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**PHARMACOLOGY AND BREASTFEEDING**

**FARMACOLOGIA E AMAMENTAÇÃO**

**FARMACOLOGÍA Y LACTANCIA MATERNA**

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## Abstract

**Introduction:** The administration of medication during the breastfeeding period requires special attention to ensure the health of both mother and baby. **Objective:** To study the influence of medication use on breastfeeding safety and the risks associated with exposure of infants to drugs. **Methodology:** The search was carried out in databases such as PubMed and EBSCO, using keywords related to “breastfeeding”, “pharmacology” and “risk assessment”, covering studies published between 2020 and 2025 in languages such as Portuguese, English and Spanish. After applying inclusion and exclusion criteria, a total of 12 research studies were selected to be analyzed. **Results:** The central topics addressed in this narrative review include: the physiological changes that occur during lactation and their effect on pharmacology; the changes in drug metabolism and excretion during this period; the passage of drugs through breast milk and the factors that affect the amount that reaches the baby; the categorization of drugs according to their safety during lactation; the drugs considered safe in this context; and finally, the main clinical guidelines for prescribing drugs to breastfeeding women. **Conclusion:** With a detailed assessment of the risk-benefit ratio and careful monitoring, it is possible to align the mother’s pharmacotherapy with breastfeeding, ensuring the well-being of the mother-baby bond in an effective and safe way.

**Keywords:** Breast Feeding; Pharmacology; Risk Assessment.

## Resumo

**Introdução:** A administração de medicamentos durante o período de amamentação exige uma atenção especial para garantir a saúde tanto da mãe quanto do bebê. **Objetivo:** Estudar a influência do uso de medicamentos na segurança da amamentação e os riscos associados à exposição dos lactentes a fármacos. **Metodologia:** A pesquisa foi realizada em bases como PubMed e EBSCO, utilizando palavras-chave relacionadas a “amamentação”, “farmacologia” e “avaliação de risco”, abrangendo estudos publicados entre os anos de 2020 e 2025 em idiomas como português, inglês e espanhol. Após a aplicação de critérios de inclusão e exclusão, um total de 12 pesquisas foram selecionadas para serem analisadas. **Resultados:** Os tópicos centrais abordados nesta revisão narrativa incluem: as alterações fisiológicas que ocorrem durante a lactação e o seu efeito na farmacologia; as alterações no metabolismo e excreção dos fármacos durante este período; a passagem dos fármacos através do leite materno e os fatores que afetam a quantidade que chega ao bebê; a categorização dos fármacos de acordo com a sua segurança durante a lactação; os fármacos considerados seguros neste contexto; e, finalmente, as principais diretrizes clínicas para a prescrição de fármacos a mulheres que amamentam. **Conclusão:** com uma avaliação detalhada da relação risco-benefício e um acompanhamento cuidadoso, é viável alinhar a farmacoterapia da mãe com a amamentação, assegurando o bem-estar do vínculo mãe-bebê de forma eficaz e segura.

**Palavras-chave:** Amamentação; Avaliação de Risco; Farmacologia.

## Resumen

**Introducción:** La administración de medicamentos durante el período de lactancia requiere una atención especial para garantizar la salud tanto de la madre como del bebé. **Objetivo:** Estudiar la influencia del uso de medicamentos en la seguridad de la lactancia materna y los riesgos asociados a la exposición de los lactantes a fármacos. **Metodología:** La búsqueda se realizó en bases de datos como PubMed y EBSCO, utilizando palabras clave relacionadas con “breastfeeding”, “pharmacology” y “risk assessment”, abarcando estudios publicados entre 2020 y 2025 en idiomas como portugués, inglés y español. Tras aplicar criterios de inclusión y exclusión, se seleccionaron un total de 12 estudios de investigación para ser analizados. **Resultados:** Los temas centrales tratados en esta revisión narrativa incluyen: los cambios fisiológicos que ocurren durante la lactancia y su efecto sobre la farmacología; los cambios en el metabolismo y la excreción de fármacos durante este período; el paso de fármacos a través de la leche materna y los factores que afectan a la cantidad que llega al bebé; la categorización de los fármacos según su seguridad durante la lactancia; los fármacos considerados seguros en este contexto; y, por último, las principales guías clínicas para la prescripción de fármacos a mujeres lactantes. **Conclusión:** Con una evaluación detallada de la relación riesgo-beneficio y un seguimiento cuidadoso, es posible alinear la farmacoterapia de la madre con la lactancia materna, garantizando el bienestar del vínculo madre-bebê de forma eficaz y segura.

**Descriptores:** Evaluación de Riesgos; Farmacología; Lactancia Materna.

## Introduction

Breastfeeding is the ideal method of feeding infants due to its multiple nutritional, immunological, and psychological benefits<sup>(22)</sup>. However, the use of drugs during this period raises concerns about the possible transfer of substances into breast milk and their effects on the infant. Understanding the pharmacokinetics of drugs in this context is essential to ensure the safety of both mother and child<sup>(12)</sup>.

Numerous studies have evaluated the safety of medication use in breastfeeding women. Factors such as the infant's age, maternal metabolism, and the pharmacokinetic properties of the drug influence the amount of medication that can pass into breast milk and its possible adverse effects<sup>(2)</sup>. Exposure poses an increased risk in premature or sick newborns, while in infants older than six months, the risks tend to be lower due to improved metabolic capacity<sup>(15)</sup>. In recent years, the development of specialized databases such as LactMed or e-lactancia, as well as pharmacokinetic models, has made it possible to more accurately assess the amount of medication that reaches the infant and its possible impact<sup>(9,17)</sup>.

