Medications & Mothers’ Milk 2017

Thomas W. Hale, PhD, & Hilary E. Rowe, PharmD
Medications & Mothers’ Milk

A Manual of Lactational Pharmacology
This book is a quick reference for health care providers practicing in primary care settings. The information has been extrapolated from a variety of professional sources and is presented in condensed and summary form. It is not intended to replace or substitute for complete and current manufacturer prescribing information, current research, or knowledge and experience of the user. For complete prescribing information, including toxicities, drug interactions, contraindications, and precautions, the reader is directed to the manufacturer’s package insert and the published literature. The inclusion of a particular brand name neither implies nor suggests that the author or publisher advises or recommends the use of that particular product or considers it superior to similar products available by other brand names. Neither the author nor the publisher makes any warranty, expressed or implied, with respect to the information, including any errors or omissions, herein.

Special discounts on bulk quantities of our books are available to corporations, professional associations, pharmaceutical companies, health care organizations, and other qualifying groups. If you are interested in a custom book, including chapters from more than one of our titles, we can provide that service as well. For details, please contact:

Special Sales Department, Springer Publishing Company, LLC
11 West 42nd Street, 15th Floor, New York, NY 10036-8002
Phone: 877-687-7476 or 212-431-4370;

Printed in the United States of America by Bang Printing
NEW CHANGES IN THIS EDITION:
The 2017 edition has many significant updates that we hope will make this book even easier for clinicians. We have spent a lot of time and effort updating old monographs and have added many new medications to this edition. Each year there are so many new medications being approved for sale around the world that it is becoming increasingly difficult to find room for all of this information in our book.

Key changes in 2017 include:

We have added four new tables to compare and contrast the safety of common medications used to treat psychiatric conditions (e.g. depression, anxiety) and pain.

We have significantly revised the radioisotope table; this version will be more user friendly and contains new data and updated recommendations.

We have added many new monographs to cover different infectious diseases.

We have removed some of the combination drug product monographs that have individual monographs for each medication to allow room for new drugs.

We have removed the drug interactions section from each monograph to allow room for new drugs.

This will also be Dr. Rowe’s second edition as co-author of Medications and Mothers’ Milk. Dr. Hilary Rowe is a Clinical Pharmacy Specialist in Maternal Fetal Medicine at Surrey Memorial Hospital in Canada. She obtained her Bachelor of Science and Doctor of Pharmacy Degrees at the University of British Columbia in Vancouver BC, Canada, and acquired her hospital residency with the Vancouver Island Health Authority in Victoria BC, Canada. Dr. Rowe started working on Medications & Mothers’ Milk in 2012; she is excited to be part of this book and is passionate about providing evidence-based information to women regarding the suitability of medications in lactation.

Lastly, we would like to thank all the medical and pharmacy students who have worked diligently to help update the monographs and would like to especially thank Dr. James Abbey for his help with this edition.

Tom & Hilary
Preface

INTRODUCTION
Everyone now agrees that human milk is best for human infants. The benefits to growth and development are obvious and confirmed by many studies. However, the use of medications in breastfeeding mothers is often controversial. This book is dedicated to reducing some of these misconceptions. The truth is most drugs don’t enter milk in levels that are hazardous to a breastfed infant. The problem is which drugs are safe and which are hazardous?

Because so few clinicians understand lactational pharmacology, the number of women who discontinue breastfeeding in order to take a medication is still far too high. Fortunately, many mothers are now becoming aware of the enormous benefits of breastfeeding and simply refuse to follow some of the advice given by their healthcare professionals. They seek out the information on their own and invariably find this book.

Because so many women ingest medications during the early neonatal period, it is not surprising that one of the most common questions encountered in pediatrics concerns the use of various drugs during lactation. Unfortunately, most healthcare professionals simply review the package insert or advise the mother not to breastfeed without having done a thorough study of the literature to find the true answer. Discontinuing breastfeeding is often the wrong decision, and most mothers could easily continue to breastfeed and take the medication without risk to the infant.

In the last 25 years we have collected a lot of data on many current medications and their use in breastfeeding. This book contains most of this knowledge.

It is generally accepted that all medications transfer into human milk to some degree, although it is almost always quite low. Only rarely does the amount transferred into milk produce clinically relevant doses in the infant. Ultimately, it is the clinician’s responsibility to review the research we have on the drugs in this book and make a clear decision as to whether the mother should continue to breastfeed.

Drugs may transfer into human milk if they:

- Attain high concentrations in maternal plasma
- Are low in molecular weight (< 800)
- Are low in protein binding
- Pass into the brain easily
However, once medications transfer into human milk, other kinetic factors are involved. One of the most important is the oral bioavailability of the medication to the infant. Numerous medications are either destroyed in the infant’s gut, fail to be absorbed through the gut wall, or are rapidly picked up by the liver. Once in the liver, they are either metabolized or stored, but often never reach the mother’s plasma.

