REVISTA BRASILEIRA DE MEDICINA DE FAMÍLIA E COMUNIDADE
RBMFC

www.rbmfc.org.br
ISSN 2179-7994

Research Article

Instructions in package inserts intended for the use of medicines for dyspepsia and constipation during lactation

Instruções em bulas destinadas ao uso de medicamentos para dispepsia e constipação durante a lactação

Instrucciones en prospectos destinados al uso de medicamentos para la dispepsia y el estreñimiento durante la lactancia

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Abstract

Introduction: The safety and effectiveness of medication use during lactation are concerns for mothers and healthcare professionals. This research analyzes the instructions on the leaflets of medications commonly prescribed for dyspepsia and constipation, which aims to provide essential information to guide therapeutic decisions during this crucial period of motherhood. **Objectives:** To analyze the information in package inserts about contraindications of drugs for dyspepsia and constipation during breastfeeding, verifying whether these are consistent with scientific evidence. **Methods:** Drugs for dyspepsia and constipation were selected according to the Anatomical Therapeutic Chemical (ATC) classification and active registry in Brazil. The presence of contraindications for the use of medications in the health professional's and patient's package inserts was compared with the information in the technical manual of the Ministry of Health, Medications and Mothers' Milk, LactMed, UptoDate, Micromedex, Documento Científico da Sociedade Brasileira de Pediatria and Reprotox. **Results:** No information about use during breastfeeding was found in 20.0 and 24.3% of leaflets for dyspepsia and constipation, respectively. The agreement between the leaflets of medications for dyspepsia and the sources consulted was low (27.2% of the leaflets contraindicated the medication during lactation, while in the sources the percentage of contraindication varied from 0 to 8.3%). In relation to medicines for constipation, 26.3% of the leaflets contraindicated them, while in the sources the percentage ranged from 0 to 4.8%. **Conclusions:** The study pointed out that at least two out of every ten package inserts for dyspepsia and constipation do not provide adequate information on the use of these drugs in infants, and also shows low concordance between the text of the package inserts and the reference sources regarding compatibility of the drug with breastfeeding.

Keywords: Breastfeeding; Mmedicine package inserts; Gastrointestinal Agents; Dyspepsia; Constipation.

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Danillo Alencar Roseno
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Funding:
During the execution of this study, Tatiana da Silva Sempé received a scientific initiation grant Process n. 128419/2022-9.
Ethical approval:
not applicable.
TCLE:
not applicable.
Procedência:
not commissioned.
Peer review:
external.
Received: 05/05/2023.
Approved: 03/06/2024.
Associate editor:
Monique Bourget.

How to cite: Roseno DA, Sempé TS, Schmalfuss TO, Giugliani C, Dal Pizzol TS. Instructions in package inserts intended for the use of medicines for dyspepsia and constipation during lactation. Rev Bras Med Fam Comunidade. 2024;19(46):3758. https://doi.org/10.5712/rbmfc19(46)3758

Resumo

Introdução: A segurança e eficácia do uso de medicamentos durante a lactação são preocupações para mães e profissionais de saúde. Esta pesquisa analisa as orientações das bulas de medicamentos comumente prescritos para dispepsia e constipação, que visa fornecer informações essenciais para orientar as decisões terapêuticas durante esse período crucial da maternidade. **Objetivos:** Analisar as informações das bulas sobre contraindicações de medicamentos para dispepsia e constipação durante a amamentação, verificando se estão de acordo com as evidências científicas. **Métodos:** Medicamentos para dispepsia e constipação foram selecionados de acordo com a classificação da Anatomical Therapeutic Chemical (ATC) e o registro ativo no Brasil. A presença de contraindicações para o uso de medicamentos nas bulas do profissional de saúde e do paciente foi comparada com as informações contidas no manual técnico do Ministério da Saúde, Medicamentos e Leite Materno, LactMed, UptoDate, Micromedex, Documento Científico da Sociedade Brasileira de Pediatria e Reprotox. **Resultados:** Nenhuma informação sobre o uso durante a amamentação foi encontrada em 20,0 e 24,3% das bulas para dispepsia e constipação, respectivamente. A concordância entre as bulas dos medicamentos para dispepsia e as fontes consultadas foi baixa (27,2% das bulas contraindicavam o medicamento na lactação, enquanto nas fontes o percentual de contraindicação variou de 0 a 8,3%). Com relação a medicamentos para constipação, 26,3% das bulas os contraindicavam, enquanto nas fontes o percentual variou de 0 a 4,8%. **Conclusões:** O estudo mostrou que pelo menos duas em cada dez bulas para dispepsia e constipação não fornecem informações adequadas sobre o uso desses medicamentos em lactentes, e também que houve baixa concordância entre o texto das bulas e as fontes de referência quanto à compatibilidade do medicamento com a amamentação.

Palavras-chave: Amamentação; Bulas de medicamentos; Agentes gastrointestinais; Dispepsia; Constipação intestinal.