One of the most controversial drug groups in the context of breastfeeding is opioids. This concern intensified after the well-known “Toronto case,” in which an infant allegedly died due to toxicity associated with exposure to codeine through breast milk. The child's mother was an ultra-rapid metabolizer of codeine to morphine due to a duplication of the CYP2D6 gene, which increased the levels of morphine in her milk<sup>(23)</sup>. As a result, many health institutions advised against the use of codeine in breastfeeding mothers, which led to the prescription of more potent opioids with a higher potential for abuse, compromising maternal health<sup>(12)</sup>. However, in the above-mentioned case, there may have been other factors, such as an unreported change in the infant's renal function or higher direct exposure<sup>(23)</sup>.

For this reason, each medication must be evaluated individually, considering its pharmacokinetics, its ability to transfer into breast milk, and its potential impact on the infant. Most medications are safe during breastfeeding if used in appropriate doses and under

professional supervision, and an adequate risk-benefit assessment is essential to protect both the health of the child and the mother<sup>(12)</sup>.

This study was conducted with the aim of studying the influence of medication use on breastfeeding safety and the risks associated with exposing infants to drugs.

## Methodology

The narrative review of the literature was conducted using scientific databases such as PubMed and EBSCO, using the keywords: “breastfeeding,” “pharmacology,” and “risk assessment,” with the Boolean operator “AND,” with a total of 326 articles. Given the high number of results, the following inclusion criteria were applied: articles published between 2020 and 2025, in Portuguese, English, and Spanish, addressing clinical, pharmacological, and safety aspects of the use of medications by lactating women. Duplicate articles between databases were excluded, as were publications focusing exclusively on pregnancy, without mention of breastfeeding, studies dealing with drugs not used in common clinical practice, and opinion pieces, letters to the editor, or abstracts without full text available.

The selected studies were analyzed descriptively and interpretively, with an emphasis on the principles of risk-benefit for the mother and infant, and pharmacokinetics during lactation.

## Results

Twelve studies were included for detailed analysis, which are presented in Table 1.

Table 1: Articles included in the review.

| Study title and authorship                                                                                                                                                                | Study type                             | Country and year             | Study objectives                                                                                                | Sample                                                                            | Results/Conclusions                                                                                                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------|-----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| Opioid Use in Breastfeeding Mothers and Neonatal Risks.<br>Thomas W. Hale, Kaytlin Krutsch.                                                                                               | Clinical perspective.                  | USA, 2021.                   | Review the transfer of opioids into breast milk and the risk to newborns.                                       | Not applicable (review based on previous studies and pharmacological parameters). | Transfer depends on the dose and stage of lactation; caution is recommended with opioids, especially in the first month postpartum.                |
| Consensus Panel Recommendations for the Pharmacological Management of Breastfeeding Women with Postpartum Depression.<br>Eleftheriou G. <i>et al.</i>                                     | Expert consensus panel.                | Italy, 2024.                 | Issue recommendations on the pharmacological treatment of postpartum depression during breastfeeding.           | Panel of 16 experts from 8 scientific societies.                                  | It is recommended to treat depression, favoring SSRI antidepressants and allowing benzodiazepines under controlled use.                            |
| Thiamine supplementation holds neurocognitive benefits for breastfed infants during the first year of life.Jeffrey R. Measelle <i>et al.</i>                                              | Randomized clinical trial.             | Cambodia, 2021.              | To evaluate the impact of maternal thiamine supplementation on infant cognitive development.                    | 335 nursing mothers and their babies.                                             | Thiamine supplementation improved language development in infants at 6 months.                                                                     |
| SafeMotherMedicine: Aiming to Increase Women's Empowerment in Use of Medications During Pregnancy and Breastfeeding.<br>Kristine Heitmann, Jan Schjøtt.                                   | Development of information service.    | Norway, 2020.                | Describe a digital information service about medications during pregnancy and breastfeeding.                    | Evaluation of 30,000 consultations performed.                                     | Safe Mother Medicine empowers women with individualized, evidence-based information.                                                               |
| The Implausibility of Neonatal Opioid Toxicity from Breastfeeding.<br>Jonathan Zipursky, David N. Juurlink.                                                                               | Mini-review.                           | Canada, 2020.                | Critically analyze the case of neonatal toxicity due to codeine and its plausibility.                           | Case analysis and review of existing literature.                                  | Significant neonatal toxicity from opioids through breastfeeding is highly unlikely.                                                               |
| Mirtazapine in pregnancy and lactation: A systematic review of adverse outcomes.<br>Anne Ostenfeld <i>et al.</i>                                                                          | Systematic review.                     | Denmark, 2024.               | Evaluate the safety of mirtazapine use during pregnancy and breastfeeding.                                      | 41 studies (cohorts, cases, and case reports).                                    | No major risks were found, except for neonatal adaptation syndrome; limited data on breastfeeding.                                                 |
| A comprehensive review on non-clinical methods to study transfer of medication into breast milk – Conception project.<br>Nina Nauwelaerts <i>et al.</i>                                   | Narrative review.                      | Belgium, 2021.               | Review non-clinical methods (in vitro, in vivo, in silico) for studying the transfer of drugs into breast milk. | Literature review, without direct sampling.                                       | Nonclinical methods offer viable alternatives for predicting infant exposure to drugs, highlighting the usefulness of PBPK models.                 |
| Lactancia materna y alojamiento en el abordaje del síndrome de abstinencia neonatal.<br>Paula Baeza-Gozalo <i>et al.</i>                                                                  | Overview review.                       | Spain, 2023.                 | Analyze the impact of breastfeeding and rooming-in on the management of neonatal abstinence syndrome.           | 11 studies included; 3,405 newborns in total.                                     | Breastfeeding and rooming-in reduce the length of hospitalization and the need for pharmacological treatment in newborns with withdrawal syndrome. |
| Glycyrrhizic Acid Nanoparticles Subside the Activity of Methicillin-Resistant <i>Staphylococcus aureus</i> by Suppressing PBP2a.<br>Patricia Rijo <i>et al.</i>                           | Experimental study.                    | Portugal/Jordan/Egypt, 2024. | Investigate the antibacterial effect of glycyrrhizic acid nanoparticles against MRSA.                           | Laboratory tests with <i>Staphylococcus aureus</i> and MRSA cultures.             | Nanoparticles significantly reduced the expression of the PBP2a gene in MRSA, demonstrating strong bactericidal activity.                          |
| Drug Safety During Breastfeeding: A Comparative Analysis of FDA Adverse Event Reports and LactMed®.<br>Hülya Tezel Yalçın <i>et al.</i>                                                   | Comparative database study.            | Turkey/Belgium, 2024.        | Compare reports of adverse events during breastfeeding between the FAERS database and the LactMed® database.    | 2628 reports of adverse events in FAERS.                                          | FAERS is useful for identifying potential adverse events during lactation, while LactMed® provides more specific guidance.                         |
| Prediction of drug concentrations in milk during breastfeeding integrating predictive algorithms within a physiologically-based pharmacokinetic model.<br>Khaled Abduljalil <i>et al.</i> | Pharmacokinetic modeling study (PBPK). | United Kingdom, 2021.        | Develop a PBPK model to predict drug concentrations in breast milk.                                             | Modeling for compounds such as acetaminophen, alprazolam, caffeine, and digoxin.  | The model effectively predicted infant exposure to drugs through milk, with good correlation with observed data.                                   |
| Informing the Risk Assessment Related to Lactation and Drug Exposure: A Physiologically Based Pharmacokinetic Lactation Model for Pregabalin.<br>Cameron Humerickhouse <i>et al.</i>      | Pharmacokinetic modeling study (PBPK). | USA, 2024.                   | Expand the application of PBPK models to predict exposure to pregabalin via breast milk.                        | Modeling with data from 10 lactating women and pediatric data.                    | The model estimated a relative infant dose of 7% of the maternal dose, which is considered safe for infants.                                       |