Drugs normally enter milk by passive diffusion, driven by equilibrium forces between the maternal plasma compartment and the maternal milk compartment. They pass from the maternal plasma through capillaries into the lactocytes lining the alveolus. Medications must generally pass through both bilayer lipid membranes of the alveolar cell to penetrate milk; although early on, they may pass between the alveolar cells (first 72 hours postpartum). During the first three days of life, large gaps between the alveolar cells exist. These gaps permit enhanced access into the milk for most drugs, many immunoglobulins, maternal living cells (lymphocytes, leukocytes, macrophages), and other maternal proteins. By the end of the first week, the alveolar cells swell under the influence of prolactin, subsequently closing the intracellular gaps and reducing the transcellular entry of most maternal drugs, proteins, and other substances into the milk compartment. It is generally agreed that medications penetrate into milk more during the colostrum period than in mature milk. However, the absolute dose transferred during the colostrum period is still low as the total volume of milk is generally less than 30-100 mL/day for the first few days postpartum.

In most instances, the most important determinant of drug penetration into milk is the mother’s plasma level. Almost without exception, as the level of the medication in the mother’s plasma rises, the concentration in milk increases as well. Drugs enter and exit milk as a function of the mother’s plasma level. As soon
as the maternal plasma level of a medication begins to fall, equilibrium forces drive the medication out of the milk compartment back into the maternal plasma for elimination. In some instances, drugs are trapped in milk (ion trapping) due to the lower pH of human milk (7.2). With drugs with a high pKa, the ionic state of the drug changes and stops its exit back into the maternal circulation. This is important in weakly basic drugs, such as the barbiturates (drugs with high pKa). There are a few known cellular pumping systems that actively pump drugs into milk. The most important is iodine. The iodine pump is the same as found in everyone's thyroid gland. Its purpose is to make sure the infant receives iodine to maintain thyroxine production.

The iodides, such as $^{131}$I or any “ionic” form of iodine, concentrate in milk due to this pump. Thus iodides, particularly radioactive ones, should be avoided as their milk concentrations are exceedingly high. Two other physicochemical factors are important in evaluating drugs in breastfeeding mothers—the degree of protein binding and lipid solubility. Drugs that are very lipid soluble penetrate into milk in higher concentrations almost without exception. Of particular interest are the drugs that are active in the central nervous system (CNS). CNS-active drugs invariably have the unique characteristics required to enter milk. Therefore, if a drug is active in the central nervous system, higher levels in milk can be expected; although, the amounts still are often subclinical. Many of the neuroactive drugs produce Relative Infant Doses of >5%. Protein binding also plays an important role. Drugs circulate in the maternal plasma, either bound to albumin or freely soluble in the plasma. It is the free component (unbound fraction) that transfers into milk, while the bound fraction stays in the maternal circulation. Therefore, drugs that have high maternal protein binding (warfarin, many NSAIDs) have reduced milk levels simply because they are excluded from the milk compartment.

Once a drug has entered the mother’s milk and has been ingested by the infant, it must traverse through the infant’s GI tract prior to absorption. Some drugs are poorly stable in this environment due to the proteolytic enzymes and acids present in the infant’s stomach. This includes the aminoglycoside family, omeprazole, and large peptide drugs, such as Heparin. Other drugs are poorly absorbed by the infant’s gastrointestinal tract and do not enter the infant’s blood stream. Thus, oral bioavailability is a useful tool to estimate just how much of the drug will be absorbed by the infant. Many drugs are sequestered in the liver (first pass) and may never actually reach the plasma compartment where they are active. Absorption characteristics such as these ultimately tend to reduce the overall effect of many drugs in breastfed infants. There are certainly exceptions to this rule, and one must always be aware that the action of a drug in the GI tract can be profound, producing diarrhea, constipation, and occasionally syndromes such as pseudomembranous colitis. One of the more popular methods for estimating risk is to determine the Relative Infant Dose (RID). The RID is calculated by dividing the infant’s dose via milk (mg/kg/day) by the mothers dose in mg/kg/day. The RID gives the clinician a feeling for just how much medication the infant is exposed to on a weight-normalized basis. However, many authors calculate the infant dose without normalizing for maternal and infant weight, so be cautious.
Relative Infant Dose

\[
RID = \frac{\text{Dose.infant}}{\text{Dose.mother}}
\]

Dose.infant = dose in infant
Dose.mother = dose in mother

Key Points About Breastfeeding and Medications

- Avoid using medications that are not necessary. Herbal drugs, high dose vitamins, unusual supplements, etc. that are simply not necessary should be avoided.

