to determine whether a drug is normally used in premature infants or newborns. Agents used in these populations are of low concern to breastfeeding women.

Certain drugs that are contraindicated in pregnancy may be completely safe during breastfeeding. Medications taken during breastfeeding are almost always ingested by the infant in lower amounts than exposure during pregnancy. During pregnancy, the fetus can be exposed to concentrations as high as 100% of the maternal concentration, although the fetus is usually exposed to less. Also during pregnancy, teratogenic effects are of concern, but adverse effects are less noticeable. Only fetal monitoring will reveal CNS depression, whereas a newborn with similar effects will be more obvious. Premature infants and infants with serious medical conditions can significantly be affected by agents that affect respiratory drive and cause sedation, and smaller amounts of drugs can cause more severe consequences.

Infant Pharmacokinetics

Pediatric pharmacokinetics differ considerably from those of adults and change rapidly from birth to 12 years of life (Fernandez 2011). The gastric pH in premature infants and newborns is essentially neutral, dropping to a low pH during the

Patient Care Scenario

PART ONE

P.D. is a 32 year-old woman (weight 78 kg) who suffers from depression. She was on an MAOI before her pregnancy, but this was discontinued during the first weeks of gestation. P.D. is now 3 months postpartum and would like to restart an antidepressant. Her physician thinks an

SSRI would be more appropriate and asks for help selecting the best agent because P.D. is breastfeeding her son (weight 6 kg). The only drug information available at the time are the pharmacokinetics of the agents.

Drug	Molecular Weight (Da)	Half-life (hr)	Volume of Distribution	Bioavailability (%)	Protein Binding (%)
Citalopram	405	36	12 L/kg	80	80
Escitalopram	414	27-32	12 L/kg	80	56
Fluoxetine	309	48-72	2.6 L/kg	100	94.5
Paroxetine	329	21	8.7 L/kg	complete	95
Sertraline	306	26	20 L/kg	complete	98

Information from: National Center for Biotechnology Information. [PubChem Compound](#) [homepage on the Internet].

ANSWER

Based on the drug characteristics alone, escitalopram has the highest molecular weight and sertraline is the lowest. However, all of the agents are small enough that passage into breast milk is expected. Molecular weight is a large influence in transfer into milk. If one agent had a significantly higher molecular weight (i.e., 800 daltons), selection would be biased towards this drug. Next, the half-life will help determine the duration of exposure. Hence, fluoxetine is not a preferred agent for this reason. Paroxetine and sertraline have the shortest half-lives, but they are still close to 24 hours. Protein binding limits the amount of drug available to enter milk. Of the five agents, citalopram and escitalopram will have a higher amount of free drug in the maternal circulation. The others are more highly protein bound, with sertraline binding the most with plasma proteins. The bioavailability for citalopram and escitalopram is lower than the other agents, but not so much lower than this factor should

make a big difference in the amount of drug able to enter the neonatal circulation. From drug characteristics alone, sertraline is the best choice given its half-life and high protein binding.

Sertraline breast milk concentrations have a wide range, but the highest reported is 173 ng/mL with 100 mg daily. P.D.'s infant, on average, will consume 150 mL/kg per day, equating to about 900 mL. The breast milk concentration multiplied by the volume ingested leads to a total of 155,700 ng or 156 mcg per day. In other words, the infant receives a dose of 156 mcg/6 kg or about 26 mcg/kg/day. P.D.'s daily dosage of 100 mg is 1.28 mg/kg/day or 1280 mcg/kg/day. The relative infant dose (RID) compares the infant dose to her dose on a mcg/kg/day basis, meaning 26 mcg/kg/day divided by 1280 mcg/kg/d leads to 0.02 or 2%. Although this RID is higher than most drugs, it is still well below the recommended maximum of 10% for the fewest amount of side effects.

PART TWO

P.D.'s primary care physician hears about a new antidepressant on the market and thinks it may work better for her. Limited information is available regarding this agent, however the physician provides some information from the drug company. The molecular weight is 730 daltons,

volume of distribution 15 L/kg, it is 98% protein bound, and the bioavailability is 50%. The average adult serum concentration is 26 mcg/mL with a dose of 60 mg and the M/P was calculated to be 2.

ANSWER

With a serum concentration of 26 ng/mL (26 mcg/L), the milk concentration should be about 52 ng/mL. Again, P.D.'s infant will consume 900 mL per day. Multiplied by the concentration in the milk sample, this equates to 46,800 ng or 47 mcg per day. Although a 3-month-old infant may still be able to absorb more drug than an adult, the value of 50% should be used to calculate exposure. Hence, this

infant would consume and absorb at least 23.5 mcg of drug daily. With a dose of 60 mg, P.D.'s daily dosage is 769 mcg/kg. The infant's daily dosage is 3.9 mcg/kg, giving a calculated RID of 0.5%. So, the newer agent in this case provides a significantly lower dose to P.D.'s newborn and would be a better choice.

1. Breitzka RL, Sandritter TL, Hatzopoulos FK. Principles of drug transfer into breast milk and drug disposition in the nursing infant. *J Hum Lact* 1997;13:155-8.
2. Newton ER, Hale TW. Drugs in breast milk. *Clin Obstet Gynecol* 2015;58:868-84.
3. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*, 10th ed. Philadelphia: Wolters Kluwer Health, 2014.
4. Hale TW. *Medications and Mothers' Milk: A Manual of Lactation Pharmacology*, 16th ed. Amarillo, TX: Hale, 2014.

first day of life and slowly rising back to neutral around day of life 10. Premature infants maintain the neutral pH in their stomachs during the first 2 weeks of life. Given these differences in gastric secretions, acid-labile drugs are usually well absorbed, and basic drugs are more rapidly absorbed, whereas weak acids have decreased absorption in infants compared with adults. Some drugs may not be broken down by the stomach as easily (e.g., immunoglobulins). Other agents may have better absorption in the intestines during early life because of lower proteolytic enzyme activity and higher intestinal permeability. Intestinal transit times are considerably longer in neonates secondary to slower mobility and peristalsis. Older infants have increased motility but also have slower intestinal transit time. Infants during the first few months of life have impaired fat digestion and decreased fat-soluble vitamin absorption because of bile secretion and pancreatic fluid variations. Intestinal bacterial colonization is determined by the type of feedings (breast milk or formula) a newborn receives, as described previously.

Distribution of drugs is also altered in neonates and infants given their higher total body water, low fat concentrations, reduced concentrations of proteins and binding capacity for drugs, and more permeable blood-brain barrier. Metabolism rates in premature infants and newborns are lower than in adults because of immature metabolic systems. The CYP enzymes 1A2 and 3A4 all have lower activity until age 2; 2C9 reaches adult activity after the first year of life. The isoenzymes 2C19 and 2D6 mature much more slowly during the first decade of life. Elimination rates are considerably lower in premature infants, and the rate increases more slowly than in full-term infants. Glomerular filtration rates reach adult values around 6 months, although other factors such as tubular secretion and tubular reabsorption also affect drug excretion. Urinary pH is lower in infants and may alter total elimination rates compared with adults.

ADVERSE INFANT EFFECTS

Newborns are most likely to have adverse reactions from drugs received through breastfeeding. Several reports document that 75%–79% of published adverse reactions occur in the first 2 months of life (Anderson 2016; Soussan 2014). This statistic is not surprising given that the premature metabolic and elimination capacity of a newborn may lead to prolonged exposure to problematic agents. Newborns may consume larger doses of drug compared with their weight, and they are more likely than older infants to be exclusively breastfed. Agents with the highest relative infant dose have the most adverse events in nursing infants. However, most drugs have low relative infant doses; thus, the incidence of adverse infant reactions is low.

The most common drugs to cause adverse reactions are those that affect the CNS. Infants have a more permeable blood-brain barrier, which can result in higher concentrations of certain drugs, including those with low CNS penetration in

adults. Effects such as sedation, lethargy, apnea, seizures, tremor, irritability, respiratory depression, and hypotonia can be caused by agents like opioids, benzodiazepines, antiepileptics, and antipsychotics. Use of two or more of these drugs concomitantly increases the risk of adverse events, including death. Gastrointestinal tract reactions such as vomiting, diarrhea, and weight loss are associated with antibiotics and antidepressants. Less commonly reported adverse events include skin reactions and bradycardia.

BREASTFEEDING IN SPECIAL SITUATIONS

Medical Conditions

Hypertension

Women with chronic hypertension usually require treatment soon after delivery because they are likely to return to baseline blood pressures near the end of pregnancy. During pregnancy, women may have been initiated on methyldopa. Methyldopa can be used postpartum because of its safety in breastfeeding, but it is not a very potent antihypertensive. In addition, its frequent (three times daily) dosing makes it less desirable than most other antihypertensives. Newer information is available regarding the use of amlodipine in breastfeeding to augment the case reports already in the literature. Amlodipine occurs in breast milk in concentrations similar to maternal serum, at least in the early postpartum period (Naito 2015). Amlodipine is a weak base, so breast milk concentrations would be expected to be higher than with nifedipine, a weak acid, but the relative infant dose is still less than 10%.