Resumen

Introducción: La seguridad y eficacia del uso de medicamentos durante la lactancia son preocupaciones para las madres y los profesionales de la salud. Esta investigación analiza las instrucciones contenidas en los prospectos de medicamentos comúnmente recetados para la dispepsia y el estreñimiento, con el objetivo de proporcionar información esencial para guiar las decisiones terapéuticas durante este período crucial de la maternidad. **Objetivos:** Analizar la información contenida en los prospectos sobre las contraindicaciones de los medicamentos para la dispepsia y el estreñimiento durante la lactancia, verificando si estas son consistentes con la evidencia científica. **Métodos:** Se seleccionaron medicamentos para la dispepsia y el estreñimiento de acuerdo con la clasificación ATC y el registro activo en Brasil. Se comparó la presencia de contraindicaciones para el uso de medicamentos en los prospectos del profesional de la salud y del paciente con la información del manual técnico del Ministerio de Salud, Medicamentos y Leche Materna, LactMed, UptoDate, Micromedex, Documento Científico da Sociedade Brasileira de Pediatria y Reprotox. **Resultados:** No se encontró información sobre su uso durante la lactancia en el 20% y el 24,3% de los prospectos para dispepsia y estreñimiento, respectivamente. La concordancia entre los prospectos de los medicamentos para la dispepsia y las fuentes consultadas fue baja (el 27,2% de los prospectos contraindicaba el medicamento durante la lactancia, mientras que en las fuentes el porcentaje de contraindicación variaba del 0% al 8,3%). Con relación a los medicamentos para el estreñimiento, el 26,3% de los prospectos los contraindicaba, mientras que en las fuentes el porcentaje osciló entre el 0% y el 4,8%. **Conclusiones:** El estudio señaló que al menos dos de cada diez prospectos para dispepsia y estreñimiento no brindan información adecuada sobre el uso de estos medicamentos en lactantes, y también muestra la baja concordancia entre el texto de los prospectos y la referencia. fuentes sobre la compatibilidad del fármaco con la lactancia.

Palabras clave: Lactancia materna; Prospectos de medicamentos; Agentes gastrointestinales; Dispepsia; Estreñimiento.

INTRODUCTION

Breastfeeding is considered one of the main strategies for child nutrition in the first years of life, promoting a reduction in infant mortality. The benefits of breastfeeding go beyond its nutritional qualities and reach immunological, cognitive and emotional aspects for the mother and baby.[1-3]

During breastfeeding, medication is often used [4]. Research shows that the drugs used in the management of gastrointestinal disorders are among the most frequent in prescriptions and dispensation for nursing mothers.[4,5] Objective information is opportune to avoid unnecessary discontinuation of a treatment or early weaning, causing harm to the mother and the child.[6]

For ethical reasons, some specific groups have restricted participation in clinical trials, including pregnant and lactating women, which leads to a lack of information that demonstrates the safe and effective use of medicines to guide decision-making by health professionals and consumers.[7]

It is known that the package insert is an information material approved by the Brazilian Health Regulatory Agency (ANVISA) and that it accompanies the medicines in order to help health professionals and consumers use these products safely.[8] However, some authors draw attention to a conflict between information on medication package inserts and scientific evidence on the use of medication during breastfeeding.[9,10]

Thus, the objective of this study was to analyze the information contained in the package inserts on contraindications and/or warnings of medicines for dyspepsia and constipation during breastfeeding, verifying whether these are consistent with scientific evidence.

METHODS

We carried out a descriptive study with a quantitative approach, integrated by qualitative data related to the information extracted from the consulted bibliographic references. The drugs selected for evaluation were those for the treatment of disorders related to gastrointestinal acid disorders and for constipation, which are widely used and easily accessible to patients, without the need to present and/or retain the prescriptions.

The initial list of drugs was obtained from the Anatomical Therapeutic Chemical (ATC/DDD) database of the World Health Organization (WHO), which classifies them into groups and subgroups (https://www.whocc.no/atc_ddd_index/). The groups/subgroups selected were: H2 receptor antagonists (A02BA), proton pump inhibitors (A02BC), other drugs (A02BX), contact laxatives (A06AB), osmotic-acting laxatives (A06AD), and (A06AG) and other constipation medications (A06AX).

From the initial list composed of the medicines identified in the ATC/DDD, we included the medicines that had an active registration with ANVISA, the national body for the regulation and sanitary control of the production and consumption of medicines, which also establishes the model texts of the standard package inserts. For drugs with an active registration, the package inserts for health professionals and patients were extracted from the ANVISA electronic package (https://consultas.anvisa.gov.br/#/bulario/).[11] The identification of drugs with active registrations and extraction of information from the package inserts took place between May and June 2021.

For reference drugs, the list of drugs of interest for this research was obtained from the lists of reference drugs A (drugs that contain a single active pharmaceutical ingredient) and B (drugs that contain two or more active pharmaceutical ingredients in a single pharmaceutical form) (https://www.gov.br/anvisa/pt-br/setorregulado/regularizacao/medicamentos/medicamentos-de-referencia/lista-de medicamentos-de-referencia). Medicines classified in other categories, such as herbal medicines and specific medicines, were extracted the ANVISA virtual page, in the medicines option, applying filters for medicines registered as herbal and specific, in the therapeutic classes analyzed and having a valid registration (https://consultas.anvisa.gov.br/#/medicamentos/).

Those drugs that were not registered in the month/year in which the survey took place and that were absent in at least one bibliographic source used to verify scientific evidence as described below were excluded.