## Discussion

The main points covered in this narrative review include: physiological changes during breastfeeding and their impact on pharmacology; changes in the metabolism and elimination of drugs during this period; the transfer of drugs through breast milk and the factors that influence the amount transmitted to the infant; the classification of drugs according to their safety during breastfeeding; drugs considered permissible in this context; and, finally, the main clinical considerations when prescribing drugs to women who are breastfeeding.

### Physiological changes during breastfeeding and their impact on pharmacology

Breastfeeding is a crucial stage in the lives of both mother and child, during which important physiological changes occur in women that affect various organ systems. These changes are not only fundamental to milk production but also have a significant impact on the pharmacokinetics of drugs<sup>(15)</sup>. In other words, the way the body absorbs, distributes, metabolizes, and eliminates drugs is altered due to the physiological changes that occur during this period. These changes can have repercussions on both the efficacy and safety of pharmacological treatments administered to lactating women<sup>(10)</sup>.

The impact of these physiological changes not only affects the treatment of the mother's medical conditions but also has implications for the safety of the infant<sup>(4)</sup>. Many drugs are excreted in breast milk, and their transfer through breast milk can have potentially harmful effects on the baby<sup>(12)</sup>. It is therefore essential that healthcare professionals carefully consider the pharmacokinetics of drugs and possible drug interactions when prescribing treatments to breastfeeding women<sup>(13)</sup>.

In addition, close monitoring of drug levels in the mother and infant, together with adequate monitoring of adverse effects, is crucial to ensure safe therapeutic treatment during breastfeeding<sup>(15)</sup>.

### Changes in metabolism and elimination of drugs during breastfeeding

One of the main physiological changes affecting the pharmacokinetics of drugs is the modification of the glomerular filtration rate<sup>(11)</sup>. During breastfeeding, the glomerular filtration rate tends to increase due to increased blood volume and greater fluid retention in the mother's body<sup>(19)</sup>. This phenomenon causes an increase in the renal elimination of many drugs, which can reduce the plasma concentration of some drugs in the mother's body<sup>(20)</sup>. As a result, a decrease in the effectiveness of certain treatments may be observed, as the drugs are eliminated more quickly than expected. This change in renal elimination may also influence the dosage required to maintain adequate therapeutic levels in the mother, which should be carefully monitored by healthcare professionals<sup>(19)</sup>.

In addition to changes in kidney function, liver enzyme activity also changes during breastfeeding. The liver is the main organ responsible for metabolizing most drugs, and variations in liver enzyme activity can influence how drugs are processed in the body<sup>(12)</sup>. Specifically, it has been observed that the activity of some enzymes in the cytochrome P450 system, which are crucial for the metabolism of a wide range of drugs, may decrease in lactating women<sup>(13)</sup>. This reduction in liver enzyme activity can cause a prolongation of the half-life of certain drugs, which increases their plasma concentration and may raise the risk of adverse effects or toxicity<sup>(15)</sup>.

Another relevant aspect is the volume of distribution of drugs, which can be altered during breastfeeding due to changes in the mother's body composition<sup>(11)</sup>. During this period, women experience an increase in extracellular fluid volume and a redistribution of fluids, which can modify how drugs are distributed in different tissues of the body<sup>(12)</sup>. As a result, some drugs may have a higher distribution volume, which may dilute their plasma concentration and affect their therapeutic efficacy<sup>(20)</sup>. On the other hand, highly lipophilic drugs (with an affinity for fats) may accumulate in adipose tissue, which may prolong their release into the mother's body.

