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Antihistamine use during breastfeeding with focus on breast milk transfer and safety in humans: A systematic literature review

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Abstract

Current data on use of antihistamines during breastfeeding and risks to the breastfed infant are insufficient. The aim of this systematic review was to provide an overview of studies measuring the levels of antihistamines in human breast milk, estimating the exposure for breastfed infants and/or reporting possible adverse effects on the breastfed infant. An additional aim was to review the antihistamine product labels available in the European Union (EU) and the United States. We searched seven online databases and identified seven human lactation studies that included 25 mother–infant pairs covering cetirizine, clemastine, ebastine, epinastine, loratadine, terfenadine and triprolidine. In addition, one study investigated the impact of chlorpheniramine or promethazine on prolactin levels among 17 women, and one study investigated possible adverse drug reactions in 85 breastfed infants exposed to various antihistamines. The relative infant dose was below 5% for all antihistamines, ranging from 0.3% for terfenadine to 4.5% for clemastine. Most product labels of the 10 antihistamines with available information in both the EU and the United States reported lack of evidence and recommended to avoid use during breastfeeding. The knowledge gap on antihistamines and lactation is extensive, and further human studies are warranted to ensure optimal treatment of breastfeeding women with allergy.

KEYWORDS
antihistamine, breast milk, breastfed, breastfeeding, lactation

1 | BACKGROUND

The World Health Organization (WHO) recommends mothers to exclusively breastfeed their infants for the first 6 months after birth for optimal infant growth and development.[1] Nevertheless, in the European Union (EU), the breastfeeding rate drops from 56%–98% immediately after birth to 13%–39% at 6 months post-partum.[2]

Unfounded concerns about risks to the breastfed infant when the mother uses medication are unfortunately one of the reasons for early weaning.[3] In general, medication is excreted in small amounts into breast milk, and few medications are contraindicated in breastfeeding women. Examples of such medications include cytotoxic drugs, amiodarone and gold compounds.[4–6] The benefits of breastfeeding to the mother and child will in most cases outweigh the potential risk of medication exposure to the breastfed child.[5] Compared with formula-fed infants, breastfed infants have a lower risk of infections, allergy and respiratory illness and a lower mortality in early life. Moreover, there is a lower risk of overweight and obesity,[7–11] in addition to better socioemotional behavioural and cognitive development.[12] Breastfeeding is also of benefit to the mother, contributing to a more rapid post-partum recovery and a decreased risk of ovarian and breast cancer, osteoporosis and Type 2 diabetes.[13]

Up to 20%–30% of women have allergic diseases that may require pharmacological treatment during pregnancy and breastfeeding.[14,15] Antihistamines are one of the most commonly used drugs for allergy conditions but also for a range of other conditions. Population-based studies show that approximately 2%–3% of all women are prescribed antihistamines during the first 3 months post-partum.[16,17] Notably, this figure does not include antihistamines for topical use and those sold over the counter. Thus, understanding the safety profile of antihistamine exposure via milk in the breastfed infant is essential for clinical decision-making.

Very few adverse drug reactions (ADRs) have been reported among infants exposed to antihistamines via breast milk. A review including 53 case reports of ADRs in breastfed infants exposed to all types of medications[18] showed that over 75% of the ADRs occurred in infants below 2 months of age and 70% of the ADRs were related to drugs acting on the central nervous system. None of the case reports involved antihistamines. A review evaluated 16 systematic studies on ADRs in breastfed infants including one antihistamine (loratadine) and reported no ADRs.[19] In another study in breastfed infants, mothers reported ADRs in 85 cases. Eight of these concerned infants were exposed to an antihistamine. These reactions were all categorized as minor (e.g. irritability and drowsiness) and did not require medical attention.[20]

Product information, that is, Summaries of Product Characteristics (SPCs), prescribing information, drug/product labels and package leaflets, hereafter called ‘product labels’, are officially approved information for healthcare professionals and patients on how medication should be used. A US review of product labels for new drugs between 2003 and 2012 concluded that less than 5% had information on lactation from humans included.[21]

Initiatives to close the knowledge gap related to medication and lactation have recently been taken: Regulators have revised guidelines highlighting when and how studies on safety in pregnancy and breastfeeding should be performed.[22,23] A Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC) was established under the US 21st Century Cures Act to identify research needs on safe and effective therapies for pregnant and lactating women.[24] In the EU, the ConcePTION initiative was launched in 2019 under the Innovative Medicines Initiative (IMI), uniting stakeholders with the aim to build a trusted and accessible ecosystem for evidence-based information regarding medication use during pregnancy and lactation.[25]

This review is in line with these initiatives: In order to make evidence-based decisions for a common condition such as allergy, it is important to summarize available evidence about safety of antihistamines during breastfeeding, identify specific knowledge gaps, make recommendations for future studies and translate findings into balanced clinical recommendations about antihistamines and breastfeeding.