Information about the compatibility of using the drug in breastfeeding was obtained from the ‘contraindications’ and ‘warning and precautions’ sections of the standard health professionals’ package inserts, and, in the patient inserts, from the sections that have the questions “When should I not use this medicine?” and “What should I know before using this medication?,” that are intended to warn about the

risks and restrictions of use, as established by ANVISA Resolution RDC 47.[12] The package inserts were classified as 'yes' when the information clearly contraindicated use during breastfeeding (or indicated discontinuation of breastfeeding while using the drug), and 'no' in other situations.

Package inserts that pointed to the incompatibility of the drug with breastfeeding through phrases such as "one should decide to discontinue breastfeeding or to interrupt the treatment", were classified as 'yes'. In the other situations (compatible use, "avoid taking medication if you are breastfeeding" or risk/benefit assessment), they were classified as 'no'. In the absence of any information that indicated or contraindicated the drugs used by nursing mothers, they were classified in the 'no information' category, pointing out that information on the use of these drugs in breastfeeding was omitted from the text of the package insert.

References consulted in the search for scientific evidence to assess compliance with medication package inserts were: Breastfeeding and Use of Medicines or other Substances (2nd edition); the book *Medications and Mothers' Milk*; the Scientific Document of the Brazilian Society of Pediatrics (SBP); and the LactMed, UptoDate, Micromedex and Reprotox bases. Risk categorization differs between the sources used, as shown in the attached table. The data collection procedures followed the steps illustrated in Figure 1.

The *Breastfeeding and the Use of Medication and Other Substances* manual provides a review of drugs and other substances transferred to breast milk and their possible effects on the infant and/or lactation, with reference to the publications of the American Academy of Pediatrics (AAP), the WHO, and the book *Medications and Mothers' Milk* (2008 edition). It has a three-tier rating system.

The above-mentioned book, by T. W. Hale, features monographs on a wide variety of drugs and natural substances, including relevant pharmacological characteristics, primary research, as well as the AAP classification. It uses a five-point numerical rating system for each drug, with regular updates every two years.

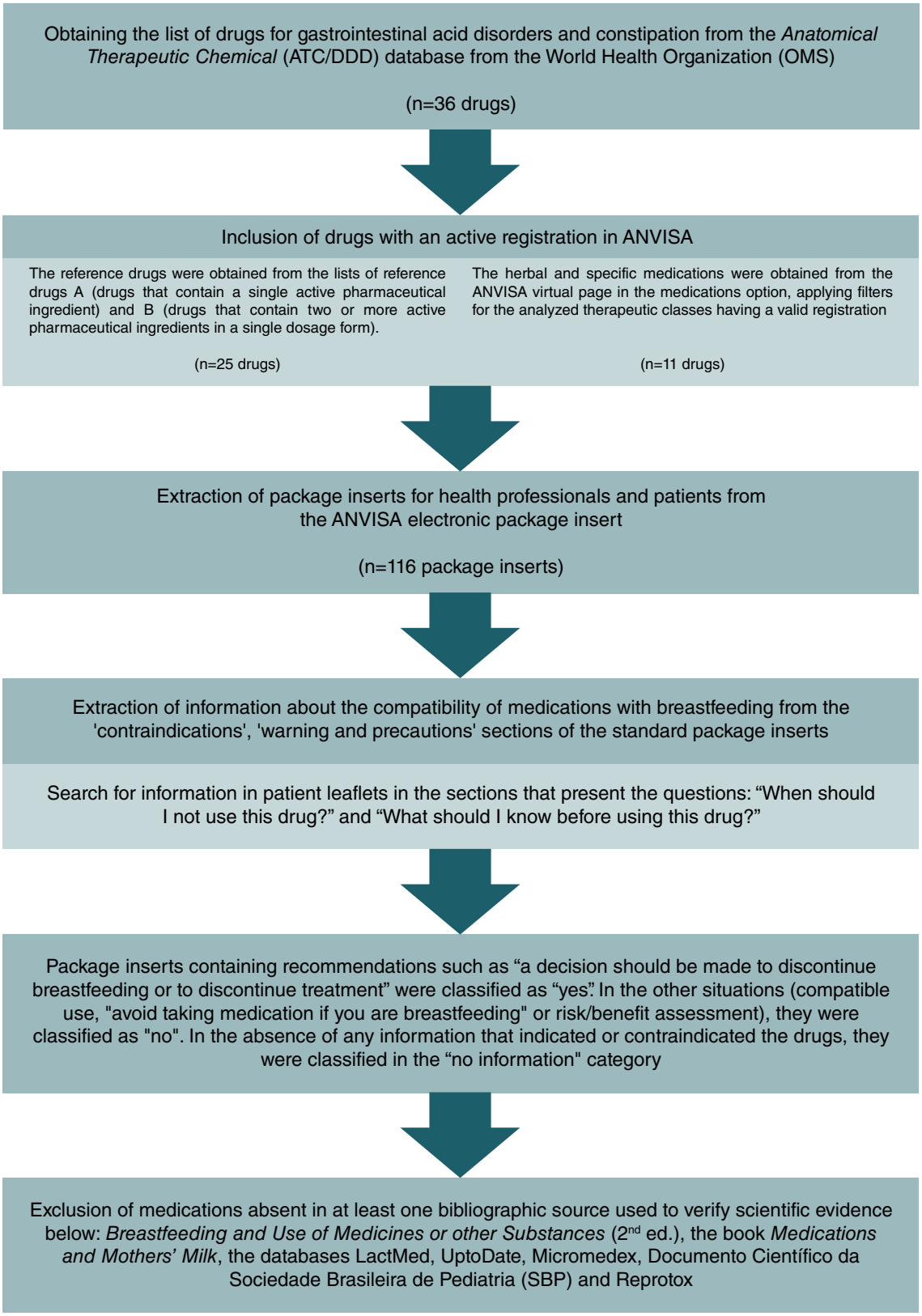
LactMed®, the National Library of Medicine's medication and breastfeeding database, is an online resource created by a panel of experts based on scientific literature, updated monthly. It includes information on drug levels in breast milk, effects on the infant, and effects on breastfeeding and breast milk. It does not present a classification system, but a descriptive summary of the drug use during breastfeeding.