The combination of these factors—an increase in glomerular filtration rate, decreased activity of certain liver enzymes, and changes in distribution volume—has a direct impact on the pharmacokinetics of drugs administered during breastfeeding<sup>(13)</sup>. These changes make lactating women more susceptible to variations in drug efficacy and safety, which underscores the need to adjust doses and choice of drugs to avoid adverse effects in the mother or infant.

#### Transfer of drugs through breast milk and factors influencing the amount transferred to the baby

The transfer of drugs into breast milk is a complex process that depends on multiple physiological and pharmacokinetic factors. These factors determine not only whether a drug will reach the milk, but also the amount that will be transmitted to the infant, which affects their exposure and, consequently, the risk of adverse effects<sup>(21)</sup>.

Next, we present Table 2 according to the pharmacological categories of risk in breastfeeding according to Thomas W. Hale, adapted by Peña<sup>(18)</sup>.

**Table 2: Categorias farmacológicas de risco na amamentação segundo Thomas W. Hale.**

| Breastfeeding risk category | Description and implications for the use of medications during breastfeeding                                                                                                                                                                                                                                                                                                                                                                      |
|-----------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>L1</b>                   | <b>Maximum safety/Compatibility:</b> Medication that has been taken by a large number of breastfeeding mothers without any increase in adverse effects on infants being observed. Controlled studies in breastfeeding women show no risk to the baby, and the possibility of harm to the infant is remote or the product is not bioavailable orally in infants.                                                                                   |
| <b>L2</b>                   | <b>Safe/Probably compatible:</b> Medication that has been studied in a limited number of breastfeeding women without any increase in adverse effects in infants being observed; and/or evidence of a probable risk associated with the use of this medication by a breastfeeding woman is remote.                                                                                                                                                 |
| <b>L3</b>                   | <b>Moderately safe/Probably compatible:</b> There are no controlled studies in breastfeeding women, however, the risk of adverse effects in the infant is possible; or controlled studies show only minimal and non-threatening adverse effects. They should only be administered if the potential benefit justifies the potential risk to the infant. (New drugs that do not have published data are automatically classified in this category). |
| <b>L4</b>                   | <b>Possibly dangerous/Potentially dangerous:</b> There is positive evidence of risk to a breastfed baby or to breast milk production, but the benefits of use may be acceptable despite the risk to the infant.                                                                                                                                                                                                                                   |
| <b>L5</b>                   | <b>Contraindicated/Dangerous:</b> Studies in breastfeeding mothers have shown that there is a significant and documented risk to the infant based on human experience, or it is a drug with a high risk of causing significant harm to the infant. The risk of using the drug in breastfeeding women clearly outweighs any possible benefit of breastfeeding. The drug is contraindicated.                                                        |

Medications can enter breast milk through various mechanisms, such as passive diffusion, active transport, and lipid co-transport<sup>(13)</sup>. The most relevant factors influencing the amount of drug transmitted to the baby are detailed below.

#### Fat solubility

One of the most decisive factors in the transfer of a drug into breast milk is its fat solubility<sup>(13)</sup>. Lipophilic, or fat-soluble, drugs have a greater affinity for breast milk, as it contains a considerable lipid fraction<sup>(4)</sup>. Since mammary epithelial cells are mainly composed of lipid membranes, lipophilic drugs can more easily cross cell barriers and be deposited in breast milk<sup>(15)</sup>.

This means that drugs with high lipid solubility tend to concentrate more in breast milk than water-soluble drugs<sup>(20)</sup>. Examples of lipophilic drugs include some analgesics, antidepressants (Table 3), and antipsychotics (Table 4), the tables presented were adapted from Villalobos<sup>(8)</sup>, it should be noted that these drugs can be transferred in significant amounts to breast milk<sup>(18)</sup>. Therefore, when prescribing medications to nursing mothers, the fat solubility of the drug should be carefully evaluated to predict its possible transfer to the baby and the associated risks, especially in antipsychotics<sup>(4)</sup>.

Table 3: Classification of antidepressants.

| Selective serotonin reuptake inhibitors | Breastfeeding risk category      |
|-----------------------------------------|----------------------------------|
| Citalopram (Celexa)                     | L3                               |
| Escitalopram (Lexapro)                  | L3 older children                |
| Fluoxetine (Prozac)                     | L2 older children<br>L3 neonates |
| Fluvoxamina (Luvox)                     | L2                               |
| Paroxetina (Paxil)                      | L2                               |
| Sertralina (Zoloft)                     | L2                               |
| <b>Other antidepressants</b>            |                                  |
| Bupropion (Wellbutrin)                  | L3                               |
| Duloxetina (Cymbalta)                   | NA                               |
| Mirtazapina (Remeron)                   | L3                               |
| Nefazodona (Serzone)                    | L4                               |
| Trazodona (Desyrel)                     | L2                               |
| Venlafaxina (Effexor)                   | L3                               |

Table 4: Classification for antipsychotics.

| Antipsychotics              | Breastfeeding risk category |
|-----------------------------|-----------------------------|
| Aripiprazol (Ablify)        | L3                          |
| Clorpromazina (Thorazine)   | L3                          |
| Clozapina (Clozaril)        | L3                          |
| Flufenazina (Prolixin)      | L3                          |
| Haloperidol (Haldol)        | L2                          |
| Loxapina (Loxitane)         | L4                          |
| Olanzapina (Zyprexa)        | L2                          |
| Perfenazina (Trilafon)      | NA                          |
| Pimozida (Orap)             | L4                          |
| Quetiapina (Seroquel)       | L4                          |
| Risperidona (Risperdal)     | L3                          |
| Tioridazina (Mellaril)      | L4                          |
| Tiothixena (Navane)         | L4                          |
| Trifluoperazina (Stelazine) | NA                          |
| Ziprasidona (Geodon)        | L4                          |

### Molecular weight

The molecular weight of a drug also plays a crucial role in its ability to cross the cell membranes of the mammary glands and reach the milk<sup>(15)</sup>. Drugs with a low molecular weight (generally less than 500 Da) are more likely to pass through mammary epithelial cells and reach breast milk<sup>(20)</sup>. This is because drugs with a lower molecular weight are smaller and easier to diffuse through biological barriers<sup>(1)</sup>.