2 | OBJECTIVE

The primary aim of this systematic review is to provide an overview of studies that (i) measured the concentration of antihistamines in human breast milk, (ii) estimated the exposure of breastfed infants to antihistamines, (iii) reported possible ADRs of antihistamines in breastfed infants and/or (iv) investigated effects on breast milk production. An additional aim was to review the content of the lactation parts in the product labels of antihistamines available in the EU and the United States.

3 | MATERIALS AND METHODS

3.1 | Systematic literature review

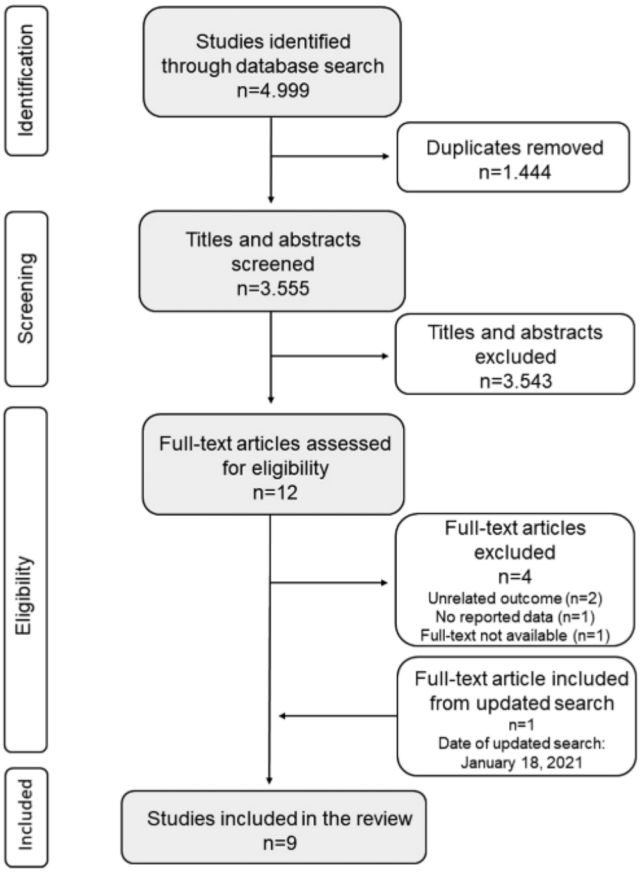
3.1.1 | Searches

The studies were selected in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines.[26] A flow chart of the selection procedure and the data extraction

is provided in Figure 1. We searched the following electronic databases: Medline, Embase, LactMed, Scopus, Web of Science, Cochrane Library and PsycINFO. Reference textbooks were additionally screened. Publications in English, Norwegian, Swedish and Danish were included from inception to 18 August 2020 and updated on 18 January 2021. See detailed search strategy in Data S1.

3.1.2 | Types of studies included

Randomized controlled trials (RCTs), cohort studies, register-based studies, case–control studies, pharmacokinetic analyses, case reports and letters were eligible for inclusion. Reviews, Delphi studies, qualitative research, editorials, commentaries, guidelines and conference abstracts were excluded. Animal studies, in vitro studies and studies presenting only the analytical methodology were not eligible for inclusion.



3.2 | Exposure

Exposure was defined as maternal use of antihistamines for systemic use (Anatomical Therapeutic Chemical [ATC] group R06),[27] nasal preparations with anti-allergic agents, excluding corticosteroids (ATC group R01AC), and ophthalmological decongestants and anti-allergics (ATC group S01G) during lactation.

Drugs with histamine H_1 receptor antagonist properties that are not classified as antihistamines, but are used for other indications (i.e. classified in other ATC groups), such as antipsychotics (ATC group N05A) were not included. Table 1 lists the 69 antihistamines included in the literature search.