Micromedex® is an online resource consisting of monographs containing indications approved by the Food and Drug Administration (FDA) agency, off-label uses and information on the drug's safety, among other information. It has its own classification on the safety of medication use during breastfeeding, divided into four categories according to available evidence and/or expert consensus. It has an AAP classification.

The scientific committee of the Brazilian Society of Pediatrics (SBP), based on the classification of Hale's book, provides a bibliographic review containing lists of drugs that are compatible and incompatible with breastfeeding.

UptoDate® is an online resource widely used by health professionals, in hospital and outpatient environments, which provides information that facilitates clinical decision-making, through revised scientific content and recommendations that support questions related to clinical practice. It is considered one of the most up-to-date sources, gathering the available evidence to support professionals' decision making, a process which also takes into account the uniqueness of each clinical situation. It does not present a classification system, but rather a descriptive summary of the use of the drug during breastfeeding and recommendations for conduct.

Reprotox® is an online database developed by the Center for Reproductive Toxicology, which is a source of complementary information for physicians, researchers and other healthcare professionals



Source: prepared by the authors (2023).

Figure 1. Flowchart of procedures and steps for data collection in package inserts and bibliographic references with scientific evidence.

on the effects of drugs, chemicals, biologicals and physical agents on reproduction, pregnancy, lactation and development. The tool does not provide a classification system, but a summary of known information about drugs from a review of published studies, with frequent updates as new studies emerge.

Chart 1 below presents the classification of the compatibility of medication use during breastfeeding, according to the bibliographic sources researched. This classification is essential to guide health professionals and breastfeeding women about the risks and benefits of using certain medications during the breastfeeding period.

Data collection was carried out independently by two reviewers. Differences in evaluations of the information were discussed among the reviewers to establish a consensus. If disagreement persisted, the information was assessed by a third reviewer. To assess the consistency of the assessment between reviewers, the Kappa coefficient was calculated to establish the level of agreement between reviewers. The interpretation followed the criteria proposed by Landis and Koch,[13] following this scale: no agreement ($k<0$), poor agreement ($0\leq k\leq 0.19$), reasonable agreement (0.20 to 0.39), moderate agreement ($0.40\leq k\leq 0.59$), substantial agreement ($0.60\leq k\leq 0.79$) and excellent agreement ($0.80\leq k\leq 1.00$). To standardize data collection, a manual was prepared to facilitate data extraction with standardized definitions and terminology.

Descriptive analysis and organization of the database were performed with the Microsoft Office Excel® software, and calculation of the Kappa coefficient was obtained using the Statistical Package for the Social Science (SPSS) software, version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 116 package inserts were analyzed, 79 of drugs for dyspepsia and 37 of drugs for constipation. Agreement between the two reviewers regarding the information in the package inserts analyzed was excellent ($k=0.802$; $p<0.001$). Of the drugs for dyspepsia, 27.2% (n=28) of the inserts contraindicated the drug and 20.0% (n=16) did not provide any information related to lactation. Of the medications for constipation, 26.3% (n=10) of the inserts contraindicated the medication and 24.3% (n=9) had no information about use during breastfeeding.

Graph 1 shows the frequency of contraindication of the use of medications in breastfeeding in the package inserts and in the bibliographic sources. It was found that 27.2% of the drug leaflets for dyspepsia contraindicated use during breastfeeding. In contrast, there was no contraindication in four of the other sources consulted. With regard to medicines for constipation, contraindications were identified in the package inserts in 26.3% of the drugs, while in the bibliographic sources the frequencies varied between 0 and 4.8%.

Table 1 shows the classifications of the drugs for dyspepsia and constipation, according to the package inserts and bibliographic sources. Agreement was observed between the package insert and the sources Lactmed and UptoDate regarding the compatibility of the use of cimetidine during breastfeeding. The Medications and Mothers' Milk sources, the scientific document from the SBP, Micromedex and Reprotox did not contraindicate the use of any of the analyzed drugs. In medicines for constipation, there was complete agreement for non-contraindication between package inserts and sources for most medicines. The drug that showed the highest contraindication agreement between the sources was tegaserod, contraindicated in only one of the seven sources of information.