On the other hand, drugs with a molecular weight greater than 1000 Da tend to have difficulty crossing the cell membrane of the mammary glands, which limits their transfer into milk<sup>(10)</sup>. This factor is especially important for large drugs, such as monoclonal antibodies, which are generally not excreted in significant amounts in breast milk<sup>(13)</sup>. In these cases, the likelihood of the infant being exposed to the drug is considerably lower, although the individual physiology of the mother and the drug in question should always be considered<sup>(15)</sup>.

### Plasma protein binding

Drugs that bind strongly to plasma proteins are less likely to be transferred into breast milk<sup>(20)</sup>. This is because protein-bound molecules cannot easily cross the cell membranes of the mammary glands. Generally, drugs with a high plasma protein binding rate remain in the mother's blood and are distributed less in other tissues, including breast milk<sup>(1)</sup>.

Plasma protein binding is an important mechanism that regulates the amount of drug available for transfer into milk. For example, drugs such as warfarin and digoxin have a strong protein binding, which limits their passage into breast milk<sup>(14)</sup>. In contrast, drugs with low plasma protein affinity are more freely distributed to tissues, including milk, and therefore may pose a greater risk to the infant<sup>(1)</sup>.

This factor also influences the overall pharmacokinetics of the drug in the mother<sup>(15)</sup>. Drugs with low plasma protein binding have a higher free fraction available in the circulation, which may increase their distribution across different compartments, including breast milk<sup>(13)</sup>.

### pKa of the drug

The pKa of a drug refers to the pH at which the drug is in its ionized and non-ionized form<sup>(20)</sup>. The ionization of the drug is a crucial factor because it determines how the drug behaves in the body and, in particular, in the mammary glands<sup>(1)</sup>. Non-ionized drugs (in their uncharged form) have a greater ability to cross cell membranes and reach breast milk<sup>(13)</sup>. On the other hand, ionized drugs have more difficulty crossing biological barriers, which limits their passage into breast milk<sup>(14)</sup>.

Breast milk has a slightly acidic pH (around 7.0-7.2), which influences the ionization of acidic and basic drugs<sup>(1)</sup>. In general, acidic drugs (low pKa) tend to accumulate in breast milk due to the difference in pH between plasma and milk<sup>(20)</sup>. Similarly, basic drugs (high pKa) are more likely to remain in the mother's blood due to the low concentration of protons in milk<sup>(14)</sup>.

Therefore, the pKa of a drug can directly affect its accumulation in breast milk and the infant's exposure. This is a critical aspect to consider, especially when administering drugs with a pKa close to the pH of breast milk, as accumulation may be greater, increasing the risk of toxicity in the infant<sup>(14)</sup>.

### Additional factors affecting pharmacokinetics during breastfeeding

In addition to physiological changes in the mother that affect the pharmacokinetics of drugs during breastfeeding, there are other important factors that can influence drug transfer and elimination<sup>(13)</sup>. These additional factors affect not only the pharmacokinetics in the mother, but also in the infant, which has direct implications for the safety and efficacy of pharmacological treatments administered during this period<sup>(15)</sup>. Some of the most relevant determinants are described below:

#### *Infant age*

The age of the infant is a crucial factor influencing the pharmacokinetics of drugs during breastfeeding<sup>(13)</sup>. Newborns and infants under two months of age have significantly lower metabolic capacity compared to older children or adults, as their hepatic and renal enzyme systems are still developing<sup>(20)</sup>. This im-

maturity in elimination and metabolism mechanisms can lead to greater exposure of infants to drugs that are excreted in breast milk<sup>(15)</sup>.

In the first few months of life, babies' liver and kidney function is not yet fully mature, which limits their ability to metabolize and eliminate drugs efficiently<sup>(10)</sup>. As a result, drugs present in breast milk may remain in the infant's body longer, increasing the risk of side effects or toxicity<sup>(20)</sup>. In addition, some drugs may accumulate in the infant's tissues due to their reduced ability to eliminate substances, highlighting the importance of adjusting maternal drug doses and considering the infant's age when prescribing treatments<sup>(4)</sup>.

#### *Frequency and duration of breastfeeding*

The frequency and duration of breastfeeding are also determining factors in the infant's exposure to drugs present in breast milk<sup>(11)</sup>. The amount of milk a baby drinks varies throughout the day, depending on the frequency of feedings and the amount of milk produced by the mother during each breastfeeding session<sup>(4)</sup>. This is important because the drugs found in breast milk are transferred to the infant in amounts that depend on the plasma concentration of the drug in the mother and the amount of milk the baby consumes<sup>(20)</sup>.

If the mother takes a drug with a long half-life and the infant consumes a large amount of milk at frequent intervals, exposure to the drug may be higher, which would increase the risk of adverse effects in the baby. On the other hand, if the mother administers a drug whose concentration in milk decreases rapidly or if the frequency of feedings is low, the amount of drug the infant receives may be lower, thus reducing the risk of adverse effects<sup>(11)</sup>.