3.3 | Data extraction

All search results from the databases were first saved in the reference management software, EndNote. All duplicates were then removed in EndNote. The remaining search results were uploaded to Rayyan,[28] a systematic review management system.

Firstly, two independent reviewers (EN and HN) individually screened titles and abstracts against the inclusion and exclusion criteria in Rayyan, blinded for each other. Disagreements about inclusion versus exclusion were discussed unblinded until consensus was reached. Secondly, EN screened the full text of all studies included based on abstract/title for final inclusion or exclusion. HN supervised this process.

3.4 | Outcomes

We extracted data on maternal antihistamine dose and body weight, the milk/plasma (M/P) concentration ratio and maximum and mean concentrations (C_{max} and C_{mean}, respectively) in maternal plasma and breast milk. C_{max} was defined as the highest concentration measured, and C_{mean} was defined as the average of all concentrations measured over a dose interval, irrespective of the time intervals between samples (Table 2). We calculated the absolute infant dose and relative infant dose using C_{max} as a worst-case scenario. We chose this approach due to unknown intraindividual variability of breast milk transfer and because we expected a low number of subjects in each study. However, if C_{max} was not available, C_{mean} was used (Box 1). Reported suspected ADRs in the infants and

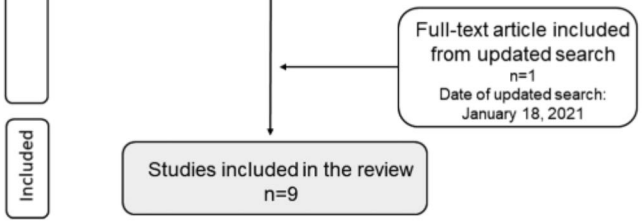


FIGURE 1 Flow chart of the identification and selection of evaluated studies. Total 4.999 studies were identified though the seven databases that were searched. Nine studies were included in the review after screening for titles, abstract and full text

intervals between samples (Table 2). We calculated the absolute infant dose and relative infant dose using C_{max} as a worst-case scenario. We chose this approach due to unknown intraindividual variability of breast milk transfer and because we expected a low number of subjects in each study. However, if C_{max} was not available, C_{mean} was used (Box 1). Reported suspected ADRs in the infants and effects on lactation were also recorded. Other variables registered were analytical techniques used and maternal outcomes. Information about infant plasma concentrations was also collected.

TABLE 1 Overview of antihistamines with published literature on transfer to human breast milk and/or with EU and US product labels with information on breast milk excretion and/or lactation

Substance	Published literature available[a]	EU product labels available	US product labels available
Acrivastine		X	X
Azelastine		X[b]	X[b]
Cetirizine	X	X	X[b]
Clemastine	X	X	X
Desloratadine		X	X
Ebastine	X	X	
Epinastine	X	X[b]	X[b]
Levocetirizine		X	X
Lodoxamide		X[b]	X[b]
Loratadine	X	X	
Olopatadine		X[b]	X[b]
Promethazine	X	X	X
Terfenadine[c]	X		
Triprolidine	X	X	

Notes: Eight antihistamines had published data on drug transfer to human breast milk. Thirteen EU and 10 US product labels were available. EU product labels were searched for on www.medicines.org.uk/emc/. US product labels were searched for on https://labels.fda.gov/getIngredientName.cfm.

[a]No information was available for astemizole, azatadine, bamipine, bromazine, brompheniramine, buclizine, carbinoxamine, chlorcyclizine, chloropyramine, chlorphenoxamine, deptropine, dexbrompheniramine, dimetindene, diphenhydramine, diphenylpyraline, doxylamine, emedastine, histapyrrodine, hydroxyethyl, isothipendyl, olopatadine, levocabastine, mebhydrolin, meclizine, mepyramine, mequitazine, methapyrilene, methdilazine, oxatomide, oxomemazine, phenindamine, pheniramine, pimethixene, pyrrobutamine, quifenadine, sequifenadine, talastine, thenalidine, thiazinam, thiethylperazine, thonzylamine, trimethobenzamide, tripelennamine and tritoqualine.

[b]Topical use only.

[c]Withdrawn from the marked worldwide due to side effects (QT-prolongation).