Chart 1. Classification of the compatibility of medication use during breastfeeding in each of the bibliographic sources researched.

Source of information	Risk classification
Technical manual Breastfeeding and Use of Medicines and Other Substances, Brazil	1. Compatible with breastfeeding: drugs whose use is potentially safe during lactation, as there are no reports of significant pharmacological effects on the infant.
	2. Careful use during breastfeeding: medicines whose use during lactation depends on a risk/benefit assessment. When used, they require clinical and/or laboratory monitoringW of the infant, and should be used for the shortest time and at the lowest possible dose. New drugs whose safety during breastfeeding has not yet been properly documented are in this category.
	3. Contraindicated use during breastfeeding: drugs that require discontinuation of breastfeeding, due to evidence or significant risk of important side effects on the infant.
Medications and Mothers' Milk, United States	L1 Compatible: a drug that has been used by a large number of breastfeeding mothers without any observed increase in adverse effects on the child. Controlled studies in breastfeeding women show no risk or possibility of harm to the child; or the product is not bioavailable for a child.
	L2 Likely Compatible: a drug that has been studied in a limited number of breastfeeding women without an increase in adverse effects on the infant and/or the evidence of risk in the use of this medication by a breastfeeding woman is remote.
	L3 Likely Compatible: there are no controlled studies in breastfeeding women; however, the risk of adverse effects for the breastfed child is possible, or controlled studies show that adverse effects are not serious, only minimal. Medications should only be given if the potential benefit justifies the potential risk to the child. (New drugs that have absolutely no published data are automatically classified in this category, regardless of how safe they may be).
	L4 Possibly Hazardous: there is no evidence of risk to the baby or breast milk production, but the benefits of the use in breastfeeding mothers may be acceptable despite the risk to the child (e.g. if the drug is needed in a life-threatening or serious illness for which safer drugs cannot be used or are ineffective).
	L5 Hazardous: the risk of using the drug in breastfeeding women clearly outweighs any possible benefit of breastfeeding. The drug is contraindicated in women who are breastfeeding a baby.
Brazilian Pediatrics Society Scientific Document, Brazil	1. Compatible: drugs with no reported adverse effects on the infant. Controlled studies in breastfeeding women have shown no risk to children and the possibility of harm to children being breastfed is remote. Also included in this category are drugs with negligible oral bioavailability.
	2. Probably compatible: drugs without controlled studies in nursing mothers. Nevertheless, undesirable effects for infants are possible, or controlled studies show only minimal, non-threatening adverse effects. Drugs should be given only if the benefit justifies the potential risk to the child. New drugs that have absolutely no published data are automatically classified in this category, regardless of how safe they may be.
	3. Possibly Hazardous: there is evidence of risk to the infant or milk production, but their use may be acceptable after assessing the risk-benefit ratio.
	4. Hazardous: studies in nursing mothers have shown that there is a significant and documented risk to infants or the drug has a high risk of causing significant harm to infants. The risk of using the drug clearly outweighs any possible benefit of breastfeeding. Breastfeeding is contraindicated while using the drug.
Micromedex®, United States	1. Risk to the infant cannot be ruled out: available evidence and/or expert consensus is inconclusive or inadequate to determine the risk to the infant when the drug is used during breastfeeding. Weighing the potential benefits of drug treatment against the potential risks before prescribing the drug while breastfeeding is advised.
	2. Risk to the infant has been demonstrated: evidence and/or expert consensus has demonstrated harmful effects on the infant when the drug is used during breastfeeding. An alternative to this drug should be prescribed or patients should be advised to discontinue the drug while breastfeeding.
	3. Risk to the infant is minimal: the level of evidence and/or expert consensus suggests that this drug poses minimal risk to the infant when used during breastfeeding.
	4. Effects on milk are possible: evidence suggests that this drug may alter milk production or composition. If an alternative to this drug is not prescribed, the infant should be monitored for adverse effects and/or adequate milk intake.

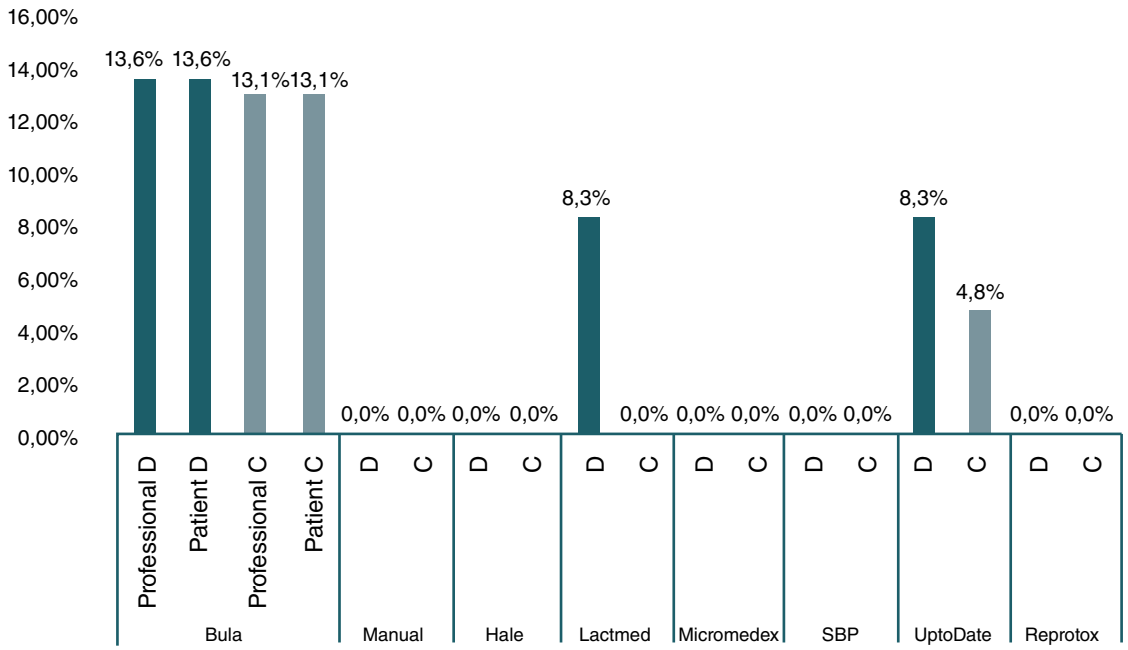
Categories in which the drug was considered contraindicated in breastfeeding were marked in gray; LactMed®, UpToDate® and Reprotox® do not have a rating system.