β -Blockers can be used for hypertension, but the class contains several weakly basic agents that become trapped in milk. β -Blockers are counterintuitive to anticipated penetration into milk. Agents that are more lipid soluble have a higher degree of protein binding (e.g., propranolol), crossing into milk at a lower concentration than agents that are less lipid soluble. However, most β -blockers are considered compatible with lactation. Although the early postpartum relative infant dose may exceed 10%, atenolol concentrations in breast milk decline over time. If atenolol is started in later months after delivery, the infant dose is less of a concern (Eyal 2010).

Doxazosin is not often used for control of hypertension, but it may be required in severe hypertension or urinary tract stones. This agent is a weak acid and highly protein bound, but the molecular weight, bioavailability, and relatively low volume of distribution suggest that some drug will transfer into breast milk. In one case report, the peak plasma and breast milk concentrations were sampled at 1 hour after the maternal dose, but no sampling was done at 1–10 hours, so it is unknown whether the peak in breast milk occurs later. Assuming the peak was at 1 hour, the infant dose was less than 0.1% of the maternal dose (Jensen 2013).

Thrombosis

Women who develop a venous thromboembolism during pregnancy will need anticoagulant therapy to complete at least 3 months of treatment followed by prophylactic therapy through the first 6 weeks postpartum, unless the treatment duration includes this time. This postpartum period is associated with a higher risk of developing thromboses than during pregnancy. Women delivering by cesarean section are at higher risk than those delivering vaginally. Heparins are the most appropriate initial management strategy for a deep venous thrombosis or pulmonary embolism. Pelvic venous thromboses rarely need therapy beyond a brief course of antibiotics and heparin.

Warfarin is highly protein bound; therefore, little to no drug passes into breast milk, leading to its status as the drug of choice for treatment in women who are breastfeeding. The newer oral anticoagulant therapies are attractive because of their limited monitoring requirements, standardized dosing, fewer drug interactions, and lack of dietary considerations. However, little is known about these agents in breast milk. Table 1-1 lists the pharmacokinetic properties of these agents, including warfarin. None of the new agents can currently be recommended for use in lactation secondary to the paucity of data and potential for severe adverse events in a newborn.

Infections

Breast Infections

Mastitis is an inflammation of breast tissue with local and usually systemic symptoms of infection. Most commonly occurring in the second and third weeks after delivery, mastitis may lead to premature discontinuation of breastfeeding. Risk factors can include issues with the nipples such as fissures or yeast infections, clogged milk ducts, inadequate emptying of the breast, and latching problems of the newborn. Treatment involves frequent drainage of the breast either through continued breastfeeding or pumping (Spencer 2008). Failure to remove milk from the breast increases the risk of abscess formation. Although it may seem risky to use

milk from the affected breast, the milk itself is not infected; however, the infant may reject this milk because of its higher sodium content. Antibiotics are often required for resolution of the mastitis and should cover skin flora. Examples of antibiotics covering this spectrum are cephalexin, dicloxacillin, clindamycin, and azithromycin. All of these are compatible with lactation, and antibiotic selection should be driven by the woman's allergies and any previous treatments. Women who do not respond to outpatient therapy may need to be admitted for intravenous therapy, at which time breast milk cultures should be done. Methicillin-resistant *Staphylococcus aureus* is becoming more prevalent and, depending on risk factors, may require vancomycin therapy for treatment (Amir 2014). Candidal infections usually present with burning nipple pain and breast pain. Antifungal therapy should be used orally or topically, with the infant simultaneously treated for thrush.

An abscess should be suspected if a specific area of the breast becomes tender, red or indurated. Ultrasonography may be required to diagnose the abscess and if present, it can also be used to either drain the collection or aspirate fluid to determine the appropriate antimicrobial coverage. Breastfeeding can continue as long as the infant is not exposed to infected tissue or drainage.

Viral Infections

Breastfeeding is not contraindicated in women with hepatitis B infections with infants who receive both hepatitis B immune globulin and hepatitis B vaccine postnatally. Women with cracked or bleeding nipples should avoid breastfeeding because of the higher risk of transmission through blood ingestion (Shi 2011). Women taking lamivudine or tenofovir for chronic hepatitis B infection can breastfeed their infants. Lamivudine appears to concentrate in breast milk; however, the amount the infant consumes through breastfeeding is considerably lower than that received during pregnancy. Tenofovir data are limited in breastfeeding, but the amount received through breast milk is again lower than the dose in utero (Ehrhardt 2015).

Table 1-1. Pharmacokinetic Properties of Oral Anticoagulants

Agent	Molecular Weight (Da)	Half-life (hr)	Volume of Distribution	Bioavailability (%)	Protein Binding (%)	pKa	Serum Peak (hr)
Apixaban	459.5	12	21 L	~50	87	13.2	3–4
Dabigatran	471.5	12–14	60–70 L	6.5	31–35	3.78	0.5–2
Edoxaban	548.1	9–11	107 L	62	55	6.7	1–2
Rivaroxaban	435.9	5–9	50 L	66–100	92–98	1.6	2–4
Warfarin	308.3	R 37–89 S 21–43	0.14 L/kg	100	99	5.08	4

Information from: National Center for Biotechnology Information. [PubChem Compound](#) [homepage on the Internet].

Mother-to-child transmission of hepatitis C during delivery occurs in only 5%–10% of infants, and transmission through breastfeeding is extremely rare. Breast milk can inactivate all major genotypes of hepatitis C and can disrupt the integrity of the envelopes of some viruses such as influenza A and herpes simplex virus (Pfaender 2013). Therefore, breastfeeding with chronic hepatitis C is not contraindicated. However, little information exists regarding the latest therapies to treat hepatitis C and their effects on nursing infants. Most of these agents have molecular weights greater than 500 Da, but lack of data makes it difficult to determine how much drug would appear in breast milk. Women desiring curative therapy should be ready to wean their infants before starting an appropriate agent or agents.

Mothers with HIV infection transmit the virus in up to 15% of infants through breastfeeding if antiretroviral agents are not used (Bode 2012). Transmission depends on duration of breastfeeding, with longer exposure leading to higher rates of infant seroconversion. One study evaluated breastfeeding in HIV-positive women; daily nevirapine in the infant for 6 months plus 1 week had a statistically lower virus transmission rate than placebo (1.1% vs. 2.4%; $p=0.049$) with 6 months of exclusive breastfeeding (Fowler 2014). Women with low CD4 counts are most likely to transmit the virus through breast milk. In women with CD4 counts less than 350 cells/mL in the active treatment arm, the transmission rate was considerably higher at 18 months (8.9% vs. 1.9% in women with a CD4 of 350 cells/mL or greater), even though no treatment was given to the infants for 1 year.

During peak seasons, the influenza virus can be more virulent in pregnancy, and infection at the time of delivery causes concern for transmission to the newborn. The breastfeeding woman should wear a mask during close contact with her infant, but separation of the dyad is unnecessary (Cantry 2014). Women should be treated with antivirals; oseltamivir is safe to use during breastfeeding. In older infants, breast milk appears to enhance the production of type 1 interferon, a protective mediator of the respiratory tract immune system (Melendi 2010).

Primary varicella infections are less common now that routine vaccination includes the varicella-zoster virus (VZV). However, should a breastfeeding mother be exposed to varicella and develop skin lesions, mother and child should be separated. Giving the infant varicella-zoster immune globulin is advised if the disease is diagnosed shortly before or within 48 hours after delivery. The breast milk will likely contain VZV DNA and maternal antibodies to the virus. Acyclovir is safe to give to the mother in severe cases or if varicella pneumonia is diagnosed. One case report described a woman who continued to breastfeed despite having active lesions on her breasts. Her infant did not receive varicella-zoster immune globulin but did not develop a varicella infection (Karabayir 2015).

Psychiatric Disorders

Anxiety

Benzodiazepine use is not contraindicated during breastfeeding, although benzodiazepines can cause sedation, poor weight gain, apnea, and irritability in the infant. When combined with other CNS depressants, the likelihood of adverse infant reactions increases proportionately. Maternal sedation with these agents is not predictive of infant sedation (Kelly 2012). If used, benzodiazepines should be given for the shortest duration required for treatment.

Other agents such as selective serotonin reuptake inhibitors (SSRIs) can be used to treat anxiety and are not contraindicated during breastfeeding. If an SSRI is needed, agents with the lowest relative infant dose are preferred. According to the limited information available, buspirone breast milk concentrations are minimal. Buspirone can elevate serum prolactin concentrations, which could be beneficial to some women.

Psychosis

Treatment of psychosis remains vitally important postpartum because of concerns for self-harm and harm of the newborn infant. Moreover, many women treated for psychiatric illnesses require more than one agent, increasing the risks of adverse events (Nulman 2014). Drug discontinuation increases the risk of psychiatric deterioration. Even with therapy, as many as 24% of women have psychotic breaks (Robinson 2012). Breastfeeding may have positive mental health benefits in this population. Table 1-2 lists properties of the second-generation antipsychotics.

Lithium is readily transferred into breast milk because of its very low molecular weight and lack of protein binding. The relative infant dose can approach 30%, making it a poor choice for the treatment of bipolar disorder in breastfeeding women. Other agents for this condition such as several anticonvulsants and antipsychotics are usually safer options.