- If the Relative Infant Dose is less than 10%, most medications are relatively safe to use. The RID of the vast majority of drugs is <10%.

- Choose drugs for which we have published data, rather than those recently introduced.

- Evaluate the infant for risks. Be slightly more cautious with premature infants or neonates.

- Medication used in the first three to four days generally produce subclinical levels in the infant due to the limited volume of milk.

- Recommend that mothers with symptoms of depression or other mental disorders seek treatment. Most of the medications used to treat these syndromes are safe.

- Most drugs are quite safe in breastfeeding mothers. The hazards of using formula are well known and documented.

- Discontinuing breastfeeding for some hours/days may be required, particularly with radioactive compounds. Follow the guidelines in the appendices of this book.

- Choose drugs with short half-lives, high protein binding, low oral bioavailability, or high molecular weight.

Lastly, it is terribly important to always evaluate the infant’s ability to handle small amounts of medications. Some infants, such as premature or unstable infants, may not be suitable candidates for certain medications. But remember that early postpartum (and in late stage lactation), the amount of milk produced (30-100 mL/day) is so low that the clinical dose of drug transferred is often low, so even premature neonates would receive only a limited amount from the milk.
Evaluation of the Infant

- Inquire about the infant—always inquire as to the infant’s age, size, and stability. This is perhaps the most important criterion to be evaluated prior to using the medication.

- Infant age—premature and newborn infants are at somewhat greater risk. Older infants are at somewhat lower risk due to high metabolic capacity.

- Infant stability—unstable infants with poor GI stability may increase the risk of using medications.

- Pediatric Approved Drugs—generally are less hazardous if long-term history of safety is recognized.

- Dose vs Age—the age of an infant is critical. Use medications cautiously in premature infants. Older, mature infants can metabolize and clear medications much easier. Remember the dose of the drug is dependent on milk supply. In mothers in late-stage lactation (>1 year), milk production is often low, so is the dose of drug delivered.

- Drugs that alter milk production—avoid medications that may alter the mother’s milk production.

**General Suggestions for the Clinician**

Determine if the drug is absorbed from the GI tract. Many drugs, such as the aminoglycosides, vancomycin, cephalosporin antibiotics (third generation), magnesium salts, and large protein drugs (heparin), are so poorly absorbed that it is unlikely the infant will absorb significant quantities. At the same time, observe for GI side effects from the medication trapped in the GI compartment of the infant (e.g., diarrhea).

Review the Relative Infant Dose (RID) and compare that to the pediatric dose if known. Most of the RID were derived from the $C_{\text{max}}$ (highest milk concentration of the drug) that were published. When possible, there are ‘ranges’ of RID, so the reader can see the various dose estimates from different studies. The milk/plasma ratio is virtually worthless unless you know the maternal plasma level. It does not provide the user with information as to the absolute amount of drug transferred to the infant via milk. Even if the drug has a high milk/plasma ratio, if the maternal plasma level of the medication is very small (such as with ranitidine), then the absolute amount (dose) of a drug entering milk will still be quite small and often subclinical.

Try to use medications with shorter half-lives as they are generally eliminated from the maternal plasma rapidly, thus exposing the milk compartment (and the infant) to reduced levels of medication.

Be cautious of drugs (or their active metabolites) that have long pediatric half-lives as they can continually build up in the infant’s plasma over time. The barbiturates,
benzodiazepines, and meperidine are classic examples where higher levels in the infant can and do occasionally occur.

If you are provided a choice, choose drugs that have higher protein binding because they are generally sequestered in the maternal circulation and do not transfer readily into the milk compartment or the infant. Remember, it’s the free drug that transfers into the milk compartment. Without doubt, the most important parameter that determines drug penetration into milk is plasma protein binding. Choose drugs with high protein binding.

Although not always true, we have generally found centrally active drugs (anticonvulsants, antidepressants, antipsychotic) frequently penetrate milk in higher (not necessarily ‘high’) levels simply due to their physicochemistry. If the drug in question produces sedation, depression, or other neuroleptic effects in the mother, it is likely to penetrate the milk and may produce similar effects in the infant. Thus, with CNS-active drugs, one should always check the data in this book closely and monitor the infant routinely.

Be cautious of herbal drugs as many contain chemical substances that may be dangerous to the infant. Numerous poisonings have been reported. Prior to using, advise the mother to contact a lactation consultant or herbalist who is knowledgeable about their use in breastfeeding mothers. Do not exceed standard recommended doses. Try to use pure forms, not large mixtures of unknown herbals. Do not overdose, use only minimal amounts.

For radioactive compounds, we have gathered much of the published data in this field into several tables. The Nuclear Regulatory Commission recommendations are quite good, but they differ from some published data. They can be copied and provided to your radiologist. They are available from the Nuclear Regulatory Commission’s web page address in the appendix.