Table 1. Drugs classification for dyspepsia and constipation present in all sources, as per the contraindication for use during breastfeeding in the package inserts of professionals, patients and bibliographic sources.

Classes	No contraindication in package inserts and all sources	Contraindication in package inserts and bibliographic sources									
	Medication (number of package inserts assessed)*	Medication (number of package inserts assessed)*	Professionals' package insert	Patients' package insert	Manual	Hale	Lactmed	SBP	Micromedex	UptoDate	Reprotox
Dyspepsia	Omeprazole (4), Omeprazole+Clarithromycin+ Amoxicillin (2), Pantoprazole (4), Lansoprazole (4), Sucralfate (2), Citric Acid+Sodium Bicarbonate+ Sodium Carbonate (12), Sodium Bicarbonate+ Calcium Carbonate+ sodium carbonate (2), Calcium carbonate 90%+ aluminum hydroxide+ magnesium hydroxide (2), Calcium carbonate+ aluminum hydroxide+ magnesium hydroxide (4), Dimethicone+aluminum hydroxide gel+magnesium hydroxide magnesium+ simethicone (2), Calcium carbonate+aluminum hydroxide+magnesium hydroxide (6), Sodium bicarbonate+ basic bismuth carbonate+ calcium carbonate+ magnesium carbonate (4), Magaldrate+simethicone (2), Dimethicone+aluminum hydroxide+magnesium hydroxide+magnesium oxide (2)	Cimetidine (4)	✗	✗			✗			✗	
		Famotidine (2)	✗	✗							
		Rabeprazole (2)	✗	✗							
		Esomeprazole (4)	✗	✗							
		Amoxicillin Trihydrate+ Clarithromycin+ Esomeprazole Magnesium Trihydrate (2)	✗	✗							
		Dexlansoprazole (2)	✗	✗							
		Aluminum hydroxide+ magnesium hydroxide+ simethicone (8)	✗a	✗a							
		Dimethicone+ aluminum hydroxide+ magnesium hydroxide (2)	✗b								
Constipation	Bisacodyl (4), Glycerol (10), Sodium Phosphate (2), Lubiprostone (2), Sodium Picosulfate (4), Sorbitol (2), Magnesium Sulfate (2).	Prucalopride (2)	✗	✗							
		Senna alexandrina mill (8)	✗	✗							
		Tegaserod (2)	✗	✗						✗	

a The professionals' and patients' package inserts of only one manufacturer contraindicated the drug in lactation.
b Only the professionals' package insert brought information that contraindicates the drug during lactation.
*116 package inserts were assessed, corresponding to 32 drugs.

Graph 1. Contraindication frequency for the use of medication for dyspepsia and constipation during breastfeeding in package inserts and bibliographic sources.



D: medicine for dyspepsia (blue); C: constipation medication (green).

DISCUSSION

This study aimed to perform an assessment of package inserts and references in the literature, based on up-to-date scientific evidence specializing in medications in lactation. The package inserts help decision making during clinical practice. Moreover, it should be noted that in Brazil it is one of the few official information documents accessible to health professionals and patients. The National Therapeutic Form, another essential official instrument on medicines, has not been updated since 2010.

Furthermore, the MedSUS application was launched by the Ministry of Health in 2014 with the aim of providing information about medicines available in the Brazilian Unified Health System — SUS. It was developed to facilitate access to information about medicines by healthcare professionals and medicine users on mobile devices.[14] However, despite recent updates, this tool contains inaccessible information, which compromises the efficiency of the application and impairs access to essential data for the correct management and use of medicines made available by SUS. The current version presents information on the list (e.g. basic, specialized, strategic component), pharmaceutical form, International Classification of Diseases (CID), documents required for acquisition and where to find them. Information for the correct use of medicines, present in the Brazilian Therapeutic Form monographs, is still unavailable.