The first-generation antipsychotics, butyrophenones and phenothiazines, have few to no adverse effects in nursing infants, but chlorpromazine can cause drowsiness or lethargy (Parikh 2014). The newer antipsychotic agents are more commonly used for psychosis but have less information available. Aripiprazole is known to transfer into breast milk. The milk concentration peaks at around 3 hours and plateaus around 12 hours after the maternal dose (Nordeng 2014). Aripiprazole is highly lipid soluble, indicating concentration in the fattier portion of the feed. In one case report, the mother's milk production was significantly lower than normal, perhaps because of aripiprazole. Risperidone seems to have low to undetectable concentrations in milk, whereas that of the active metabolite 9-hydroxyrisperidone is higher (Weggehaar 2011). The limited information available seems to suggest that adverse events are uncommon in infants exposed to this agent. Olanzapine data in three women showed that

Table 1-2. Characteristics of Second-Generation Antipsychotics

Agent	Molecular Weight (Da)	Half-life (hr)	Volume of Distribution	Bioavailability (%)	Protein Binding (%)	pKa
Aripiprazole	448.4	75, metabolite 94	4.9 L/kg	87	> 99	
Asenapine	401.8	24	20–25 L/kg	35	96	
Clozapine	326.8	12	Unknown	12–81	97	7.5
Lurasidone	492.7	18, 40 mg 29–37, > 40 mg	6173 L	9–19	99.8	
Olanzapine	312.4	21–54	1000 L	~100	93	5, 7.4
Paliperidone	426.5	23	487 L	28	74	8.76
Quetiapine	383.5	6, metabolite 12	6–14 L/kg	100	83	
Risperidone	410.5	20	1.2 L/kg	~100	90	
Ziprasidone	412.9	7	1.5 L/kg	60	99	14.89

Information from: National Center for Biotechnology Information. [PubChem Compound](#) [homepage on the Internet].

even though milk concentrations were 57%–94% of maternal concentrations, the drug was undetectable in the serum of infants, who were all about 2 weeks old (Stiegler 2014). Olanzapine appears to peak in breast milk 2–4 hours after the maternal serum peak. In one case report, maternal and infant serum and breast milk concentrations were evaluated over 5 months. The infant serum concentration at 4 months was much higher than expected, but then was almost undetectable for the rest of the measurements. The authors attributed the significant decrease in infant concentrations to the initial expression and improved activity of CYP1A2 (Whitworth 2010).

Quetiapine does transfer into milk and can achieve concentrations in the infant's plasma. The M/P was 0.29 in one study with a relative infant dose of 0.09% (Rampono 2007). Clozapine is not recommended during breastfeeding. Not only is there a risk of decreased infant WBC counts, but adverse effects such as sedation, irritability, restlessness, seizures, decreased suckling reflex, cardiac instability, and delayed speech acquisition have also been reported (Robinson 2012; Mendhekar 2007).

CNS Disorders

Epilepsy

In general, most antiepileptic agents are considered safe in lactation. Doses received through breastfeeding are lower than during pregnancy. Carbamazepine, phenytoin, and valproic acid are the safest agents during lactation. However, phenobarbital, primidone, and ethosuximide have a higher potential to cause adverse neonatal effects. Gabapentin, levetiracetam, and oxcarbazepine have less information available, but they occur in low concentrations in breast milk with

no reports of adverse infant effects (Davanzo 2013). Lamotrigine transfer into milk is highly variable. The relative infant dose can be as high as 9.5%, but no adverse events have been reported in nursing infants. Serum concentrations can be measurable in nursing infants. One case of apnea has been reported (Hutchinson 2013).

Zonisamide has little information regarding breastfeeding safety. A case series published in 2013 reported on breast milk and maternal serum concentrations (Ando 2014). Breast milk samples were taken 4.5–24 hours after various doses, so it is unknown when the drug peaks in milk. Milk/plasma ratios were always less than 1, but relative infant doses were considerably higher than considered safe (up to 45%). Neither woman exclusively breastfed after the first 2 weeks after delivery, and no adverse infant outcomes occurred during breastfeeding.

Topiramate information during lactation is limited. Its rapid absorption, low protein binding, and long half-life lead to significant transfer into breast milk. The relative infant dose can be as high as 23%, with a measurable serum concentration in some infants. No reports of adverse events have been reported in infants. Monitoring for sedation and diarrhea in breastfed infants has been recommended (Davanzo 2014).

Headaches

Migraine headaches plague many women of reproductive age, and managing them during breastfeeding is an important concern. During pregnancy, women may have fewer migraines, and those who exclusively breastfeed have fewer migraines than women who bottle feed. Treatment with NSAIDs is generally considered safe, with the exception of analgesic doses of aspirin. Other salicylates should also

Table 1-3. Drug Characteristics of Serotonin 1B/1D Receptor Agonists

Agent	Molecular Weight (Da)	Half-life (hr)	Volume of Distribution	Bioavailability (%)	Protein Binding (%)
Almotriptan	335.5	3–5	180–200 L	~70	35
Eletriptan	382.5	4, active metabolite 13	138 L	~50	85
Frovatriptan	243.3	~26	3 L/kg	~30	15
Naratriptan	335.5	6	170 L	~70	28–31
Rizatriptan	269.4	2–3	110 L	~45	14
Sumatriptan	295.4	2–3	2.4 L/kg	~15 PO, IN 97 SC	14–21
Zolmitriptan	287.36	3	7 L/kg	40	25

IN = intranasal; PO = by mouth; SC = subcutaneous.

Information from: National Center for Biotechnology Information. [PubChem Compound](#) [homepage on the Internet].

be avoided because of the risk of thrombocytopenia and tinnitus in a nursing infant. The serotonin receptor agonist “triptan” agents have little information regarding safety in breastfeeding; most have no data regarding transfer into breast milk. Sumatriptan has the most information, with no reports of adverse events in breastfed infants. If other triptans are used, consideration of their half-life, protein binding, and active metabolites should drive drug selection. Pharmacokinetics for each agent are listed in Table 1-3. Caffeine for the treatment of migraines should be used cautiously because agitation, irritability, and sleep disturbances can occur with large maternal intake. Ergot agents should be

avoided because of their potential to decrease the milk supply by lowering prolactin concentrations. Metoclopramide can be used for acute treatment and may benefit milk production (Davanzo 2014).

Migraine prophylaxis should be offered to women who have several migraines monthly. Select agents from antihypertensive, antidepressant, and anticonvulsant drug classes are effective in preventing migraine headaches. These agents should be selected according to patient characteristics, concomitant drug therapy, and responses to previous therapy. Table 1-4 lists common drugs used for prophylaxis and their pharmacokinetic properties.

Table 1-4. Characteristics of Selected Migraine Prophylactic Agents

Agent	Molecular Weight (Da)	Half-life (hr)	Volume of Distribution	Bioavailability (%)	Protein Binding (%)	pKa
Atenolol	266.3	6–7	50–79 L	~50	5–15	9.6
Metoprolol	267.4	3–4	3.2–5.6 L/kg	40–50	~10	9.7
Propranolol	259.3	3–6	4 L/kg	25	~90	9.5
Verapamil	454.6	4.5–12	3.89 L/kg	20–35	~90	8.8
Amitriptyline	277.4	13–36	18–22 L/kg	43–46	>90	9.4
Gabapentin	171.2	5–7	58 L	27–60	<3	3.68, 10.7
Lamotrigine	256.1	24–35	0.9–1.3 L/kg	98	55	5.7
Topiramate	339.4	19–23	0.6–0.8 L/kg	~80	15–41	8.7
Valproic acid	144.2	9–11	0.2 L/kg	90	80–90	4.8

Information from: National Center for Biotechnology Information. [PubChem Compound](#) [homepage on the Internet].

Pain Management

Postpartum pain management is important to maintain comfort for the mother, especially after a cesarean section or significant vaginal or perineal lacerations. Breastfeeding requires oxytocin for milk letdown, which causes uterine contractions and leads to maternal abdominal and pelvic discomfort. Uncontrolled pain can have negative effects on breastfeeding. Acetaminophen and NSAIDs should be first line. Ibuprofen, naproxen, and ketorolac are secreted into milk at low concentrations and are considered compatible with lactation. Ibuprofen is often preferred for longer-term use because of better data supporting its safety in breast milk.

Opioids should be used for more severe pain and at the lowest dose that controls pain (Montgomery 2012). Excessive use of opioids can affect the alertness and suckling ability of newborns. Codeine is contraindicated because of alterations in CYP2D6 metabolism in some women, which can lead to excessive amounts of morphine in breast milk. This same enzyme is responsible for oxycodone and hydrocodone metabolism, so women at high risk of having an ultrarapid metabolizer status should use these agents with caution. Duplications of the *CYP2D6* gene causing higher enzyme activity are most likely to occur in Ethiopians, Middle Easterners, and North Africans. Morphine is a better choice in these women. Several reports of adverse infant effects, including death, have been attributed to maternal codeine ingestion.