TABLE 2 Overview of the time intervals from dose intake to maternal plasma and breast milk concentration measurements and milk sampling method

Substance, reference	Time of measurements of concentration after drug intake in hours
Cetirizine[31]	Breast milk: 0, 1, 2, 4, 6, 8, 10, 12, and 24[a]
Clemastine[32]	Maternal plasma and breast milk: 20[b]
Ebastine[33]	Breast milk: 3.9, 11.3, 17.2, 24.3, and 27.3[b]
Epinastine[34]	Maternal plasma and breast milk: 2, 4, and 10[b]
Loratadine[35]	Maternal plasma: ½, 1, 2, 4, 6, 8, 1, 24, 36, and 48; breast milk: 0–2, 2–4, 4–6, 6–8, 8–12, 12–24, 24–36, and 36–48[a]
Terfenadine[36]	Maternal plasma and breast milk: 0, ½, 1, 1 ½, 2, 3, 4, 6, 8, 12, 24, and 30[c]
Triprolidine[37]	Maternal plasma: ½, 1, 2, 4, 6, and 12; breast milk: ½, 1, 1 ½, 2, 3, 4, 7, 12, 14, 24, 36, and 48[a]

[a]Milk were obtained from both breasts and mixed before analysis.

[b]Milk sampling method not specified.

[c]Full breast milk emptying with an electric pump.

BOX 1 Calculation of key exposure variables via breast milk[1]

Absolute infant dose (μg/kg/day) = C_{max} (μg/ml) × 150 ml breast milk per kg infant body weight per day

Relative infant dose (%)[2] = absolute infant dose (μg/kg/day) × maternal body weight (kg) × 100/mean maternal dose (μg/day)

3.5 | Information in EU and US product labels

All medications marketed in the EU have a product label approved by the national competent authority or the European Medicines Agency (EMA). According to the guidelines, section 4.6 of the product label should provide recommendations on the use of the medication during breastfeeding.[29]

The outline of section 8.2 in the product label approved by the US Food and Drug Administration (FDA) should include a risk summary, which provides summarized information of a drug in human milk, the effects of the drug on the breastfed infant and the effect on milk production. This section should also include clinical considerations and data that provide a basis for the risk summary and clinical considerations given.[30]

On 15 January 2021, we searched the European Electronic Medicines Compendium (EMC; www.medicines.org.uk/emc/) and the FDA Prescribing Information Database (https:/labels.fda.gov/getIngredientName.cfm) for all antihistamines included in the search strategy as listed in Table 1. EMC is a licensed information site in the United Kingdom, with more than 14 000 product labels. We extracted information about medication use while breastfeeding from relevant sections as stated.

4 | RESULTS

4.1 | Systematic literature review

We identified 4999 publications from inception to 18 August 2020, from the seven electronic databases searched. After the deletion of duplicates, 3555 publications remained. A total of 3543 studies were excluded based on title and abstract. The full text of the 12 remaining studies was screened for eligibility. After full-text screening, four studies were excluded due to (i) unrelated outcome, that is, studies on laboratory methods ($n = 2$); (ii) no reported data ($n = 1$); and (iii) full text not available ($n = 1$). The updated search on 18 January 2021 identified one case report[31] that was eligible for inclusion in this review after the screening process (Figure 1).

Thus, a total of nine studies were finally included. Seven of these (with a total of 25 mother–infant pairs) included the following antihistamines: cetirizine,[31] clemastine,[32] ebastine,[33] epinastine,[34] loratadine,[35] terfenadine[36] and triprolidine[37] (Table 3). One study including 17 women investigated the impact of chlorpheniramine or promethazine on prolactin levels.[38] Another study investigated possible adverse reactions in breastfed infants exposed to medications in general[20] and included 85 breastfed infants exposed to antihistamines. All included studies were in English. Table 2 presents details on when the milk and plasma samples for drug

4.2 | Transfer of antihistamines into breast milk

All studies except the study on promethazine[38] had calculations on the absolute infant dose and relative infant dose (Table 3). The relative infant dose was lowest for terfenadine (0.3%)[36] and highest for clemastine (4.5%).[32] It was 0.4%–2.5% for epinastine,[34] whereas all the remaining relative infant doses were below 2% for cetirizine, ebastine, loratadine and triprolidine.[31,35–37]

Given the maternal doses listed in Table 3, absolute infant doses via breast milk per kilogram body weight per day are presented in Table 4. Based on these numbers, an exclusively breastfed infant weighing 5 kg would have been exposed to an absolute infant dose of 15.5 μg cetirizine, 7.5 μg clemastine, 8.8 μg ebastine, 23.0 μg of epinastine, 34.0 μg loratadine, 30.0 μg, terfenadine or 1.8 μg triprolidine[32–37] every 24 h.

4.3 | Effect on breast milk production

No studies investigated the effect on breast milk production directly. However, one pharmacokinetic study analysed the effect on serum prolactin levels after single injections of 100 mg promethazine or 20 mg chlorpheniramine. The injections were given 1 day post-partum.[38] The prolactin concentrations decreased significantly the first 30 min after the injection of promethazine but increased again over time (0 min: 235 ± 22 ng/ml [mean ± standard deviation], 30 min: 101 ± 10 ng/ml, 60 min: 121 ± 11 ng/ml, 90 min: 161 ± 18 ng/ml). The prolactin concentrations decreased significantly also after the chlorpheniramine injection (0 min: 223 ± 22 ng/ml, 30 min: 74 ± 12 ng/ml). However, when the chlorpheniramine injection was given immediately before the onset of breastfeeding, the prolactin concentration increased at 30-min blood sample (0 min: 225 ± 43 ng/ml, 30 min: 428 ± 33 ng/ml).

4.4 | ADRs

Four studies (one case report on clemastine, two pharmacokinetic studies on epinastine and loratadine and one follow-up study on antihistamines in general) had investigated possible ADRs in the infants (Table 4). A 10-week-old infant who was fully breastfed while the mother used clemastine, phenytoin and carbamazepine showed drowsiness, irritability, refusal to feed and high-

fenadine[36] and triprolidine[37] (Table 3). One study including 17 women investigated the impact of chlorpheniramine or promethazine on prolactin levels.[38] Another study investigated possible adverse reactions in breastfed infants exposed to medications in general[20] and included 85 breastfed infants exposed to antihistamines. All included studies were in English. Table 2 presents details on when the milk and plasma samples for drug analyses were obtained in relation to dose intake. Information about the study characteristics and their results is presented in Tables 3 and 4.

Four studies (one case report on clemastine, two pharmacokinetic studies on epinastine and loratadine and one follow-up study on antihistamines in general) had investigated possible ADRs in the infants (Table 4). A 10-week-old infant who was fully breastfed while the mother used clemastine, phenytoin and carbamazepine showed drowsiness, irritability, refusal to feed and high-pitch cry.[32] No ADRs were observed in the infants aged 4–21 months in the pharmacokinetic studies, irrespective of whether the infant was exclusively breastfed or not.[34,35] None of the studies included in this review

TABLE 3 Overview of concentration of antihistamines in plasma and breast milk, milk/plasma ratio, relative infant dose, number of women included in the study, mean maternal dose and limit of detection in published studies

Substance, reference	No. of women included	Maternal weight (kg)	Mean maternal dose (mg/day)	LOD/LLOQ (ng/mL)	Half-life (h)	Plasma C_{max} (ng/mL)	Milk C_{max} (ng/mL)	Plasma C_{mean} (ng/mL)	Milk C_{mean} (ng/mL)	Relative infant dose (%)
Cetirizine[31]	3	56.2	10 (single dose)	NR	8–9	NR	49	NR	21.2	1.8
Clemastine[32]	1	60	2 (for 3 days)	2 (LOD)	10–30[a]	NR	NR	20[b]	5-10	4.5[c]
Ebastine[33]	1	53	10 (daily before and during pregnancy)	0.02 (LOD)	10–19[a]	NR	6.3 5.4[d]	NR	NR	0.5[e]
Epinastine[34]	7	53	20 (for 7 days)	NR	6.5[a]	NR	NR	9.6	21.9	0.4–2.5
Loratadine[35]	6	63	40 (for 2 days)	0.3 (LLOQ)	8–14 17–24[f]	30.5 (±18.3) 18.6 (±7.9)[f]	29.2 (±7.1) 16 (±7.4)[f]	NR	NR	1.1[g]
Terfenadine[36]	4	60	120 (for 2 days)	NR	14	309 (±120.5)	41 (±16.4)	NR	NR	0.3
Triprolidine[37]	3	58	2.5 (single dose)	NR	4–7	NR	NR	NR	2.4	0.9

Note: Numbers in parentheses represent standard deviations.

Abbreviations: LLOQ, lower limit of quantification; LOD, limit of detection; NR, not reported.

[a]Half-life data from *World Allergy Organization Journal* and *Journal of Clinical Pharmacology*.[46,47]

[b]Based on a single sample.

[c]Calculated from C_{mean}.

[d]For the active metabolite carebastine.

[e]Including the active metabolite carebastine.

[f]For the active metabolite desloratadine.

[g]Including the active metabolite desloratadine.

TABLE 4 Overview of the absolute infant doses of antihistamines and potential adverse drug reactions reported

Substance, reference	No. infants included	Infant age	Infant body weight (kg)	Exclusively breastfed (yes/no)	Absolute infant dose via breast µg/kg/day	Adverse drug reactions
Cetirizine[31]	3	5–6 months	NR	No	3.1	Not examined
Clemastine[32]	1	10 weeks	NR	Yes	1.5[a]	Drowsiness, irritability, refusal to feed, high-pitch cry[b]
Ebastine[33]	1	5 days	3.5 kg	Yes	1.76[c]	Not examined
Epinastine[34]	7	4–21 months	5.4–10.8 kg	No	4.6[a]	No change in health conditions was observed
Loratadine[35]	6	1–12 months	NR	No	6.8[d]	No ADRs were reported by the mothers
Terfenadine[36]	4	5–12 months	NR	NR	6.0	Not examined
Triprolidine[37]	3	5–8 months	NR	No	0.36[a]	Not examined

Notes: Absolute infant dose calculated from C_{max}. If C_{max} was not reported, we used C_{mean} to calculate the absolute infant dose.
Abbreviation: NR, not reported.
[a]Calculated from C_{mean}.
[b]Including the active metabolite carebastine.
[c]The mother was also using phenytoin 300 mg/day and carbamazepine 800 mg/day.
[d]Including the active metabolite desloratadine.

reported infant plasma concentrations. The study on antihistamines in general showed that eight out of 85 infants exposed had minor symptoms considered to be ADRs.[20] Irritability was the most common of these. However, no infant required any medical attention, and none of the studies evaluated the reactions as consequential.

4.5 | Information in EU and US antihistamine product labels

We identified 10 antihistamines with available product labels with information on use during breastfeeding in both the EU and the United States (acrivastine, azelastine, cetirizine, clemastine, desloratadine, epinastine, levocetirizine, lodoxamide, olopatadine and promethazine). Table S1 (product labels for systemic use) and Table S2 (product labels for topical use) in Data S2 present the lactation section of product labels, for example, products containing each of these 10 antihistamines. An additional three product labels (ebastine, loratadine and triprolidine) had product labels with information on use during breastfeeding only in EU (Table S3 in Data S2).

4.6 | Systemic use

breastfeeding. Product labels for cetirizine, desloratadine and levocetirizine recommended cautionary use and that decision for use should take into account the benefit and risk for the child and the mother. Both EU and US product labels for clemastine did not recommend use during breastfeeding without any specific further information given. The EU and US product labels for acrivastine and promethazine gave divergent advice for use during lactation. The US product label for promethazine was for a combination product with codeine, which may explain the more restrictive recommendation.

4.7 | Topical use

Four antihistamines had available information on use during breastfeeding in the EU and the United States (Table S2). Product labels for azelastine, epinastine and lodoxamide in both the EU and the United States recommended cautionary use. The reason for these recommendations was that no information on the excretion of drug to breast milk was available. The EU product label for olopatadine did not recommend use during breastfeeding based on animal studies, in contrast to the US product label, which recommended caution.

5 | DISCUSSION

histamines. An additional three product labels (ebastine, loratadine and triprolidine) had product labels with information on use during breastfeeding only in EU (Table S3 in Data S2).

4.6 | Systemic use

There were six antihistamines with available product labels in both the EU and the United States (Table S1). None of the product labels recommended use during

mendations was that no information on the excretion of drug to breast milk was available. The EU product label for olopatadine did not recommend use during breastfeeding based on animal studies, in contrast to the US product label, which recommended caution.

5 | DISCUSSION

We reviewed the literature on breast milk transfer and safety for 69 antihistamines and identified published data

in human milk for only nine. These numbers demonstrate that the available literature on transfer of antihistamines into breast milk and possible infant adverse effects is insufficient. This fact clearly contrasts with the wide use of antihistamines in women of childbearing age.[14,15] Most modern antihistamines are probably compatible with breastfeeding, but due to the lack of evidence on their safety, product labels often warn against their use. The FDA workshop position paper on medications and breastfeeding[39] in 2017 explicitly recommends to prioritize products that are commonly used by women of reproductive age and drugs that for which no data are available in the literature. Thus, several of the antihistamines could be strong candidates for prioritization.