It is known that gastrointestinal disorders are common situations in postpartum women, and the drugs for treating these symptoms are mostly over-the-counter, without the need to retain prescriptions.[15] A Dutch study aimed at identifying the prevalence of medication use in breastfeeding women, safety and

influence on the decision to start breastfeeding pointed out that medications for constipation and dyspepsia were included in the medications used by this group.[5]

In our research, we identified inconsistencies between the package inserts analyzed and the references consulted. For every ten medications assessed, considering both dyspepsia and constipation medications, approximately three had a package insert contraindicating their use during breastfeeding. This finding contrasts with the information found in the bibliographic sources. Agreement between the package inserts for dyspepsia drugs and the sources consulted was low: 27.2% of package inserts 335 contraindicated, while in the sources the percentage of contraindication ranged from 0 to 8.3%. Similarly, agreement between the package inserts for constipation medications was low: 26.3% of package inserts contraindicated them, against 0 to 4.8% in the consulted references.

Other studies showed incompleteness of the Brazilian package inserts regarding information on the compatibility of breastfeeding with the use of the drug. Pizzol et al.[16] observed that, among anti-depressant medication package inserts and bibliographic references, 62.5% contraindicated the drugs during breastfeeding, while in the consulted sources the percentage varied between 0 and 25%.

Another study by Pizzol et al.[17] assessed the compatibility of the use of contraceptives and anti-infectives during breastfeeding. As an outcome, the authors concluded that the package inserts for anti-infectives showed greater disagreement with the bibliographic sources consulted in relation to package inserts for contraceptives.

Arguello et al.[18] identified deficiencies in information in European package inserts regarding indication for use during breastfeeding and information that demonstrates the safety of use by lactating women. In this study, 61.4% of the package inserts analyzed did not contain information on drug excretion in human milk. The recommendation for use during breastfeeding was ambiguous in 16.5% of the package inserts, and use of medication was restricted in more than 90% of the package inserts during pregnancy and breastfeeding, despite the lack of information to support these restrictions. Furthermore, the authors highlighted a lack of updating of the package inserts after the drug is first authorized to be introduced on the market and a lack of post-use information review based on evidence.

A worrying finding in our research was the lack of any information in the package inserts of some drugs (20.0% of dyspepsia medications and 24.3% of constipation medications). This information gap impairs decision making by health professionals and patients with regard to interrupting treatment or weaning the infant.

Resolution RDC 47 establishes guidelines to prepare package inserts for medicines used in Brazil. It is noticed that the Brazilian package inserts present information gaps in specific sections, so that information such as drug excretion in milk, pre-clinical and clinical studies and clinical experience describing the use of the drug during lactation are practically non-existent and not mandatory.[12] As a defensive measure, pharmaceutical companies choose not to go into further research and/or suppress such information to avoid possible litigation.[19]

Inaccurate information in the package inserts such as ‘not recommended’ or ‘use with caution’ and variations of the same meaning allow an open interpretation as to whether the drug is totally contraindicated and what the possible harms to the infant may be. Vague information was also observed in studies that analyzed the recommendations of European package inserts in other clinical areas, such as renal failure.[20]

Deciding on the use of medication during breastfeeding or discontinuation of use requires the adoption of reliable and detailed information that provides, in addition to the conservative stance of pharmaceutical laboratories, pharmacological and toxicological data.[19] Such information should not only be restricted to

the drug's excretion in milk, but also to the clinical consequences and harmful effects on the infant's health and on the breastfeeding process. In this way, the need becomes evident to update the current Brazilian regulations regarding the content of drug package inserts to include information based on the results of post-marketing studies and/or the adoption of reliable sources, based on scientific evidence.

A limitation of this study is the exclusion of medicines that were absent in at least one bibliographic source consulted, due to the non-commercialization of these medicines in the countries in the databases. This gap makes it difficult to verify the consistency between the information available in the literature and in the leaflets, highlighting a fragility resulting from the absence or insufficiency of data on the topic.

CONCLUSION

This study found that the package inserts for medicines used in Brazil to treat dyspepsia and constipation do not present information consistent with the literature, or even provide information that allows these drugs' safe use by nursing mothers. These data suggest a defensive position on the part of the pharmaceutical industries in disclosing concrete information, making it difficult to make a decision about the use of these medications during breastfeeding. In this way, we recommend that the regulation that guides the preparation of package inserts in Brazil be reviewed. Likewise, sufficient information based on evidence in the specific sections is required as a necessary condition for registration and/or renewal with ANVISA.

CONFLICT OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

AUTHORS' CONTRIBUTIONS

Conceptualization: DAR and TSDP. Data curation: DAR, TSS, TOS, CG and TSDP; Formal analysis: DAR and TSDP. Funding acquisition: DAR and TSDP. Investigation: DAR and TSDP. Methodology: DAR, TSS, TOS, CG e TSDP. Project administration: DAR and TSDP. Software: DAR and TSDP. Supervision: TSDP. Visualization: DAR, TSS, TOS, CG and TSDP. Writing – original draft: DAR and TSDP. Writing – review & editing: DAR and TSDP.