Oxycodone is often used for postpartum pain control as well as after surgical procedures. Oxycodone transfers into breast milk easily because of its high bioavailability and moderate protein binding; it is a weak base, which may lead to higher concentrations in breast milk. Women who have sedation with oxycodone doses are more likely to have infants who also have CNS depression, although any infant breastfed by a mother taking opioids should be monitored for lethargy and poor suckling, which indicate possible opioid intoxication (Lam 2012). Hydrocodone has a lower clearance in neonates, making it less desirable than other opioids, especially in premature newborns. Tramadol has been used in the peripartum period, but little is known about its use in lactation the first few days after delivery. Tramadol – and its active metabolite, to a much lesser degree – are transferred into milk in low concentrations (Bloor 2012). Because tramadol requires metabolism through CYP2D6, the higher rate of parent drug into milk could lead to a lower rate of adverse effects in the infant.

Anesthesia may be required for surgical procedures in women who are breastfeeding. Even though most anesthetic agents are very lipophilic, low amounts of propofol and etomidate enter breast milk. Rapid elimination of these agents also makes them less likely to have high breast milk concentrations because of the transfer back into the maternal serum. Therefore, once a woman is awake enough to breastfeed, she should be allowed to do so. Inhalational agents have low oral bioavailability and rapid elimination, so breast milk concentrations should be minimal, and their use is not contraindicated

in lactating women. Neuromuscular blocking agents are usually ionized at physiologic pH and hence cannot cross into breast milk. Succinylcholine is often the neuromuscular blocker of choice in pregnancy; shorter-acting agents during lactation may also be preferable. Local anesthetics are highly lipid soluble, but depending on the route of administration and whether the agent is administered as a continuous infusion through a catheter or a single dose, the breast milk concentration may be negligible. Local anesthetics used subcutaneously or intradermally are unlikely to enter into breast milk, and any drug that enters is unlikely to be absorbed by the infant (Dalal 2014). Ketamine has a low molecular weight, low protein binding, and a pKa of 7.5, making it likely to cross into breast milk. However, its large volume of distribution and short half-life suggest that transfer should be relatively low with minimal consequence to the nursing infant. Single doses of ketamine should be given with caution, observing a breastfed infant closely, or women may want to wait 12 hours after the dose to resume breastfeeding.

Inflammatory Bowel Disorder Agents, Biological Therapies, and Immunosuppressants

Crohn disease and ulcerative colitis are common intestinal disorders that affect women of childbearing age. Several advances have been made in recent years to improve the lives of women living with these conditions. Some treatment and maintenance agents (e.g., the aminosalicylic acid class) act locally on the intestines and are generally considered safe during lactation. Small amounts do enter into breast milk, but few adverse effects have been reported with sulfasalazine and mesalamine; thus, they are considered safe during lactation. Women breastfeeding infants with hyperbilirubinemia or an unknown glucose-6-phosphate dehydrogenase (G6PD) deficiency status should use sulfasalazine with caution.

Oral budesonide is likely safe given its low bioavailability, large volume of distribution, and metabolism to inactive metabolites. Leflunomide has a very long half-life with many toxic adverse effects; it is contraindicated in lactation (Sammaritano 2014). Hydroxychloroquine, despite having a weak base with low protein binding and a long half-life, appears to have low transfer into breast milk. Similar to sulfasalazine, the G6PD deficiency status of the infant should be known before starting therapy.

Biologic therapies (e.g., tumor necrosis factor inhibitor therapies) are often continued during pregnancy, but very little information exists about their safety in lactation. Case reports document very low to undetectable concentrations of infliximab, adalimumab, and certolizumab pegol in breast milk (Horst 2014). The overall dose is minimal with the agents, and they are not absorbed orally, so they may be safe in breastfeeding women (Grosen 2014). Etanercept is also present in breast milk, but again, these concentrations are low, becoming unmeasurable 3 days after the dose (Sammaritano 2014). A case report found that most transfer of etanercept occurs

during pregnancy, not during breastfeeding; infant concentrations decrease quickly during the first 3 weeks of life. At 12 weeks, infant serum concentrations were undetected, suggesting that therapy was safe, especially if started after the first month of life (Murashima 2009). These monoclonal antibodies are IgG, whereas breast milk contains primarily IgA. Newborn infants may be able to absorb these antibodies because of the differences in their GI tracts; in older infants, these drugs are more likely to be destroyed or broken into their protein components.

Interleukin-1 receptor antagonists are normally present in breast milk; thus, using anakinra during lactation is likely low risk (Witzel 2014). Natalizumab, which can be detected in breast milk, accumulates during therapy. Infant effects from natalizumab are unknown, but given the severe complications that can occur with maternal therapy, breastfeeding is regarded as unsafe until more information is available (Baker 2015). Interferon beta-1a, used in relapsing-remitting multiple sclerosis, is bound to T-cell lymphocytes and other immunologic cells. Its high molecular weight combined with low maternal blood concentrations mean that transfer into breast milk should be low. Oral absorption is thought to be nominal, making this agent likely safe in breastfeeding (Hale 2012).

Cyclosporine and tacrolimus have several applications outside organ transplantation. Although relatively safe in pregnancy, they have less information available during breastfeeding. Cyclosporine is transferred into breast milk and increases in concentration over time, similar to the maternal serum. In one case report, breast milk concentrations were measured 2 hours after the maternal dose on four separate occasions. Milk concentrations were about half of those obtained from serum; infant serum concentrations were measured, but only the first sample on day 10 had a detectable concentration of cyclosporine. The mother had taken cyclosporine during her pregnancy, which may account for the positive initial infant serum sample. The calculated daily dose for the infant was less than 0.055 mg/kg (Mazzuoccolo 2014). Although milk concentrations are low when used for psoriasis, cyclosporine is an immunosuppressant and could have adverse effects in a breastfed infant.

Tacrolimus achieves low milk concentrations but is associated with the same concerns as cyclosporine. Several case reports available in the literature suggest that the infant exposure is negligible (Zheng 2013). Azathioprine does appear in breast milk in low concentrations; studies with small numbers of women have failed to find any adverse outcomes for neonates. Women with altered thio-purine metabolism (*TPMT* genotypes) could pass on higher amounts to their infants (Yarur 2013). Methotrexate given once weekly results in low breast milk concentrations. However, little is known about its safety in nursing infants. Women using methotrexate may want to pump and dump milk for 24 hours after each dose to minimize methotrexate exposure (Sammaritano 2014).

Prednisone, which occurs in low concentrations in breast milk, is considered compatible. High doses of methylprednisolone may be needed to treat flares or relapses. These doses also appear to be safe in breastfeeding women. Case reports have obtained measurable concentrations in breast milk, with the peak in milk occurring about 1 hour after an intravenous infusion was complete. Within 12 hours, the drug is no longer detectable in milk. One report calculated the relative infant dose as 1.15%–1.45% (Cooper 2015), whereas another report determined an infant would receive about 40% more cortisol than the normal daily production if breastfeeding occurred earlier than 8 hours after a dose (Strijbos 2015). However, the amount is still less than the recommended dose for neonatal treatment with methylprednisolone.

Radiologic Contrast Agents

Postpartum women may require radiologic imaging to help diagnose various medical conditions. These procedures cause much confusion about the need to pump and dump milk or allow a woman to continue breastfeeding. Recommendations from Italy may be helpful to counsel women (Cova 2014). Radiographic contrast media can be water-soluble iodine, non-water-soluble barium sulfate, or lipophilic iodine-based agents. Iodine-containing contrast agents are excreted into breast milk in low amounts; this iodine is organically bound, and only free iodine can be absorbed. This small amount is poorly absorbed from the infant's intestines, making the risk to the infant low. Barium preparations are not absorbed from the maternal GI tract and pose no risk to a breastfeeding infant.

Magnetic resonance contrast agents primarily contain gadolinium, a lanthanide group metal. These agents do not bind to proteins, are water soluble, and have a half-life of 1.5–2 hours. The limited data with gadopentetate suggest breast milk concentrations are less than 0.04% of the maternal dose. However, even though gadolinium is chelated to minimize toxicity, it can cause nephrogenic systemic fibrosis. European recommendations make these agents contraindicated in premature infants and newborns during the first month of life. Overall, the cumulative amount received by the infant is less than 1% of the 1% excreted into breast milk; this amount is also lower than the amount an infant would receive for his or her own imaging procedure. Moreover, several radiologic societies around the world do not recommend cessation of breastfeeding. Women may still opt to pump and dump milk, especially those with young infants.

Smoking

Smoking rates are now lower than in previous years, but many women continue to use tobacco during pregnancy and while breastfeeding. Women may be able to abstain during pregnancy, but a large percentage of these women relapse within 1 year after delivery. Cigarettes produce more than 4000 chemicals, many of which are known carcinogens. During

pregnancy, fetal nicotine concentrations exceed the maternal concentration. Smoking exposes newborns to compounds through breast milk and secondhand smoke. Women who smoke have lower prolactin concentrations than nonsmokers and may produce less milk. Unfortunately, their breast milk contains less antioxidant properties, which could lead to higher amounts of reactive oxygen species. In turn, this increased oxidative stress is connected with several complications of premature infants such as necrotizing enterocolitis and bronchopulmonary dysplasia (Zagierski 2012).