Use the Relative Infant Dose. The box below shows the calculation. In general, a Relative Infant Dose of < 10% is considered safe, and its use is becoming increasingly popular by numerous investigators.

Most importantly, it is seldom required that a breastfeeding mother discontinue breastfeeding just to take a medication. It is simply not acceptable for the clinician to stop lactation merely because of heightened anxiety or ignorance on their part. The risks of formula feeding are significant and should not be trivialized. Few drugs have documented side effects in breastfed infants, and we know most of these.

The following review of drugs, and even diseases, is a thorough review of what has been published and what we presently know about the use of medications in breastfeeding mothers.

The authors make no recommendations as to the safety of these medications during lactation, but only review what is currently published in the scientific literature. Individual use of medications must be left up to the judgement of the physician, the patient, and other healthcare consultants.

Thomas W. Hale & Hilary E. Rowe
How To Use This Book

This section of the book is designed to aid the reader in determining risk to an infant from maternal medications and in using the pharmacokinetic parameters throughout this reference.

**Drug Name and Generic Name:**

Each monograph begins with the generic name of the drug. Several of the most common USA trade names are provided under the Trade section.

**Other Trades:**

This book is used all over the world. Thus many other trade names from other countries are now included in this section.

**Category:**

This lists the class or ‘family of drugs’ that the medication belongs to and gives a general idea of the pharmacology, mechanism of action and probable use of the drug.

**Drug Monograph:**

The drug monograph lists what we currently understand about the drug, its ability to enter milk, the concentration in milk at set time intervals, and other parameters that are important to a clinical consultant. We have attempted at great length to report only what the references have documented.

**Dr. Hale’s Lactation Risk Category:**

**L1 Compatible:**

Drug which has been taken by a large number of breastfeeding mothers without any observed increase in adverse effects in the infant. Controlled studies in breastfeeding women fail to demonstrate a risk to the infant and the possibility of harm to the breastfeeding infant is remote; or the product is not orally bioavailable in an infant.

**L2 Probably Compatible:**

Drug which has been studied in a limited number of breastfeeding women without an increase in adverse effects in the infant. And/or, the evidence of a demonstrated risk which is likely to follow use of this medication in a breastfeeding woman is remote.
L3 Probably Compatible:

There are no controlled studies in breastfeeding women; however, the risk of untoward effects to a breastfed infant is possible, or controlled studies show only minimal non-threatening adverse effects. Drugs should be given only if the potential benefit justifies the potential risk to the infant. (New medications that have absolutely no published data are automatically categorized in this category, regardless of how safe they may be.)

L4 Potentially Hazardous:

There is positive evidence of risk to a breastfed infant or to breastmilk production, but the benefits from use in breastfeeding mothers may be acceptable despite the risk to the infant (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective.)

L5 Hazardous:

Studies in breastfeeding mothers have demonstrated that there is significant and documented risk to the infant based on human experience, or it is a medication that has a high risk of causing significant damage to an infant. The risk of using the drug in breastfeeding women clearly outweighs any possible benefit from breastfeeding. The drug is contraindicated in women who are breastfeeding an infant.

Adult Concerns:

This section lists the most prevalent undesired or bothersome side effects listed for adults. As with most medications, the occurrence of these is often quite rare, generally less than 1-10%. Side effects vary from one patient to another, with most patients not experiencing untoward effects.

Pediatric Concerns:

This section lists the side effects noted in the published literature as associated with medications transferred via human milk. Pediatric concerns are those effects that were noted by investigators as being associated with drug transfer via milk. In some sections, we have added comments that may not have been reported in the literature, but are well known attributes of this medication.

Infant Monitoring:

This section provides advice to the clinician regarding potential side effects that may occur in the infant from exposure to a medication in breastmilk. The infant monitoring parameters can be used by the clinician to educate the mother about potential side effects that could occur in the infant.
Relative Infant Dose:

The Relative Infant Dose (RID) is calculated by dividing the infant’s dose via milk in “mg/kg/day” by the maternal dose in “mg/kg/day” (see page 9). This weight-normalizing method indicates approximately how much of the “maternal dose” the infant is receiving. Many authors now use this preferred method because it gives a better indication of the relative dose transferred to the infant. We report RID ranges, as this gives the reader an estimate of all the Relative Infant Doses published by the various authors.

Please understand, however, that many authors use different methods for calculating RID. Some are not weight-normalized. In these cases, their estimates may differ slightly from this book. While we often place the ‘authors’ estimates of Relative Infant Dose, the RID range that we calculate is based on a 70 kg mother and is weight-normalized in all instances. So RID may be slightly different according to how it is calculated.