REFERENCES

1. Brasil. Ministério da Saúde. Saúde da criança: nutrição infantil, aleitamento materno e alimentação complementar. Brasília: Ministério da Saúde; 2009.
2. Victora CG, Bahl R, Barros AJ, França GV, Horton S, Krasevec J, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. Lancet 2016;387(10017):475-90. https://doi.org/10.1016/S0140-6736(15)01024-7
3. Moimaz SAS, Rós DDT, Saliba TA, Saliba NA. Estudo quanti-qualitativo sobre amamentação exclusiva por gestantes de alto risco. Ciênc Saúde Coletiva 2020;25(9):3657-68. https://doi.org/10.1590/1413-81232020259.30002018
4. Saha MR, Ryan K, Amir LH. Postpartum women's use of medicines and breastfeeding practices: a systematic review. Int Breastfeed J 2015;10:28. https://doi.org/10.1186/s13006-015-0053-6
5. de Waard M, Blomjous BS, Hol ML, Sie SD, Corpeleijn WE, van Goudoever JHB, et al. Medication use during pregnancy and lactation in a Dutch population. J Hum Lact 2019;35(1):154-64. https://doi.org/10.1177/0890334418775630
6. Silveira MPT, Possignollo J, Miranda VIA, Silveira MFD, Pizzol TDSD, Serrate S, et al. Breastfeeding and risk classification of medications used during hospitalization for delivery: 2015 Pelotas Birth Cohort. Rev Bras Epidemiol 2020;23:e200026. https://doi.org/10.1590/1980-549720200026

7. Hill M. Critical caveats in using product information/pregnancy categories for pregnant or breastfeeding patients. Aust J Gen Pract 2018;47(12):883-8. https://doi.org/10.31128/AJGP-03-18-4530
8. dal Pizzol TS, Moraes CG. Bulas e embalagens de medicamentos como instrumentos de educação em saúde. In: Spinillo CG, Trotta T. Design da informação em saúde. Curitiba: BRioi; 2019. p. 13-47. ISBN 978-85-906855-1-7
9. Anderson PO, Pochop SL, Manoguerra AS. Adverse drug reactions in breastfed infants: less than imagined. Clin Pediatr (Phila) 2003;42(4):325-40. https://doi.org/10.1177/000992280304200405
10. Lamounier JA. Atualização sobre o uso de medicamentos durante amamentação. Salud(i)ciencia 2005;13(4):10-13.
11. Agência Nacional de Vigilância Sanitária (ANVISA). Bulário Eletrônico da Agência Nacional de Vigilância Sanitária [Internet]. [cited on January 15, 2021]. Available at: https://consultas.anvisa.gov.br/#/bulario/
12. Agência Nacional de Vigilância Sanitária (ANVISA). Resolução – RDC no 47, de 8 de setembro de 2009. Estabelece regras para elaboração, harmonização, atualização, publicação e disponibilização de bulas de medicamentos para pacientes e para profissionais de saúde. Diário Oficial da União, 9 set. 2009.
13. Landis JR, Koch GG. An application of hierarchical Kappa-type statistics in the assessment of majority agreement among multiple observers. Biometrics 1977;33(2):363-74. https://doi.org/10.2307/2529786
14. Brasil. Ministério da Saúde. Aplicativo MedSUS é disponibilizado para população: Atualização fornece informações e facilita acesso a medicamentos disponíveis no SUS. Brasília: Ministério da Saúde; 2024 [Internet]. [cited on Feb 15, 2024]. Available at: https://www.gov.br/saude/pt-br/assuntos/noticias/2024/janeiro/aplicativo-medsus-e- disponibilizado-para-populacao.
15. Friedrich C, Richter E, Trommeshauser D, De Kruif S, Van Lersel T, Mandel K, et al. Absence of excretion of the active moiety of bisacodyl and sodium picosulfate into human breast milk: an open-label, parallel-group, multiple-dose study in healthy lactating women. DMPK 2011;26(5):458-64. https://doi.org/10.2133/dmpk.DMPK-11-RG-007
16. Pizzol TDSD, Moraes CG, Diello MV, Campos PM, Pletsch JT, Giugliani C. Uso de medicamentos antidepressivos na amamentação: avaliação da conformidade das bulas com fontes bibliográficas baseadas em evidências científicas. Cad Saúde Pública 2019;35(2):e00041018. https://doi.org/10.1590/0102-311X00041018
17. Pizzol TDSD, Pinto AN, Silveira MPT, Caetano MCDC, Giugliani C. Amamentação e utilização de medicamentos: qual a orientação presente nas bulas de anticoncepcionais e anti-infecciosos?. Ciênc Saúde Coletiva 2021;26(10):4783-94. https://doi.org/10.1590/1413-812320212610.30702020
18. Arguello B, Salgado TM, Fernandez-Llimos F. Assessing the information in the Summaries of Product Characteristics for the use of medicines in pregnancy and lactation. Br J Clin Pharmacol 2015;79(3):537-44. https://doi.org/10.1111/bcp.12515
19. Davanzo R. Controversies in breastfeeding. Front Pediatr 2018;6:278. https://doi.org/10.3389/fped.2018.00278
20. Weersink RA, Timmermans L, Monster-Simons MH, Mol PG, Metselaar HJ, Borgsteede SD, et al. Evaluation of information in summaries of product characteristics (SmPCs) on the use of a medicine in patients with hepatic impairment. Front Pharmacol 2019;10:1031. https://doi.org/10.3389/fphar.2019.01031