Smoking cessation strategies such as nicotine replacement and bupropion therapy are safer during breastfeeding, although bupropion has been causally related to seizure activity in a newborn. Because of the potential psychiatric disturbances associated with varenicline, use during breastfeeding should be discouraged. The molecular weight of this agent suggests that it will enter breast milk.

Alcohol

After refraining from alcohol during pregnancy, many women look forward to resuming consumption after delivery. However, alcohol use can impair breast milk production by lowering the prolactin response from suckling. Ethanol is highly lipid soluble and small in size, with no protein binding, and it peaks in breast milk within 30–60 minutes after intake. Concentrations in milk are similar to the maternal plasma, so breastfeeding should be avoided for at least 2 hours after imbibing. Infants exposed to alcohol may have altered sleep patterns and psychomotor development (Reece-Stremtan 2015).

Altered Milk Supply

Using a galactagogue to augment milk production can help women continue breastfeeding in the setting of lower milk production. Women who are separated from their infants and expressing milk rather than breastfeeding, with hospitalized newborns and infants or with returning to school or work, often have a decrease in milk supply. Expressing milk thoroughly and often will help maintain adequate milk supply, although suckling has more of an effect on increasing prolactin. Maternal caloric and fluid intake is also essential to maintain milk supply. Medical reasons for decreased milk supply should be eliminated such as maternal stress (illness, emotional), pregnancy, primary or secondary breast tissue insufficiency, Sheehan syndrome, retained placenta, heavy alcohol or cigarette use, and use of certain drugs (ABM 2011).

Measuring milk production increase is difficult because of the nature of the process. Indirect measurements such as weighing the infant before and after the feeding can be used. More commonly, electric pump or hand expression is used to determine the volume of milk. The ultimate measurement is infant weight gain, but this result is not often reported in the literature. Nonpharmacologic techniques such as relaxation and deep breathing should be tried before using drug therapy

or herbal supplements to increase milk supply. Moreover, applying warm compresses or taking a warm shower may help. If natural or pharmacologic therapies are warranted, they should be effective within days. If they provide no benefit to milk volume, cessation of the therapy is recommended.

Drug therapy involves increasing concentrations of prolactin by inhibiting dopamine. Metoclopramide is the best-studied agent used for this purpose. Metoclopramide is usually given three times daily for up to 2 weeks, but it has been studied for longer periods (Forinash 2012). Studies have had mixed results involving heterogeneous populations, making it difficult to determine metoclopramide's benefit for increasing milk supply. Metoclopramide does have some significant adverse reactions, so women should be evaluated for concomitant drug therapy, renal function, and medical history before recommending therapy. The infant receives only small amounts of drug through breastfeeding, so its use is generally considered safe. Women with prolactin concentrations in the normal range for lactation may or may not benefit from metoclopramide use. Domperidone has also been recommended by some providers to increase milk production. One small study showed a significant increase in milk supply in women with premature infants (ABM 2011). The agent is not available in the United States, and the FDA has issued warnings regarding its use as a galactagogue, stating that the risk of arrhythmias, cardiac arrest, and sudden death far outweighs any benefits. However, domperidone is commonly used for this purpose elsewhere.

Herbal supplements have been used for years as galactagogues in women. Although herbs can be used to help enhance breast milk production, randomized controlled trials documenting their efficacy are lacking. The most widely used herb, fenugreek (*Trigonella foenum-graecum*), has produced conflicting results, although many anecdotal reports attest to an increase in milk supply with its use. Fenugreek can have hypoglycemic effects, cause GI distress, possibly exacerbate asthma, and enhance the risk of bleeding if used with anticoagulants. It should be avoided in women with allergies to chickpeas, peanuts, soybeans, and other pea family foods and can impart a maple syrup odor to the mother and infant (Mortel 2013; Forinash 2012).

Shatavari (*Asparagus racemosus*), related to common asparagus, is commonly used in India to increase prolactin concentrations. Studies evaluating its efficacy have shown significant activity in one study and none in another. Milk thistle (*Silybum marianum*), also called silymarin, showed benefit in one small trial in Peru. Other herbs that may be combined in teas designed for breastfeeding or used alone include alfalfa, blessed thistle, goat's rue, fennel, raspberry leaf, brewer's yeast, anise, and caraway seeds, but these have limited information regarding safety and efficacy. Caution should be exercised with the use of these herbals because they may interact with drugs or cause adverse effects in the mother or infant.

Excessive breast milk production without emptying the breasts can be associated with plugged milk ducts, acute mastitis, chronic breast pain, and milk leakage. Full breasts slow milk production through a negative feedback loop involving nonneural secretion of serotonin, previously called the feedback inhibitor of lactation (Eglash 2014). Engorgement is common in the first days after delivery when milk comes in. The mother's body adjusts milk production to the infant's needs during this time. However, occasionally, women continue to struggle with overproducing breast milk. One technique to help reduce milk supply is to breastfeed only on one side or the other for blocks of time throughout the day, allowing no stimulation of one breast for several hours. Herbal agents can be used to reduce supply either for hypergalactia or women wishing to wean their infant. Sage, as tea or an extract, is the most commonly used herb. Topical jasmine flowers and peppermint oil as well as parsley or chasteberry taken orally may also reduce prolactin concentrations and hence milk production (Eglash 2014). Women taking these agents are potential candidates for supplying milk to national banks to help other women struggling with appropriate milk volumes.

Contraindicated Substances

Medications

Only a few drugs are truly contraindicated during breastfeeding. They fall into two categories, depending on whether the hazard is posed to breast milk production (Table 1-5) or to the nursing infant (Table 1-6). The mechanism of action of drugs should be evaluated to determine whether they are detrimental to healthy development in infants. Drugs that are not recommended in children are not necessarily contraindicated during breastfeeding. In most cases, the infant dose through breastfeeding is considerably lower or minimal. If women only need to withhold breastfeeding for a short time, pumping and saving extra milk will allow her infant to continue receiving breast milk. Banked milk from donors is an alternative for women required to discontinue breastfeeding or pump and discard milk for an extended duration.

Chemotherapy

Some women will be given a diagnosis of cancer either during their pregnancy or early postpartum. Cytotoxic agents are usually contraindicated during lactation because of the possibility of significant adverse events in the infant. Once the

Table 1-5. Agents Contraindicated During Lactation, Hazardous to Milk Production

Drug Class	Agents	Comments
Antiestrogens	Danazol GNRH agonists (e.g., leuprolide)	Ovarian suppression through pituitary-ovarian axis, inhibiting hormone production
	Anastrozole	Estrogen suppression through aromatase inhibition
Antiviral	Amantadine	Can suppress lactation by increasing dopamine
Dopamine agonists	Ropinirole Selegiline Rotigotine Dopamine	Lower serum prolactin concentrations, preventing lactation
Decongestants	Pseudoephedrine Propylhexedrine Phenylephrine	Oral intake can suppress milk production with single doses; topical application has a significantly lower risk unless overused
Ergots	Ergotamine Dihydroergotamine	Inhibit prolactin, preventing lactation
Ergot derivatives	Bromocriptine Cabergoline	Likely safe if treating hyperprolactinemia; otherwise contraindicated
Ethanol	Alcohol	Chronic ingestion will suppress milk production
Nicotine	Cigarettes	Decreased prolactin concentrations, reduced antioxidant properties of breast milk
Selective estrogen receptor antagonists	Tamoxifen Raloxifene	Inhibit estrogen effects in breast tissue

GNRH = gonadotropin-releasing hormone.

Table 1-6. Agents Contraindicated During Lactation, Hazardous to the Infant

Drug Class	Agents	Comments
Antiarrhythmic	Amiodarone	Several potential toxicities (e.g., pulmonary)
Anticholinergic	Dicyclomine	Contraindicated in infants < 6 months, apnea
Anti-infectives	Dapsone	Hemolytic anemia
	Rifabutin	Rash, suppression of white blood cells
	Flucytosine	Bone marrow suppression
	Foscarnet	Renal toxicity, seizures
CNS stimulants	Dextroamphetamine Amphetamines Methylphenidate	Not recommended; monitor infant for adverse events and appropriate weight gain
Cytotoxic agents	Antimetabolites, alkylating agents, etc Hydroxyurea	High potential of toxicity for the infant, including immunosuppression
Illicit substances	Cocaine, heroin, marijuana, etc.	High potential for significant toxicities in the infant
Immunosuppressants	Cyclosporine Tacrolimus	Not recommended; if used, monitor infant (for serum concentrations and adverse events)
	Everolimus Sirolimus	Not recommended until more information is available on these agents
	Mycophenolate	Not recommended, increase in infection rate
Leprostatic	Thalidomide	Several potential toxicities
Mood stabilizer	Lithium	High potential of toxicity in the infant, near therapeutic serum levels
Monoamine oxidase inhibitors	Isocarboxazid Phenelzine Selegiline Tranlycypromine	No information is available regarding these agents in breastfeeding. Other antidepressants are better options
Radioactive substances	I^{131} , etc.	Transfer of radioactive agents to the infant, destruction of thyroid tissue
Skeletal muscle relaxant	Tizanidine	Sedation, hypotension
Tetracyclines	Tetracycline Doxycycline Minocycline	Low penetration into milk, but therapy > 3 wk is not recommended due to potential of staining of teeth or changes in bone growth
Tricyclic agent	Doxepin	Significant sedation, respiratory depression
Vitamin A derivatives	Etretinate Isotretinoin	Excessive vitamin A intake and related toxicities, including liver damage and death

contraindicated agent is gone from the maternal system and milk, the woman can resume breastfeeding. Because many regimens are dosed at regular intervals for months, only women quite motivated to breastfeed will be able to maintain their milk supply.