Therefore, it is important for healthcare professionals to consider not only the dose and type of medication administered to the mother, but also the baby's breastfeeding pattern<sup>(10)</sup>. Appropriate adjustment of pharmacological treatment based on the frequency and duration of breastfeeding can minimize risks and optimize safety for both the mother and the infant<sup>(15)</sup>.

### *Nutritional status and health of the mother*

The nutritional status and overall health of the mother play an important role in the pharmacokinetics of drugs during breastfeeding<sup>(12)</sup>. Factors such as malnutrition, liver or kidney disease can significantly affect the metabolism and excretion of drugs<sup>(13)</sup>. In cases of malnutrition, liver function may be impaired, which would alter the metabolism of drugs and potentially increase their plasma concentrations in the mother<sup>(20)</sup>. This, in turn, could increase the amount of drug transferred to breast milk, raising the risk of side effects in the infant<sup>(23)</sup>.

In addition, in women with preexisting liver or kidney disease, the ability to metabolize and eliminate drugs may be reduced<sup>(1)</sup>. This can result in an accumulation of drugs in the mother's body, with the possibility that larger amounts of the drug will be excreted in breast milk<sup>(19)</sup>. Changes in the passage of drugs into breast milk can have adverse effects on infants, especially those with less mature metabolic systems<sup>(11)</sup>. Mothers with liver or kidney disease should be carefully monitored, and in many cases, drug dosages should be adjusted to prevent excessive transfer into milk and protect the health of the infant<sup>(15)</sup>.

Also, adequate nutritional status is crucial for maintaining optimal function of the mother's enzyme systems, which in turn can influence how drugs are processed and eliminated<sup>(12)</sup>. Nutritional deficiencies can affect the production of liver enzymes essential for drug metabolism, thereby altering the pharmacokinetics of drugs<sup>(13)</sup>.

There are other additional factors that can also influence the pharmacokinetics of drugs during breastfeeding<sup>(13)</sup>. Factors such as the mother's general health, age, body weight, consumption of alcohol, tobacco, or other substances, as well as the presence of other medical conditions, can modify the absorption, distribution, metabolism, and elimination of drugs<sup>(15)</sup>. Psychological factors, such as stress or fatigue, can also influence the mother's body's ability to metabolize and excrete drugs efficiently. Together, these factors highlight the complexity of pharmacokinetics in breastfeeding and the need for an individualized approach to prescribing medications to lactating women<sup>(13)</sup>. Healthcare professionals should consider a

number of variables when making therapeutic decisions, taking into account both the mother's health and the infant's safety<sup>(11)</sup>. For example, some drugs such as sedatives or certain antidepressants can be transferred into breast milk and have sedative effects on the infant, which can interfere with their ability to feed or breathe properly. Similarly, medications that can alter the baby's gut microbiota, such as certain broad-spectrum antibiotics, should be used with caution and under supervision<sup>(7)</sup>.

### *Classification of drugs according to their safety during breastfeeding*

The safety of drugs during breastfeeding is a crucial aspect that must be considered to protect both the mother and the infant. According to APILAM (Association for the Promotion and Scientific and Cultural Research of Breastfeeding) (2025)<sup>(3)</sup> of the following e-lactancia application, it is possible to verify and analyze the influence and safety of each drug during the breastfeeding period. This tool is an essential resource for supporting evidence-based clinical decision-making, promoting the protection of maternal and child health. As many drugs are excreted in breast milk, it is essential to be aware of their possible effects and risks<sup>(22)</sup>. A key aspect of prescribing drugs during breastfeeding is to avoid those that have documented adverse effects in infants<sup>(11)</sup>. There are several medications that can cause serious adverse reactions in babies, such as excessive sedation, respiratory problems, effects on development, or even toxicity. Therefore, it is important to review clinical guidelines and available medical literature to identify those medications that pose risks to the health of the infant<sup>(6)</sup>. In general, drugs are classified according to their safety during breastfeeding, with those that are well tolerated by infants and have a low risk of adverse effects being considered safe for use<sup>(15)</sup>. Below are some of the most commonly used drug groups during breastfeeding, along with their safety profile<sup>(15)</sup>.

### Medications permitted during breastfeeding

#### *Pain relievers and fever reducers*

Paracetamol and ibuprofen are two of the most widely used and recommended analgesics and antipyretics during breastfeeding<sup>(15)</sup>. These drugs are characterized by low concentrations in breast milk, which minimizes the infant's exposure to them<sup>(10)</sup>. Several studies have shown that both paracetamol and ibuprofen have a favorable safety profile for infants, given that their concentrations in milk are minimal and there is no evidence that they have a negative impact on the baby's development or health<sup>(4)</sup>.

According to the Departamento de Salud del Gobierno Vasco<sup>(15)</sup> (Table 5), paracetamol, which is known for its analgesic and antipyretic properties, is considered safe for use by both mothers and infants, even at therapeutic doses<sup>(5)</sup>. Ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), is also classified as safe due to its low transfer to breast milk and low risk of toxicity<sup>(6)</sup>. However, as with all medications, it is recommended that these drugs be used sparingly and under medical supervision, especially if the mother requires treatment for prolonged periods<sup>(5)</sup>.

It is important to keep in mind that, although both drugs are safe for the infant, NSAIDs such as ibuprofen should be used with caution in mothers with a history of gastric ulcers or kidney problems, as they may cause adverse effects in the mother<sup>(5)</sup>.