Many researchers now suggest that anything less than 10% of the maternal dose is probably safe. This is usually correct. However, some drugs (metronidazole, acetaminophen) actually have much higher Relative Infant Doses, but because they are quite non-toxic, they do not often bother an infant. To calculate this dose, we chose the data we felt was best, and this often included larger studies with AUC calculations of mean concentrations in milk. We also chose an average body weight of 70 kg for an adult. Thus, the RIDs herein are calculated assuming a maternal average weight of 70 kg and a daily milk intake of 150 mL/kg/day in the infant. Please note, many authors fail to normalize their data for weight. Others provide a RID for ‘each’ feeding, not a daily average. Therefore, our values may vary slightly from others simply due to differences in the method of calculation.

Adult Dosage:

This is the usual adult oral dose provided in the package insert. While these are highly variable, I chose the dose for the most common use of the medication.

Alternatives:

Drugs listed in this section may be suitable alternate choices for the medication listed above. In many instances, if the patient cannot take the medication or it is a poor choice due to high milk concentrations, these alternates may be suitable candidates. WARNING: The alternatives listed are only suggestions and may not be at all appropriate for the syndrome in question. Only the clinician can make this judgment. For instance, nifedipine is a calcium channel blocker with good antihypertensive qualities, but poor antiarrhythmic qualities. In this case, verapamil would be a better choice.

\[ T^{1/2} = \]

This lists the most commonly recorded adult half-life of the medication. It is very important to remember that short half-life drugs are preferred. Use this parameter
to determine if the mother can successfully breastfeed around the medication by nursing the infant, then taking the medication. If the half-life is short enough (1-3 hours), then the drug level in the maternal plasma will be declining when the infant feeds again. This is ideal. If the half-life is significantly long (12-24 hours) and if your physician is open to suggestions, then find a similar medication with a shorter half-life (compare ibuprofen with naproxen).

Vd=

The volume of distribution is a useful kinetic term that describes how widely the medication is distributed in the body. Drugs with high volumes of distribution (Vd) are distributed in higher concentrations in remote compartments of the body and may not stay in the blood.

For instance, digoxin enters the blood compartment and then rapidly leaves to enter the heart and skeletal muscles. Most of the drug is sequestered in these remote compartments (100 fold). Therefore, drugs with high volumes of distribution (1-20 L/kg) generally require much longer to clear from the body than drugs with smaller volumes (< 1 L/kg). For instance, whereas it may only require a few hours to totally clear gentamycin (Vd=0.28 L/kg), it may require weeks to clear amitriptyline (Vd=10 L/kg), which has a huge volume of distribution. In addition, some drugs may have one half-life for the plasma compartment, but may have a totally different half-life for the peripheral compartment, as half-life is a function of volume of distribution. We have found that drugs with high Vd also produce lower milk levels. For a complete description of Vd, please consult a good pharmacology reference. In this text, the units of measure for Vd are L/kg.

T_{\text{max}} =

This lists the time interval from administration of the drug until it reaches the highest level in the mother’s plasma (C_{\text{max}}), which we call the peak or “time to max”, hence T_{\text{max}}. Occasionally, you may be able to avoid nursing the baby when the medication is at the peak. Rather, wait until the peak is subsiding or has at least dropped significantly. Remember, drugs enter breastmilk as a function of the maternal plasma concentration. In general, the higher the mother’s plasma level, the greater the entry of the drug into her milk. If possible, choose drugs that have short peak intervals, and suggest mom not breastfeed when the drug is at C_{\text{max}}.

MW=

The molecular weight of a medication is a significant determinant as to the entry of that medication into human milk. Medications with small molecular weights (< 200) can easily pass into milk by traversing small pores in the cell walls of the mammary epithelium (see ethanol). Drugs with higher molecular weights must traverse the membrane by dissolving in the cells’ lipid membranes, which may significantly reduce milk levels. As such, the smaller the molecular weight, the higher the relative transfer of that drug into milk. Protein medications (e.g., heparin), which have enormous molecular weights, transfer at much lower concentrations and are virtually excluded from human breastmilk. Therefore,
when possible, choose drugs with higher molecular weights to reduce their entry into milk.

\[ \text{M/P=} \]

This lists the milk/plasma ratio. This is the ratio of the concentration of drug in the mother's milk divided by the concentration in the mother's plasma. If high (> 1-5), it is useful as an indicator of drugs that may sequester in milk in high levels. If low (< 1), it is a good indicator that only minimal levels of the drug are transferred into milk (this is preferred). While it is best to try to choose drugs with low milk/plasma ratios, the amount of drug which transfers into human milk is largely determined by the level of drug in the mother’s plasma compartment. Even with high M/P ratios and low maternal plasma levels, the amount of drug that transfers is still low. Therefore, the higher M/P ratios often provide an erroneous impression that large amounts of drug are going to transfer into milk. This simply may not be true.

\[ \text{PB=} \]

This lists the percentage of maternal protein binding. Most drugs circulate in the blood bound to plasma albumin and other proteins. If a drug is highly protein bound, it cannot enter the milk compartment as easily. The higher the percentage of binding, the less likely the drug is to enter the maternal milk. Try to choose drugs that have high protein binding in order to reduce the infant’s exposure to the medication. Good protein binding is typically greater than 90%.

\[ \text{Oral=} \]

Oral bioavailability refers to the ability of a drug to reach the systemic circulation after oral administration. It is generally a good indication of the amount of medication that is absorbed into the blood stream of the patient. Drugs with low oral bioavailability are generally either poorly absorbed in the gastrointestinal tract, are destroyed in the gut, or are sequestered by the liver prior to entering the plasma compartment. The oral bioavailability listed in this text is the adult value; almost none have been published for children or neonates. Recognizing this, these values are still useful in estimating if a mother or perhaps an infant will actually absorb enough drug to provide clinically significant levels in the plasma compartment of the individual. The value listed estimates the percent of an oral dose that would be found in the plasma compartment of the individual after oral administration. In many cases, the oral bioavailability of some medications is not listed by manufacturers, but instead terms such as “Complete”, “Nil”, or “Poor” are used. For lack of better data, we have included these terms when no data are available on the exact amount (percentage) absorbed.

\[ \text{pKa=} \]

The pKa of a drug is the pH at which the drug is equally ionic and nonionic. The more ionic a drug is, the less capable it is of transferring from the milk compartment to the maternal plasma compartment. Hence, the drug becomes trapped in milk.
(ion-trapping). This term is useful because drugs that have a pKa higher than 7.2 may be sequestered to a slightly higher degree than one with a lower pKa. Drugs with higher pKa generally have higher milk/plasma ratios. Hence, choose drugs with a lower pKa.
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>Angiotensin converting enzyme inhibitor</td>
</tr>
<tr>
<td>AUC</td>
<td>Area under the Curve</td>
</tr>
<tr>
<td>BID</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Cmax</td>
<td>Plasma or milk concentration at peak</td>
</tr>
<tr>
<td>d</td>
<td>Day</td>
</tr>
<tr>
<td>et. al</td>
<td>“and others”</td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>h</td>
<td>Hour</td>
</tr>
<tr>
<td>LRC</td>
<td>Lactation Risk Category</td>
</tr>
<tr>
<td>M/P</td>
<td>Milk/Plasma Ratio</td>
</tr>
<tr>
<td>MAOI</td>
<td>Monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>mg/L</td>
<td>Milligram per liter</td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter. One cc</td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole of weight</td>
</tr>
<tr>
<td>MW</td>
<td>Molecular Weight</td>
</tr>
<tr>
<td>ng/L</td>
<td>Nanogram per liter</td>
</tr>
<tr>
<td>NR</td>
<td>Not rated</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>Oral</td>
<td>Oral bioavailability (adult)</td>
</tr>
<tr>
<td>PB</td>
<td>Percent of protein binding in maternal circulation</td>
</tr>
<tr>
<td>pg</td>
<td>Picogram</td>
</tr>
<tr>
<td>PHL</td>
<td>Pediatric elimination half-life</td>
</tr>
<tr>
<td>PRN</td>
<td>As needed</td>
</tr>
<tr>
<td>QD</td>
<td>Daily</td>
</tr>
<tr>
<td>QID</td>
<td>Four times daily</td>
</tr>
<tr>
<td>RID</td>
<td>Relative Infant Dose</td>
</tr>
<tr>
<td>SNRIs</td>
<td>Serotonin norepinephrine reuptake inhibitors</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Selective serotonin reuptake inhibitors</td>
</tr>
<tr>
<td>T½</td>
<td>Adult elimination half-life</td>
</tr>
<tr>
<td>TCAs</td>
<td>Tricyclic antidepressants</td>
</tr>
<tr>
<td>TID</td>
<td>Three times daily</td>
</tr>
<tr>
<td>Tmax</td>
<td>Time to peak plasma level (PK)</td>
</tr>
<tr>
<td>Vd</td>
<td>Volume of Distribution</td>
</tr>
<tr>
<td>X</td>
<td>Times</td>
</tr>
<tr>
<td>mCi</td>
<td>Millicurie of Radioactivity</td>
</tr>
<tr>
<td>μCi</td>
<td>Microcurie of Radioactivity</td>
</tr>
<tr>
<td>μg/L</td>
<td>Microgram per liter</td>
</tr>
<tr>
<td>μmol</td>
<td>Micromole of weight</td>
</tr>
</tbody>
</table>
Droperidol is a powerful tranquilizer. It is sometimes used as a preanesthetic medication in labor and delivery because of fewer respiratory effects in neonates. In pediatric patients 2-12 years of age, it is sometimes used as an antiemetic (0.01-0.015 mg/kg IV). There are no data available on secretion into breastmilk. Due to the potent sedative properties of this medication, caution is urged.

<table>
<thead>
<tr>
<th>T 1/2</th>
<th>2.2 h</th>
<th>M/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax</td>
<td>10-30 minutes (IM)</td>
<td>PB 85-90%</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td>Vd  1.5 L/kg</td>
</tr>
<tr>
<td>MW</td>
<td>379</td>
<td>pKa 7.46</td>
</tr>
<tr>
<td>RID</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Adult Concerns:** Sedation, hypotension, dizziness, unusual ocular movements, extrapyramidal symptoms, chills, shivering.

**Adult Dose:** 0.625-1.25 mg IM or IV.

**Pediatric Concerns:** None reported via milk at this time.

**Infant Monitoring:** Sedation, irritability, not waking to feed/poor feeding, weight gain and extrapyramidal symptoms.

**Alternatives:** Haloperidol.

**References:**

**DULOXETINE**

**Trade:** Ariclaim, Cymbalta, Duceten, Xeristar, Yentreve

**Category:** Antidepressant, other

**LRC:** L3 - Limited Data-Probably Compatible

Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) that is indicated for depression and for patients with neuropathic pain. The primary role of SNRIs is as an alternative in patients with major depressive disorder who have responded poorly to other agents (e.g., tricyclics or SSRIs).

The transfer of duloxetine into breastmilk was studied in 6 women who were at least 12 weeks postpartum and taking 40 mg twice daily for 3.5 days. Paired blood and breastmilk samples were taken at 0, 1, 2, 3, 6, 9, and 12 hours post-dose. The milk/plasma ratio was reported to be about 0.267. The daily dose of duloxetine was estimated to be 7 µg/day (range= 4-15 µg/day). According to the manufacturer, the weight-adjusted infant dose would be approximately 0.141% of the maternal dose. Further, even this is unlikely absorbed, as duloxetine is unstable under acid conditions of the infants stomach. In a more recent study in a mother consuming duloxetine (60 mg daily), levels in milk were 31 µg/L and 64 µg/L at trough and peak respectively. The milk/plasma ratios were 1.29 (trough) and 1.21 (peak). These authors suggest a relative infant dose of 0.14%.
An investigation was undertaken to study the transfer of duloxetine across placenta as well as breastmilk in a 31 year old mother who received 60 mg duloxetine daily throughout her pregnancy and continued it during lactation. An assessment of maternal and cord blood concentrations immediately at birth revealed that the placental transfer for duloxetine is low. No withdrawal symptoms or malformations occurred in the infant. Breastmilk samples were obtained at 18 days post-delivery. The first milk sample was obtained just prior to the morning dose, and subsequently 8 more milk samples were obtained over a period of 22.5 hours following the morning dose. A mean milk concentration of 51 µg/L rendered a mean relative infant dose (RID) of 0.81%. This RID for duloxetine is low as compared to some of other commonly used SSRIs/SNRIs such as venlafaxine, desvenlafaxine, citalopram, mirtazepine, fluoxetine. Further, it was found that the concentration of duloxetine in hindmilk was 1.5-2 times that in foremilk, suggesting a lipid co-transport for duloxetine. The authors of this study concluded that the placental and milk transfer of duloxetine is low as compared to a few other SSRIs/SNRIs commonly used. No untoward effects were reported in the infant.

<table>
<thead>
<tr>
<th>T 1/2</th>
<th>12 h</th>
<th>M/P</th>
<th>0.267-1.29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax</td>
<td>6 h</td>
<td>PB</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Oral</td>
<td>&gt;70%</td>
<td>Vd</td>
<td>23.4 L/kg</td>
</tr>
<tr>
<td>MW</td>
<td>333</td>
<td>pKa</td>
<td>9.5</td>
</tr>
<tr>
<td>RID</td>
<td>0.1% - 1.1%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Adult Concerns:** Fatigue, dizziness, somnolence, insomnia, blurred vision, dry mouth, nausea, vomiting, constipation, diarrhea, decreased appetite, changes in liver function, tremor, sweating, erectile dysfunction.