Cisplatin, a common agent in many treatment regimens, does transfer into breast milk. Reports conflict regarding breast milk concentrations; some associate cisplatin with minimal concentrations, others report infant concentrations equivalent to 9% of the maternal dose (Pistilli 2013). After a

Patient Care Scenario

M.M. is a 30-year-old woman 2 months postpartum who develops a deep venous thrombosis. She is initiated on enoxaparin and warfarin as an outpatient. Six days into her overlapping therapy, her INR is therapeutic, and enoxaparin is discontinued. Her INR 3 days later is 5. For the next several weeks, her INR alternates between subtherapeutic and supratherapeutic. M.M. is becoming frustrated with the frequency of blood tests and having difficulty remembering what warfarin dose she should be taking. It has

ANSWER

This case poses a significant challenge because little information exists regarding the transfer of these agents into breast milk, and the potential for adverse reactions in a breastfed infant is high. Factors that should be closely evaluated include molecular weight, protein binding, volume of distribution, pKa (if known), lipid solubility, and the bioavailability of the agent. All the DOACs have a molecular weight greater than 200 Da, with edoxaban weighing more than 500 Da. Edoxaban may have lower penetration into milk than other DOACs. In reviewing all the factors, apixaban is a relatively poor choice. Because of its lower molecular weight, low volume of distribution, moderate absorption and protein binding, and high pKa leading toward accumulation in milk, other drugs are likely better. Edoxaban has a higher molecular weight, larger volume of distribution, and moderate absorption and protein binding, making it a reasonable option, but less is currently known about this agent overall. Rivaroxaban and dabigatran have more favorable properties preventing

changed so often, and she is overwhelmed with a newborn and other daily responsibilities. She refuses to restart enoxaparin and is now adamant about starting one of the direct oral anticoagulants (DOACs) she has heard about on television. She is extensively counseled on the current lack of information about lactation. She has accepted the risks and wants to start therapy. Which DOAC would be best to recommend?

transfer into breast milk, making them more reasonable choices. Dabigatran has a slightly higher molecular weight, a larger volume of distribution, and low absorption, but protein binding is low, allowing most circulating drug to enter breast milk. Its twice-daily dosing allows for higher concentrations throughout the day, with the possibility of more drug transfer into milk. The infant dose will likely be minimal because of dabigatran's poor bioavailability. Rivaroxaban has a small volume of distribution and is well absorbed, but it has the shortest half-life and is highly protein bound, leaving little available drug to penetrate into milk. It is known to cross into milk in small quantities. It is also dosed once daily after a 3-week loading period, which offers lower concentrations in the maternal circulation during certain times of the day. If the evening meal is delayed, the peak in maternal serum and hence the peak in breast milk will likely occur after the last feeding session of the day.

1. Breitzka RL, Sandritter TL, Hatzopoulos FK. Principles of drug transfer into breast milk and drug disposition in the nursing infant. *J Hum Lact* 1997;13:155-8.
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single dose of cisplatin, breast milk concentrations remain detectable for at least 2.5 days (Hays 2013). Although the bioavailability of cisplatin is low, the GI adverse effects of oral cisplatin consumption could be of concern in young infants. Breastfeeding would likely be safe to resume 3 days after a weekly dose. Carboplatin is also a common agent in many therapy regimens, as is paclitaxel. Both agents transfer into breast milk, with high concentrations of paclitaxel in breast milk in one case report. Carboplatin concentrations were lower but still detectable 13 days after a dose (Griffin 2012). It would be reasonable to withhold breastfeeding for about 3 weeks after each course of chemotherapy with these agents.

Mitoxantrone appears to maintain concentrations in milk for weeks after therapy. It is most prudent to discontinue breastfeeding when using this agent. However, fluorouracil is rapidly converted into inactive metabolites and has a very short half-life, making transfer into milk unlikely (Pistilli 2013). However, this does not indicate that breastfeeding would be safe in women receiving this agent. Fortunately,

chemotherapy does not affect cells in the breast, allowing for normal milk production and volume during and after chemotherapy.

Ipilimumab, a monoclonal antibody used for metastatic melanoma, reaches high concentrations in milk 5 days after the first infusion. If therapy continues, milk concentrations continue to increase after subsequent infusions. Although milk concentrations are low, a breastfed infant will consume more and more ipilimumab each day over a 12-week treatment (Ross 2014). Methotrexate peaks in milk at 4–10 hours after an intravenous dose. Because of the potential of infant tissue accumulation with high-dose methotrexate, its use during breastfeeding is contraindicated (Sammaritano 2014).

Illicit Substances

Women who abuse alcohol or illicit substances may elect to breastfeed their newborns. Unfortunately, most of these agents are found in breast milk after maternal ingestion. Of all opioid-dependent women, those involved in opioid substitution programs are the best candidates to safely breastfeed

their infants. Methadone, regardless of dose, has low concentrations in breast milk; however, the dose received by the infant is unlikely to help completely manage neonatal abstinence syndrome (NAS), which may occur when exposed to methadone as a fetus. Newborns with NAS may have difficulties breastfeeding, which may discourage women from continuing with this nutritional method. Buprenorphine, a highly lipid-soluble drug with a large volume of distribution, high protein binding, and a fairly low bioavailability, has a long half-life when taken sublingually. The combination of these properties contributes to low concentrations in breast milk that may not prevent NAS in infants (Reece-Stremtan 2015; D'Apolito 2013).

Marijuana is also lipid soluble, with the active compound D⁹-tetrahydrocannabinol concentrating in milk, producing an M/P of up to 8:1. Because marijuana distributes into the brain and fat tissues, it can remain in the infant for weeks to months after maternal use. Adverse effects of a breastfeeding infant include sedation, muscle relaxation and poor tone, reduced ability to suckle, and resultant lower growth. Brain development can be affected by exposure, leading to long-lasting effects on cognitive function and emotional conduct. In addition to ingesting marijuana metabolites in breast milk, an increased risk of sudden infant death syndrome is associated with secondhand marijuana smoke (Rapano 2015; D'Apolito 2013).

Less is known about maternal cocaine, heroin, and phenacyclidine hydrochloride use during breastfeeding. Cocaine presence in breast milk can vary, but its high lipid solubility, molecular weight, and pKa of 8.6 contribute to easier passage into breast milk. Infants consuming cocaine can have agitation, irritability, seizures, hypertension, and tachycardia, which requires emergency care in some cases (Cressman 2012). Heroin is metabolized to morphine and easily transfers into breast milk because of its lipid solubility and low protein binding. Although morphine is not contraindicated in breastfeeding, doses of morphine from heroin metabolism are considerably larger, placing the infant at risk of sedation and respiratory depression (D'Apolito 2013). Phencyclidine hydrochloride occurs in high concentrations in human milk (Reece-Stremtan 2015). Use of any of these substances, as well as 3,4-methylenedioxy-methamphetamine (ecstasy), is contraindicated during breastfeeding.

Radioactive Agents

Radioactive agents used either diagnostically or therapeutically are contraindicated in breastfeeding. Some isotopes have half-lives as short as 6 hours, whereas others are as long as 2 months. Radioactive iodine (I¹³¹) has a long half-life, so women who require treatment should be ready to discontinue breastfeeding at the time of therapy. This iodine concentrates in breast milk because of active transport, exposing the infant to excessive iodine and radioactivity. After certain other isotopes, such as ^{99m}Tc with a half-life of about 6 hours, it may be possible to pump and discard milk for 5 to 10 half-lives.

Although, most providers may not know or research the half-life of the particular radiopharmaceutical used and the safe time to resume breastfeeding, some women may be told to discontinue breastfeeding when this is not actually required in all cases.

REFERENCES FOR LACTATION INFORMATION

Primary literature is the most up-to-date information available but is subject to publication bias. Newer drugs often have no information available, or only reports that document problems may exist. Milk sampling may be performed at inappropriate times that would not determine the actual peak concentrations. Breast milk concentrations always peak after maternal serum peak concentrations and will remain in milk until the drug clears the maternal circulation. Case reports offer limited insight into variable doses consumed by women as well as different infant ages. Because of this, available case reports may not correspond well to a particular woman who needs advice. However, these reports are crucial to establishing a baseline knowledge because drug companies are not required to furnish this information. Finding a laboratory with the ability to conduct breast milk analyses can be difficult. Information involving rat lactation is unreliable. Most drugs enter murine milk, including many agents known not to enter human milk.

Secondary literature will provide further information because of the collective nature of these documents, and eventually, package inserts will be required to present data on lactation for medications approved after June 30, 2001. The lactation section in package inserts will discuss information such as breast milk concentrations and potential infant effects because of drug exposure. The three sections – risk summary, clinical considerations, and data – will provide information from animal and human data and will address specific issues concerning a woman who is breastfeeding. Drugs approved before mid-2001 and OTC agents are excluded from this requirement. Hence, information in these documents inadequately addresses lactation safety.