#### *Antibiotics*

Antibiotics are an important category of drugs that may be necessary during breastfeeding to treat infections<sup>(15)</sup>. Drugs such as amoxicillin, cephalixin, listed in Table 5, and erythromycin have been extensively studied and classified as safe during breastfeeding<sup>(10)</sup>. These antibiotics have low excretion in breast milk, which reduces the risk of exposure of the infant to significant concentrations of these drugs<sup>(7)</sup>. In addition, these drugs have not been found to have significant adverse effects on the development or health of the infant, making them viable options for treating infections in the mother without compromising the safety of the baby<sup>(4)</sup>.

However, some antibiotics, especially broad-spectrum ones, can alter the infant's gut microbiota<sup>(7)</sup>. This can predispose the infant to digestive problems or alter their bacterial flora, which, although not usually a serious risk, may require additional monitoring, especially in prolonged treatments<sup>(10)</sup>. In such cases, it is recommended to closely monitor the infant's progress and consider alternatives or adjustments to the treatment if necessary<sup>(4)</sup>.

It is essential that healthcare professionals follow current recommendations on the use of antibiotics during breastfeeding and avoid administering drugs that may have known adverse effects on infant health or breast milk production<sup>(15)</sup>.

#### *Antiemetics*

Antiemetics are medications used to treat nausea and vomiting, which may also be necessary for some breastfeeding mothers<sup>(11)</sup>. According to the Departamento de Salud del Gobierno Vasco<sup>(15)</sup> (Table 6), drugs such as metoclopramide and ondansetron are generally considered safe during breastfeeding, as their excretion in breast milk is minimal and no significant adverse effects on infants have been reported<sup>(8)</sup>.

Metoclopramide is especially effective in treating nausea and vomiting and is commonly used in breastfeeding women<sup>(10)</sup>. However, one aspect to consider is that metoclopramide can increase levels of prolactin, the hormone responsible for milk production<sup>(15)</sup>. This increase in prolactin can influence the amount of breast milk produced, so it is important that mothers are monitored if they use this medication for a prolonged period<sup>(15)</sup>.

On the other hand, ondansetron, a widely used antiemetic drug, does not present this risk associated with prolactin, making it a safer option for mothers who need treatment for nausea and vomiting without compromising milk production<sup>(11)</sup>.

Table 5: Analgesics and Antibiotics.

| Drug               | Comment                                                                   | Compatibility with breastfeeding                 |
|--------------------|---------------------------------------------------------------------------|--------------------------------------------------|
| <b>Painkillers</b> |                                                                           |                                                  |
| Paracetamol        | It is a commonly used pain reliever, considered safe.                     | Compatible, does not pass in large quantities.   |
| Ibuprofen          | It is a nonsteroidal anti-inflammatory drug (NSAID) used to relieve pain. | Compatible with normal doses and short duration. |
| Codeine            | An opioid analgesic used for moderate to severe pain.                     | Caution, may cause drowsiness in infants         |
| Diclofenac         | NSAID, used for muscle or joint pain.                                     | Compatible, but caution is advised.              |
| <b>Antibiotics</b> |                                                                           |                                                  |
| Amoxicillin        | It is a broad-spectrum antibiotic used in common infections.              | Compatible, excretes in low amounts.             |
| Cephalexin         | An antibiotic from the cephalosporin family.                              | Compatible, excretes in low quantities.          |
| Ciprofloxacin      | An antibiotic belonging to the fluoroquinolone class.                     | Avoid during breastfeeding.                      |
| Clindamycin        | Antibiotic used in infections caused by anaerobic bacteria.               | Compatible, minimal excretion in milk.           |

### Medicines for chronic diseases

Women with chronic conditions such as hypertension or diabetes may need to take medication to manage these conditions while breastfeeding<sup>(15)</sup>. In general, many medications used to treat chronic conditions are safe during breastfeeding, although in some cases it may be necessary to adjust doses or choose alternatives to minimize risks to the infant<sup>(8)</sup>.

Antihypertensive drugs such as labetalol and enalapril are often prescribed to breastfeeding women because they have a low risk of excretion in breast milk and have not been shown to adversely affect the infant<sup>(19)</sup>. However, it is important to note that some antihypertensive drugs can alter the mother's blood pressure, so it is crucial to closely monitor the effects on the mother while the treatment is being adjusted<sup>(4)</sup>.

As for antidiabetic drugs, insulin and metformin are generally considered safe options during breastfeeding<sup>(15)</sup>. Insulin does not pass into breast milk in significant amounts, making it a safe option for controlling diabetes in mothers without risk to the infant<sup>(19)</sup>. Metformin, a drug used to treat type 2 diabetes, is also considered safe during breastfeeding, although its use should be supervised by a doctor, especially in mothers with kidney failure or liver function changes<sup>(15)</sup>.

However, some medications for cardiovascular and endocrine diseases may require dosage adjustments or additional monitoring to avoid possible adverse effects on the infant<sup>(10)</sup>. Therefore, it is essential that pharmacological treatment in women with chronic diseases, and in the opinion of the Departamento de Salud del Gobierno Vasco<sup>(15)</sup> (Table 6), be managed on an individualized basis and with adequate monitoring<sup>(19)</sup>.

Table 6: Antiemetics and Drugs for chronic diseases.

| Drug                                  | Comment                                                        | Compatibility with breastfeeding                   |
|---------------------------------------|----------------------------------------------------------------|----------------------------------------------------|
| <b>Antiemetics</b>                    |                                                                |                                                    |
| Metoclopramide                        | Used for nausea and vomiting, including during pregnancy.      | Compatible in low doses and for short periods.     |
| Ondansetron                           | Antiemetic used to prevent nausea, especially in chemotherapy. | Compatible, minimal excretion.                     |
| Domperidone                           | Used for nausea and as a galactagogue in some cases.           | Compatible, but use with caution is recommended.   |
| <b>Medicines for chronic diseases</b> |                                                                |                                                    |
| Hypertension: Enalapril               | An ACE inhibitor to control hypertension.                      | Compatible, excreted in low quantities.            |
| Diabetes: Metformin                   | Used to control blood glucose in type 2 diabetes.              | Compatible, passes in small quantities.            |
| Asthma: Salbutamol                    | A bronchodilator is used in the treatment of asthma.           | Compatible, excreted in small amounts.             |
| Arthritis: Methotrexate               | Used in autoimmune diseases such as rheumatoid arthritis.      | Avoid it, as it may affect the infant.             |
| Epilepsy: Valproic acid               | Anticonvulsant medication used for epilepsy.                   | Avoid, as it passes in large quantities into milk. |

### Clinical considerations in prescribing drugs during breastfeeding

Prescribing medications to breastfeeding mothers should be done with a careful approach, considering both the health of the mother and the infant<sup>(20)</sup>. It is crucial that healthcare professionals follow a set of clinical considerations to ensure that treatment does not endanger the infant while appropriately addressing the mother's medical condition<sup>(5)</sup>. The following guidelines should be considered when choosing and administering medications during breastfeeding:

*Assess the risk-benefit balance for the mother and infant*

The first step in prescribing medication during breastfeeding is to conduct a thorough assessment of the drug's risks and benefits for both mother and infant. This involves a detailed analysis of the mother's medical condition, the potential risk to the infant due to drug exposure through breast milk, and the severity of the disease or disorder being treated. In some cases, the benefit of treating a serious condition in the mother with a medication may outweigh the potential risk to the infant, while in others, it may be necessary to seek safer therapeutic alternatives<sup>(11)</sup>.

The healthcare professional should consider the availability of alternative treatments that are equally effective and pose a lower risk to the infant. For example, if a medication with a limited safety profile during breastfeeding is necessary to treat a serious condition in the mother, the decision may be made to adjust the treatment to reduce exposure to the infant or switch to another medication with a safer profile for the infant<sup>(23)</sup>.

*Choose drugs with low excretion in breast milk*

A crucial factor when choosing a medication for a nursing mother is the amount of the drug excreted in breast milk<sup>(15)</sup>. Medications with low excretion in breast milk are preferable because their transfer to the infant will be minimal, reducing the risk of adverse effects<sup>(1)</sup>. Medications with a high affinity for plasma proteins or those that are highly metabolized in the mother's body generally have lower transfer into breast milk<sup>(11)</sup>.

To ensure infant safety, medications with a short half-life and that do not accumulate in breast milk over time should be chosen<sup>(5)</sup>. Antibiotics such as amoxicillin and cephalexin are examples of medications that have low excretion in breast milk and are considered safe for use during breastfeeding<sup>(1)</sup>. Furthermore, analgesics and antipyretics such as acetaminophen and ibuprofen also have low concentrations in milk and are considered safe for both mother and baby<sup>(5)</sup>.

It is essential that healthcare professionals use up-to-date, evidence-based information to select appropriate medications that minimize infant exposure<sup>(5)</sup>.

*Adjust the dose or frequency of administration to minimize infant exposure*

In some cases, it is not possible to completely avoid infant exposure to a medication needed to treat a maternal condition<sup>(5)</sup>. In these cases, adjusting the dose or frequency of administration is recommended to minimize the amount of drug reaching the infant through breast milk<sup>(11)</sup>. This may include reducing the dose of the medication, modifying the dosing frequency, or using dosage forms that release the drug more slowly, which may reduce infant exposure<sup>(1)</sup>.

Additionally, if the medication has a long half-life, you may choose to administer it soon after breastfeeding to maximize the time between medication intake and the next feeding, which will reduce the amount of medication present in breast milk at the time of the next feeding<sup>(12)</sup>.

It is important for breastfeeding mothers to carefully follow their doctor's instructions regarding medication administration and to inform their doctor of any unexpected side effects they may notice in their baby<sup>(11)</sup>.

## Final Considerations

Medication during breastfeeding continues to be a concern for both mothers and healthcare professionals. Throughout this document, it has been demonstrated that, while breastfeeding is essential for the baby's growth and health, it can be safely administered alongside medical treatments, if the necessary precautions are taken.

During this period, a woman's body undergoes a series of physical changes that affect how medications are metabolized. These changes can influence the absorption, distribution, metabolism, and elimination of medications, as well as their effectiveness and the risk of adverse effects for both mother and baby.

Furthermore, not all medications behave the same way. Some transfer more easily into breast milk, while others barely do. Factors such as fat solubility, molecular weight, and how drugs bind to proteins in the blood directly affect this transfer. It's also important

to consider the baby: their age, health status, and feeding frequency can significantly alter their level of exposure to medication.

This study analyzed the use of opioids, which have been a source of great concern in the past. However, by delving deeper into scientific evidence, it becomes clear that many of these concerns stem from isolated cases and do not reflect a real risk when opioids are prescribed correctly and under professional supervision.

From this analysis, it can be concluded that the key is not to indiscriminately avoid medications, but rather to consider each case individually. There are many medications that are safe to use during breastfeeding, as long as they are carefully selected, doses are adjusted as necessary, and ongoing monitoring is maintained.

In short, it's not about choosing between the health of the mother and the health of the baby. The goal is to achieve a balance that allows mothers to receive appropriate treatment without compromising breastfeeding or the well-being of their child. To achieve this, it is essential that healthcare professionals are well-trained, have up-to-date information, and offer support to mothers with empathy and rigor. Caring for the mother also means caring for the baby.

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