**Adult Dose:** 40-60 mg/day.

**Pediatric Concerns:** None reported via milk at this time.

**Infant Monitoring:** Sedation or irritability, not waking to feed/poor feeding and weight gain.

**Alternatives:** Venlafaxine, sertraline, citalopram.

**References:**
Echinacea is a popular herbal remedy in the central US and has been traditionally used topically to stimulate wound healing and internally to stimulate the immune system. The plant contains a complex mixture of compounds and, thus far, no single component appears responsible for its immunostimulant properties. A number of in vitro and animal studies have documented the activation of immunologic properties although most of these are via intraperitoneal injections, not orally. Three recent studies have reported echinacea may not be a active against the common cold,\textsuperscript{1,2,3} but more studies are presently underway. Thus far, little is known about the toxicity of this plant although its use has been widespread for many years. Apparently, purified Echinacea extract is relatively non-toxic even at high doses.\textsuperscript{3,4} No data are available on its transfer into human milk or its effect on lactation.\textsuperscript{4}

**Adult Concerns:** Dizziness, nausea, rash.

**Adult Dose:**

**Pediatric Concerns:** None reported via milk.

**Infant Monitoring:**

**Alternatives:**

**References:**


**ECONAZOLE**

**Trade:** Spectazole

**Category:** Antifungal

**LRC:** L3 - No Data-Probably Compatible

Econazole nitrate is a typical azole antifungal and is indicated for topical application in the treatment of tinea pedis, tinea cruris, and tinea corporis.\textsuperscript{1} Absorption following topical administration is minimal to nil, less than 1% of the applied dose was recovered in the urine and feces of humans. It is not known whether econazole nitrate is excreted in human milk, but the levels here are probably far subclinical if even detectable.

**Adult Concerns:** Erythema, burning sensation, stinging, pruritus.

**Adult Dose:** Apply topically 1-2 times daily.

**Pediatric Concerns:**

**Infant Monitoring:** Vomiting, diarrhea.
**FINGOLIMOD**

**Trade:** Gilenya

**Category:** Immune Modulator

**LRC:** L5 - No Data-Hazardous

Fingolimod is an immune modulator and prodrug that binds to the surface of lymphocytes and redirects them from the blood and graft sites to the lymph nodes, thus reducing the immune response in patients with Multiple Sclerosis (MS). It reportedly assists in the repair of brain glial and precursor cells following injury in this syndrome. Fingolimod reportedly slows the progression of disability and reduces the frequency and severity of symptoms in patients with MS. While it decreases the heart rate, it increases the risk of infection and raises liver enzymes. Asthmatic patients may have an increase in the use of their rescue inhalers. The most common side effects include headache, flu, diarrhea, back pain, abnormal liver enzymes, and cough. It is unknown if fingolimod passes into human breastmilk but it is excreted into rat milk. Due to its high volume of distribution and high protein binding, levels in human milk are expected to be low.

However, several deaths have been reported, and the FDA has recommended that all patients starting fingolimod treatment be monitored for signs of bradycardia for at least 6 hours after the first dose. The FDA is now recommending hourly pulse and blood pressure monitoring for all patients starting treatment,
with electrocardiogram monitoring prior to dosing and at the end of the observation period; monitoring should continue until any symptoms resolve. The period should extend past 6 hours in patients at higher risk, in some cases overnight. This product is hazardous and breastfeeding is not recommended.

<table>
<thead>
<tr>
<th>T 1/2</th>
<th>6-9 days</th>
<th>M/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>T max</td>
<td>12-16 h</td>
<td>PB</td>
</tr>
<tr>
<td>Oral</td>
<td>93%</td>
<td>PB</td>
</tr>
<tr>
<td>MW</td>
<td>307.5</td>
<td>pKa</td>
</tr>
</tbody>
</table>

**Adult Concerns:** Headache, flu, diarrhea, back pain, abnormal liver enzymes, cough, macular edema, weakness, dizziness, bradycardia, hypertension.

**Adult Dose:** 0.5 mg daily.

**Pediatric Concerns:**

**Infant Monitoring:** Breastfeeding is not recommended.

**Alternatives:**

**References:**

**FLAVOXATE**

**Trade:** Urispas

**Category:** Renal-Urologic Agent

**LRC:** L3 - No Data-Probably Compatible

Flavoxate is used as an antispasmodic to provide relief of painful urination, urgency, nocturia, urinary frequency, or incontinence. It exerts a direct smooth muscle relaxation on the bladder wall and has been used in children for enuresis. No data are available on its transfer into human milk.

<table>
<thead>
<tr>
<th>T 1/2</th>
<th>2 h</th>
<th>M/P</th>
</tr>
</thead>
<tbody>
<tr>
<td>T max</td>
<td>2 h</td>
<td>PB</td>
</tr>
<tr>
<td>Oral</td>
<td>Complete</td>
<td>PB</td>
</tr>
<tr>
<td>MW</td>
<td>391</td>
<td>pKa</td>
</tr>
</tbody>
</table>

**Adult Concerns:** Drowsiness, dry mouth and throat, nervousness, headache, confusion, nausea, vomiting, blurred vision. Do not use with pyloric or duodenal obstruction, gastrointestinal hemorrhage, or obstructive uropathies.

**Adult Dose:** 100-200 mg three to four times daily.