Tertiary literature exists in online databases, often within drug monographs, or as references specifically for lactation. The NIH [LactMed database](#) and the WHO document titled "[Breastfeeding and Maternal Medication](#)" provide information, and the WHO database also contains information on drugs not available in North America. Printed references include Medications and Mothers' Milk: A Manual of Lactation Pharmacology (Hale 2014) and Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk (Briggs 2014). Hale has created lactation safety categories that rate medications from safe to contraindicated, depending on the risk-benefit ratio to the mother and infant. Briggs's recommendations include the amount of human data and compatibility with lactation.

COUNSELING BREASTFEEDING WOMEN AND THE PHARMACIST'S ROLE

Assessing a woman's knowledge regarding drugs in breastfeeding is a critical first step. Providers may not evaluate a drug's safety record in lactation but simply decide the woman should not initiate or discontinue breastfeeding when starting the agent. Providers may consult a reference that conflicts with other resources, causing patient confusion. Few drugs are contraindicated in lactation, so it is wise to gather information from several sources to present to a patient.

Pharmacists are in a good position to help recommend drug therapy for breastfeeding women. In hospitalized women, order review can allow for early intervention to recognize and recommend alternatives for inappropriate therapy. Consult services may not be completely aware of the lactating status of a woman and recommend therapy that may not be best for a breastfeeding infant. Identifying these women can be a challenge because many computer systems and generic warnings can create alert fatigue among providers and pharmacists alike.

Often, women are unaware of OTC agents that can affect their milk supply (e.g., pseudoephedrine). Directing women toward more appropriate therapy is an important part of drug counseling. Although it may be awkward to ask a woman if she is breastfeeding, it is important to prevent potentially hazardous drugs from being prescribed or ingested by the patient.

Minimizing Infant Exposure

Necessity of Therapy

Providers should evaluate the necessity of treatment against a potentially problematic therapy in a breastfeeding woman. Is the untreated condition or disease more harmful than drug therapy, or will a delay in therapy reduce the likelihood of a successful treatment? All non-essential drugs should be avoided. Conditions such as permanent treatment of hyperthyroidism, onychomycosis, or mild autoimmune diseases can likely be treated after a woman weans her infant. Other therapies such as cancer treatments often cannot wait, and the woman will need to make an informed decision about breastfeeding. If interested, some women may want to maintain their milk supply during contraindicated therapy and can breastfeed when the drug clears from milk.

Drug Selection

Pharmacokinetic drug properties are important in determining which agent is best for therapy. Topical routes and intranasal, inhalational, vaginal, and dermal applications have the lowest degree of absorption, providing the least amount of drug to a breastfed infant. Any topical agent applied to the breast should be removed and the area cleaned with soap before breastfeeding. Intravenous drugs are usually not absorbed orally, making them preferable for breastfed infants. However, convenience for the mother is also important. If

possible, select an agent with a large molecular weight, poor absorption, high protein binding, a large volume of distribution and low serum concentrations, a short half-life, and low lipid solubility. Most oral drugs do not fit many of these characteristics because they need to cross the GI mucosa; in fact, few drugs can be categorized as having all of these properties. Molecular weight and protein binding likely have the most influence on drug transfer into milk. When comparing agents with similar molecular weights, review the amount of drug absorbed and the serum concentrations.

Peak Milk Concentrations

Peak milk concentration timing is often unknown, making the determination of better times to breastfeed during this time difficult. Low-molecular-weight drugs with high lipid solubility (e.g., fentanyl) will peak in about 45 minutes, but the similarly sized cephalexin takes 4 hours to peak in milk. With newborns, feeding should be on demand, so trying to avoid feeding at peak milk concentrations is futile. However, some agents with short half-lives that continue to exert pharmacologic effects for 24 hours are best taken before the infant's longest sleep to allow the drug to enter and exit breast milk during this time. Otherwise, drugs can be taken immediately before or after a feeding session. If taken before, the drug can be absorbed while breastfeeding. Extended-release dosage forms provide better concentrations for the mother but may not be best during breastfeeding because of sustained systemic concentrations.

Practice Points

In determining the most appropriate pharmacotherapy for a breastfeeding woman, practitioners should consider the following:

- Drug-specific characteristics such as molecular weight, lipid solubility, protein binding, volume of distribution, and half-life should be evaluated.
- Drugs with high molecular weight, low lipid solubility, high protein binding, large volume of distribution, and short half-lives are preferred for the lowest transfer into breast milk. Selecting medications with several of these characteristics should offer a lower risk to the breastfed infant.
- Pharmacokinetics of both the mother and the infant should be considered. Drugs that are poorly absorbed from the GI tract are preferred because of the low likelihood of absorption by infants older than 1 month.
- The risk-benefit ratio should be evaluated carefully. Medications that may cause more adverse effects in the mother and infant but that are required for the treatment of serious illnesses may be appropriate, but agents with this risk should not be used for minor reasons.
- Drugs given to premature infants and neonates are safe to use during lactation. Agents that have a high risk of adverse effects if given to young children or that are hazardous to normal childhood development should be avoided, especially if transfer into milk occurs in significant amounts.

CONCLUSION

Although few drugs are truly contraindicated in breastfeeding, medications enter breast milk and produce various concentrations, some leading to higher exposure in a nursing infant. Women often need treatment of both acute and chronic illnesses while breastfeeding. Having knowledge of important drug factors to limit drug transfer and knowing where and how to find this information are key to providing the best care for women and their infants. Women can be subject to many reasons to discontinue breastfeeding. Those who are less interested in breastfeeding after delivery are more likely to discontinue for minor reasons. Pharmacists are in a unique position to help select medications that are safer in lactation and prevent inadvertent recommendations to discontinue breastfeeding by a less well-informed health care professional.

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Self-Assessment Questions

1. A woman at 2 months postpartum has periodic migraine headaches. She used caffeine/ergotamine before pregnancy and has tried sumatriptan in the past; it worked well, but she felt “weird” after the dose and declines to take this triptan again. Which one of the following drugs would be best to recommend next for this patient?
 - A. Naratriptan
 - B. Frovatriptan
 - C. Eletriptan
 - D. Zolmitriptan
2. At 5 months postpartum, an overweight woman has had enough migraines to warrant prophylaxis. Which one of the following is best to recommend for this patient?
 - A. Propranolol
 - B. Topiramate
 - C. Amitriptyline
 - D. Atenolol

Questions 3–5 pertain to the following case.

W.A. is a 24-year-old Saudi woman (weight 58 kg) who is breast-feeding her 2-month-old infant. Her infant weighs 4 kg and was hospitalized 2 weeks ago with a respiratory infection. W.A. was carrying her infant and fell, using her hand to break her fall. She has been taking acetaminophen for the pain in her wrist.

3. W.A. takes acetaminophen 650 mg every 6 hours. The peak breast milk concentration is 14 mcg/mL when her serum concentration is 7 mcg/mL. A typical acetaminophen dose for her infant is 40 mg. Which one of the following statements best describes the dose W.A.’s infant is receiving?
 - A. The infant’s dose per day is more than a single-time pediatric dose.
 - B. The infant’s dose is no more than 5% of the maternal dose adjusted for weight.
 - C. The infant’s dose is about half of that received in utero.
 - D. The infant’s dose is 0.04% of the maternal dose adjusted for weight.
4. W.A.’s wrist pain has not improved, despite scheduled acetaminophen, and she now takes ibuprofen 600 mg every 6 hours. She presents to her primary care provider for something stronger. Which one of the following agents would be best to recommend for W.A.?
 - A. Give oxycodone 5 mg every 6 hours as needed.
 - B. Give choline magnesium trisalicylate 1000 mg twice daily.
 - C. Give tramadol 50 mg every 6 hours as needed.
 - D. Change to naproxen 500 mg twice daily.
5. W.A. followed the recommendation, but 2 days later her pain became acutely worse. A radiograph of her wrist reveals a displaced Colles fracture. She is scheduled with orthopedics for fixation. Which one of the following options is best to recommend if W.A. wants to breast-feed immediately after the procedure?
 - A. Infiltrative 2% lidocaine 10 mL (200 mg)
 - B. Intramuscular ketamine 500 mg
 - C. Intravenous midazolam 4 mg
 - D. Intravenous etomidate 0.6 mg
6. Which one of the following agents would have the lowest penetration into breast milk?
 - A. Drug A weighs 807 Da and is 50% protein bound, with low lipid solubility and a pKa of 8.2.
 - B. Drug B weighs 12,000 Da and is 30% protein bound, with high lipid solubility and a pKa of 6.8.
 - C. Drug C weighs 211 Da and is 96% protein bound, with moderate lipid solubility and a pKa of 7.
 - D. Drug D weighs 443 Da and is 80% protein bound, with moderate lipid solubility and a pKa of 7.6.
7. A woman with an exclusively breastfed 3-month-old infant was treated for pyelonephritis during her pregnancy and given suppressive therapy with cephalexin until delivery. She is now back to work at a day care center, but she was given a diagnosis of mastitis soon after returning to work. Which one of the following antibiotics would best treat this patient’s mastitis?
 - A. Cephalexin 500 mg orally every 6 hours
 - B. Clindamycin 300 mg orally every 6 hours
 - C. Vancomycin 1 g intravenously every 12 hours
 - D. Dicloxacillin 500 mg orally every 6 hours
8. A mother breastfeeding her infant daughter needs to start an antihypertensive agent. She wants to expose her infant to the least amount of drug. Which one of the following would be best to recommend given the following drug characteristics?
 - A. Nifedipine 30 mg extended release daily, 346.3 Da, 45%–75% absorption, half-life 7 hours, 92%–98% protein bound, pKa 5.3.
 - B. Nadolol 40 mg daily, 309.4 Da, 30%–40% absorption, half-life 14–24 hours, 30% protein bound, pKa 9.67.
 - C. Hydrochlorothiazide 25 mg daily, 297.7 Da, 70% absorption, half-life 9.5 hours, 40% protein bound, pKa 7.9.
 - D. Lisinopril 10 mg daily, 405.5 Da, 30% absorption, half-life 12 hours, no protein binding, pKa 2.5.