For optimal infant growth and development, the WHO recommends mothers to exclusively breastfeed their infants for the first 6 months of their life.[1] However, the rate of breastfeeding in the EU drops from 56%–98% immediately after birth to 13%–39% at 6 months.[2] Unfounded concerns about the risks to breastfed infants are unfortunately one of the common reasons for unnecessary cessation of breastfeeding.[3] Human lactation studies, updated information and tailored evidence-based advice could counteract this.

The nine studies identified in our review covered analyses on nine antihistamines: cetirizine, chlorpheniramine, clemastine, ebastine, epinastine, loratadine, promethazine, terfenadine and triprolidine. The studies showed that the relative infant doses were below 5%, implying that the risk of pharmacological effects in breastfed infants is minimal.[40] However, in addition to the RID, other pharmacokinetic and pharmacodynamic factors (e.g. bioavailability and potency) as well as maternal (e.g. time from drug intake to breast feeding, full vs. partial breastfeeding) and infant factors (e.g. infant age), are important to assess when discussing safety in breastfed infants.[41] Neonates, and particularly premature infants, eliminate drugs at a considerably slower rate than older children and adults, as their liver and kidney functions are not yet fully developed. These factors could be of particular concern when used during long-term treatment with drugs with long elimination half-lives. When interpreting the results, we should bear in mind that the 5% limit is only a rule of thumb, implying a higher risk of ADRs in breastfed infant when RID is higher than 5%. There are also other factors that can apply, such as time interval between drug exposure and breastfeeding, amount of breast milk consumed by the infant and the inherent potency of the drugs. However, it is important to include the half-life of the antihistamines in the assessment, as antihistamines with longer half-life will have a higher risk of accumulation in the breastfed infant during continuous use. Only three of the studies were published after 2019.[31,33,34] The remaining studies were published between 1982 and 1995, that is, almost more than three decades ago where use of antihistamines and allergy treatment among breastfed women may not have been as common as today, particularly for second-generation antihistamines. Notably, few studies systematically monitored the breastfed infants for possible ADRs. The studies that did monitor possible ADRs did not report any causality assessment between the antihistamine and the suspected ADRs.

5.1 | Clinical interpretation: First- versus second-generation antihistamines

Due to the sparseness of data, it is unclear whether there is a difference in risks for breastfed infants between first-generation 'sedating' and second-generation 'non-sedating' antihistamines. The pharmacological properties and the known risks of drowsiness and irritability in infants exposed to first-generation antihistamines at infant therapeutic doses[20] make, however, these drugs a second-line choice. Second-generation antihistamines, such as loratadine and cetirizine, given their low levels of transfer into breast milk and better ADR profile, seem to be the currently preferred choice of antihistamines for breastfeeding women. Nevertheless, none of the studies included in this review, irrespective of the presence or not of sedative properties, showed a concerning high relative infant dose. Moreover, none of the studies reported any significant adverse effects among the infant, and none of them needed medical attention.

5.2 | Impact on breast milk production

Prolactin is an essential hormone for stimulating milk production.[42] Interestingly, one study found decreased prolactin levels in women after single injections of promethazine or chlorpheniramine.[38] However, when chlorpheniramine was given immediately before breastfeeding, prolactin levels increased. This may imply that the suckling-induced increase in prolactin levels outweighs a potential antihistamine-induced decrease in prolactin levels. These findings, together with results from other studies,[43] suggest that inhibition of histamine H_1 receptors decreases prolactin secretion, offering a plausible biological mechanism for the effect of antihistamine in breast milk production. In addition, first-generation antihistamines have anticholinergic effects inhibiting the prolactin secretion in women, but not in

men. This may indicate that the female hormonal conditions modulate the prolactin response.[44] As such, the impact of certain antihistamines on the prolactin response in women warrants further investigation. Currently, it is assumed that a slight reduction in serum prolactin for a short time will have no clinically significant effect on breast milk production as prolactin levels increase once lactation is established.[45]

5.3 | Antihistamine labelling: Potential for improvement

Over half of the antihistamine product labels in the EU and the United States recommended cautionary use during lactation and state that the decision about use of the antihistamine or not should take into account the benefit and possible risk for the child and the mother. Yet, no product label presented the magnitude of these risks or compared exposure via breast milk to recommended therapeutic infant doses, if available. As it is not possible to perform a meaningful risk/benefit evaluation when risks are unknown, use of such wording in product labelling is worthless. Nevertheless, these texts can affect practices and advice of caregivers. The product label of cetirizine includes unpublished data stating that it is excreted in human milk at concentrations representing 25%–90% of those measured in plasma. We encourage the Marketing Authorization Holders to submit their data for publication in peer-review journals to increase transparency and to report absolute drug concentrations in breast milk.

Some of the product labels were consistently strict in their recommendations, that is, for cetirizine. Both product labels for cetirizine stated that caution should be exercised, due to the excretion in human breast milk. In contrast, the published study on cetirizine[31] concludes that milk transfer is minimal and unlikely to pose a significant risk to the breastfeeding infant. Recent initiatives[24,25] that engage and encourage market authorization holders to perform human lactation studies hold great promise if they can be accompanied by updating and improving the lactation section of product labels.

The vast majority of drugs for topical administration including antihistamines will not be detected in breast milk due to the low bioavailability. Despite this, none of the product labels for topical antihistamines stated that

5.4 | Limitations

This systematic review has some limitations that should be taken into consideration when interpreting the results. All studies included low numbers of mother–infant pairs and very few studies monitored ADRs. The few studies that evaluated and did report ADRs related to antihistamines found mild reactions in all cases and only for infants up to 10 weeks of age. All ADRs were self-reported by the infants' mothers, and no causality assessments were performed. These limitations strengthen the importance to promote reporting of ADRs in breastfed infants and carry out more methodologically sound, observational and experimental human lactation studies for antihistamines.

Moreover, studies analysing the extent of breast milk transfer of cetirizine, clemastine, loratadine, terfenadine and triprolidine were only based on either a single-dose intake or maximum of 3 days of treatment.[31,35,37,38] Studies including women using antihistamines with long half-lives over extended periods are needed to confirm the low breast milk transfer.

We have chosen to calculate absolute and relative infant doses based on C_{max} in milk. It could be argued that using C_{max} instead of C_{mean} tends to overestimate risk estimates, but we consider it being important to present worst-case scenarios, particularly taking into account the low number of subjects included in the studies and the unknown extent of inter- and intraindividual variability in pharmacokinetics related to milk excretion of the drugs investigated. It should, however, be noted that it was not reported whether time interval of concentration measurements and milk sampling were captured at the peak concentrations. C_{max} data were not available for clemastine, epinastine and triprolidine, and C_{mean} was used for these drugs. This may have resulted in lowered estimated infant doses for these drugs. Nevertheless, the highest relative infant dose for antihistamines found in this review is still below 5%.[40]

Finally, it should be taken into consideration that we limited our search strategy to antihistamines for systemic use (ATC group R06) in English and the Scandinavian languages. Therefore, other medications with histamine H_1 receptor antagonist properties like hydroxyzine (belongs to ATC group N05B Anxiolytics) and those classified as antipsychotics (ATC group N05A) were not included. Some relevant studies in other languages may therefore have been excluded in this process.

In conclusion, few antihistamines have been studied

ies hold great promise if they can be accompanied by updating and improving the lactation section of product labels.

The vast majority of drugs for topical administration including antihistamines will not be detected in breast milk due to the low bioavailability. Despite this, none of the product labels for topical antihistamines stated that the drug could be safely used by breastfeeding mothers. As the theoretical risk of ADRs is minimal, we consider that there is a need to update product labels for topical antihistamines.

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In conclusion, few antihistamines have been studied in relation to breast milk transfer and infant safety, and consequently, product labels generally recommend a cautious approach. In contrast, the sparse publically available data indicate low breast milk transfer and low risks

during breastfeeding for the most commonly used antihistamines. Nevertheless, given the wide use of antihistamines, they should be a prioritized group for future human lactation studies. These studies should be performed according to recommendations in regulatory guidelines, and product labels should be updated accordingly.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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ENDNOTES

[1]C_{max} was used to present the worst-case scenarios. C_{mean} was used if C_{max} was unavailable.

[2]Given that the infant is exclusively breastfed.

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SUPPORTING INFORMATION

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