9. Which one of the following infants would most likely have an adverse reaction to the agent their mother is prescribed? Each mother weighs 68 kg.
- Infant A is a 3-month-old boy (weight 7.5 kg). His mother takes oneprolol 60 mg daily, resulting in a milk concentration of 189 ng/mL.
 - Infant B is a 1-month-old boy (weight 5 kg). His mother takes namoxetine 40 mg daily, resulting in a milk concentration of 75 ng/mL.
 - Infant C is a 4-month-old girl (weight 8 kg). Her mother takes bidezpine 3 mg three times daily, resulting in a milk concentration of 280 ng/mL.
 - Infant D is a 2-month-old girl (weight 4.3 kg). Her mother takes trilanzapine 20 mg daily, resulting in a milk concentration of 80 ng/mL.
10. A breastfeeding woman develops symptoms of a UTI in the day after delivering her preterm infant. Standard testing of her newborn has not yet been performed to rule out genetic and metabolic disorders. Which one of the following antibiotics is best to recommend for this mother?
- Cephalexin
 - Sulfamethoxazole/trimethoprim
 - Ciprofloxacin
 - Nitrofurantoin
11. A woman exclusively breastfeeding her 3-month-old son has developed a cold. Which one of the following agents is best for this patient?
- Pseudoephedrine 60 mg orally four times daily as needed
 - Fluticasone intranasally 100 mcg per nostril daily
 - Oxymetazoline intranasally 2 sprays twice daily for 3 days
 - Diphenhydramine 25 mg orally every 6 hours as needed
12. A woman with rheumatoid arthritis held her NSAID during her pregnancy but would now like to start a disease-modifying therapy. She is 2 weeks postpartum and wants to breastfeed for at least 6 months. Which one of the following therapies would be best to recommend for this patient?
- Adalimumab 40 mg every other week
 - Etanercept 50 mg once weekly
 - Hydroxychloroquine 400 mg daily
 - Methotrexate 10 mg weekly
13. A woman with twins is struggling to produce enough milk for her infants. She consumes a large amount of non-caffeinated fluids daily and rests as much as she can while caring for two newborns. She would like a recommendation to help increase her milk supply, but alerts you to her significant peanut butter allergy. Which one of the following is best to recommend for this patient?
- Oral domperidone
 - "Nursing" tea
 - Oral fenugreek
 - Oral shatavari
14. A woman is given a diagnosis of placental site tumor, and EMA-CO (etoposide, methotrexate, and actinomycin-D, followed a week later by cyclophosphamide and vincristine) is recommended to best treat her trophoblastic disease. Every other week, she receives etoposide (4–11 hours), methotrexate (3–10 hours), and actinomycin (36 hours) or cyclophosphamide (3–12 hours) and vincristine (19–155 hours). She is dedicated to breastfeeding and wants to know when she can start using her milk again. Assuming her system will be clear of drug at 5 half-lives (listed above in parentheses) and allowing an additional 24 hours for breast milk elimination, which one of the following is best to recommend regarding resumption of breastfeeding?
- She should be discouraged from breastfeeding.
 - Use milk collected 34 days after her last vincristine dose.
 - Wait 8 weeks after completing chemotherapy.
 - Breastfeeding is appropriate with infant monitoring.
15. A woman who is breastfeeding her 9-month-old son needs a second-generation antipsychotic. Which one of the following would be best to recommend for this patient?
- Paliperidone
 - Quetiapine
 - Lurasidone
 - Aripiprazole
16. A woman with bipolar depression discontinues lithium before her pregnancy and decides to breastfeed postpartum. Because lithium is not recommended during lactation, which one of the following is best to recommend for this patient?
- Clonazepam 1 mg twice daily for 2 months
 - Risperidone long-acting injection 25 mg every 2 weeks
 - Carbamazepine 200 mg twice daily
 - Lamotrigine 25 mg daily
17. A woman at 4 months postpartum develops a cardiac arrhythmia requiring drug therapy. Assuming all agents are appropriate, which one of the following agents would provide the lowest absorbed dose for her 7-kg infant?
- Mexiletine, milk/plasma ratio (M/P) 1.45, maternal concentration 2 mcg/mL, bioavailability (F) 90%
 - Sotalol, M/P 5.4, maternal concentration 0.5 mg/mL, F 90%

- C. Flecainide, M/P 2.6, maternal concentration 1 mcg/mL, F 95%
 - D. Disopyramide, M/P 1.06, maternal concentration 3 mcg/mL, F 70%
18. A woman develops an acute sinus infection at 10 weeks postpartum. She wants to expose her infant to the lowest amount of antibiotic possible while continuing to exclusively breastfeed. She is prescribed 500 mg amoxicillin three times daily. If the peak in breast milk occurs around 5 hours after her dose, which one of the following schedules is best for this patient?
- A. Take the dose at 6 a.m., noon, and 6 p.m. with breastfeeds at 7 a.m., 10 a.m., 1 p.m., 4 p.m., and 8 p.m.
 - B. Take the dose at 8 a.m., 4 p.m., and 8 p.m. with breastfeeds around 6 a.m., noon, 5 p.m., and 9 p.m.
 - C. Take the dose at 7 a.m., 2 p.m., and 9 p.m. with breastfeeds around 6 a.m., 10 a.m., 2 p.m., 5 p.m., 8 p.m., and 11 p.m.
 - D. Take the dose at 6 a.m., 2 p.m., and 10 p.m. with breastfeeds around 5 a.m., 8 a.m., 11 a.m., 3 p.m., 7 p.m., and 11 p.m.
19. A woman who is 1 month postpartum develops a *Candida* infection of her breast. She is given fluconazole 200 mg daily. She weighs 52 kg, and her infant weighs 3.6 kg. The peak fluconazole breast milk concentration is 2.93 mcg/mL. Which one of the following best reflects the relative infant dose her infant is receiving?
- A. 0.79%
 - B. 8.6%
 - C. 11%
 - D. 41%
20. A woman with insomnia has a 5-month-old infant. Which one of the following is best to recommend for this patient's insomnia?
- A. Eszopiclone 3 mg, half-life 6 hours, 100% bioavailable, 52%–59% protein bound
 - B. Ramelteon 8 mg, half-life 1–2.6 hours, 1.8% bioavailable, 82% protein bound
 - C. Zaleplon 5 mg, half-life 1 hour, 100% bioavailability, 45–75% protein bound
 - D. Zolpidem 5 mg, half-life 2.5 hours, 70% bioavailable, 93% protein bound

Learner Chapter Evaluation: Drug Principles in Lactation

As you take the posttest for this chapter, also evaluate the material's quality and usefulness, as well as the achievement of learning objectives. Rate each item using this 5-point scale:

- Strongly agree
- Agree
- Neutral
- Disagree
- Strongly disagree

1. The content of the chapter met my educational needs.
2. The content of the chapter satisfied my expectations.
3. The author presented the chapter content effectively.
4. The content of the chapter was relevant to my practice and presented at the appropriate depth and scope.
5. The content of the chapter was objective and balanced.
6. The content of the chapter is free of bias, promotion, or advertisement of commercial products.
7. The content of the chapter was useful to me.
8. The teaching and learning methods used in the chapter were effective.
9. The active learning methods used in the chapter were effective.
10. The learning assessment activities used in the chapter were effective.
11. The chapter was effective overall.

Use the 5-point scale to indicate whether this chapter prepared you to accomplish the following learning objectives:

12. Evaluate relative infant doses to determine preferable agents in breastfeeding infants.
13. Classify potentially hazardous agents as relatively or completely contraindicated in breastfeeding.
14. Estimate the lactation safety of a new drug with no human data.
15. Devise a safe medication plan for treating breastfeeding women with an acute disease state.
16. Develop a medication regimen for women with a chronic medical condition.
17. Synthesize strategies for breastfeeding women to minimize the quantity of drug their infant consumes.
18. Please provide any specific comments relating to any perceptions of bias, promotion, or advertisement of commercial products.
19. Please expand on any of your above responses, and/or provide any additional comments regarding this chapter:

