Brief description of patient problem/setting : A 32 year old woman who is exclusively breastfeeding her 3 month old infant presents to the clinic with symptoms of allergic rhinitis, including nasal congestion, sneezing, and rhinorrhea. Her symptoms are affecting her daily activities and sleep. She has a history of seasonal allergies and previously used diphenhydramine for symptom relief prior to pregnancy. She is now concerned about the safety of antihistamines while breastfeeding, particularly their potential effects on her infant and milk supply, and is asking whether she can continue her previous medication or if there are safer alternatives.

Search Question: Are second-generation antihistamines safer than first-generation antihistamines for breastfeeding women regarding infant adverse effects and milk supply?

Question Type: What kind of question is this?

☐Prevalence ☐Screening ☐Diagnosis ☐Prognosis ☐**Treatment** ☐**Harms**

Assuming that the highest level of evidence to answer your question will be meta-analysis or systematic review, what other types of study might you include if these are not available (or if there is a much more current study of another type)?

Although systematic reviews and meta-analyses provide the highest level of evidence, they are limited for this topic, especially in breastfeeding populations. If higher-level evidence is not available or is outdated, I would include other study designs such as randomized controlled trials, cohort studies, and human lactation pharmacokinetic studies. Randomized controlled trials would be useful if available, as they provide strong evidence on clinical outcomes; however, they are often limited in breastfeeding populations due to ethical considerations. Cohort or observational studies can provide valuable real-world data on infant outcomes and potential adverse effects. Additionally, human lactation studies are particularly important in this topic, as they directly measure drug transfer into breast milk and estimate infant exposure, which is highly relevant to safety.

PICO search terms:

P	I	C	O
Breast feeding women	First-generation antihistamines	Second generation antihistamines	Infant sedation
Lactation	Diphenhydramine	Loratadine	Neonatal adverse effect
Lactating women	Hydroxyzine	Cetrizine	Milk supply
Nursing mothers	Clemastine	Fexofenadine	Breast milk production

Postpartum women	Sedating antihistamines	Levocetirizine	Lactation suppression
Human Milk		Non-sedating antihistamines	Drug transfer into breast milk
			Relative Infant dose

Search Strategy

	Pubmed	Cochrane Library	Google Scholar
Search Terms	(breastfeeding OR lactation OR lactating women) AND (diphenhydramine OR first generation antihistamines OR sedating antihistamines) AND (loratadine OR cetirizine OR second generation antihistamines OR non sedating antihistamines) AND (infant OR neonatal OR adverse effects OR sedation OR milk supply OR breast milk)	antihistamines lactation safety	antihistamines breastfeeding safety infant sedation milk supply
Filters	Publication date: 2016 - 2026, English language, Humans, MEDLINE indexed	Publication date: January 2015 - January 2026	Results were sorted by relevance and Reviewed articles Publication date within 5 years
Results	About 11	About 4	About 147
Selected	Choose 1 articles	none	Choose 2 articles

- After completing searches across PubMed, Cochrane Library, and Google Scholar, I identified approximately 11, 4, and 147 results, respectively, after applying filters. I first screened titles within the first 1-2 pages to exclude studies that clearly did not match my clinical question, including those focused on pregnancy only, pediatric populations, or medications unrelated to antihistamines.I then reviewed abstracts of few articles to determine whether the studies specifically evaluated antihistamine use in breastfeeding women, with emphasis on breast milk transfer, infant exposure, and potential adverse effects such as sedation or changes in milk supply. Studies that lacked breastfeeding-specific data or did not address safety outcomes were excluded. Priority

was given to higher levels of evidence, including systematic reviews and human studies, particularly those that provided measurable outcomes such as relative infant dose or reported infant effects. When multiple studies addressed similar outcomes, preference was given to the most recent and clinically relevant articles. Ultimately, three key articles were selected, including a systematic review, a human lactation pharmacokinetic study, and a clinical review. These were chosen because they directly addressed the safety of antihistamines during breastfeeding and provided the most relevant and applicable evidence to answer the clinical question.

Results found:

<u>Article # 1 :</u> Antihistamine use during breastfeeding with focus on breast milk transfer and safety in humans: A systematic literature review

Ngo E, Spigset O, Lupattelli A, et al. Antihistamine use during breastfeeding with focus on breast milk transfer and safety in humans: A systematic literature review. Basic & Clinical Pharmacology & Toxicology. 2022;130(1):171-181. doi:10.1111/bcpt.13663

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.

- This article was selected because it is a systematic review, which represents a high level of evidence. It included a comprehensive search across multiple databases and focused specifically on antihistamine use during breastfeeding, which directly aligns with my PICO question. The study evaluated both first-generation antihistamines (such as clemastine, chlorpheniramine, and triprolidine) and second-generation antihistamines (such as cetirizine, loratadine, and terfenadine), allowing for a direct comparison between the two groups. One thing I found especially useful was that it provided relative infant dose (RID) data for multiple antihistamines, showing that exposure through breast milk

was generally low (ranging from 0.3% to 4.5%). This is important when evaluating safety in breastfeeding. The article also discussed reported infant outcomes and highlighted that adverse effects were minimal, although the overall data is limited.

Key Findings:

- All antihistamines had a relative infant dose (RID) below 5%, which is well under the 10% threshold generally considered safe in breastfeeding.
- Second-generation antihistamines consistently showed lower RIDs compared to first-generation agents. For example, terfenadine had the lowest RID at 0.3%, followed by loratadine at around 1.0% and cetirizine at about 1.9%,
- First-generation agents such as triprolidine and clemastine had higher values, with clemastine reaching up to 4.5%.
- In terms of infant outcomes, one study included in the review evaluated 85 breastfed infants exposed to antihistamines and found that reported adverse effects were generally mild, with irritability being the most common. No serious adverse effects requiring medical intervention were reported.
- The review also addressed milk supply, noting that one study specifically evaluated chlorpheniramine and promethazine and found potential effects on prolactin levels, suggesting that first-generation antihistamines, due to their anticholinergic properties, may have a theoretical risk of decreasing milk production.
- Additionally, the authors reviewed product labeling from both the U.S. and Europe and found that many antihistamines are labeled as not recommended during breastfeeding; however, this was largely due to limited available data rather than evidence of actual harm. Overall, the authors emphasized that there is still a significant knowledge gap in this area and that more human studies are needed.
- Based on these findings, second-generation antihistamines, such as cetirizine and loratadine, appear to have lower infant exposure compared to first-generation agents, supporting their preferential use in breastfeeding women.

<u>Article #2:</u> Supporting Lactation in Otolaryngology Patients Through Medication Optimization, Radiology Considerations, and More

Elder E, Pianosi K, Lawlor CM, Graham ME. Supporting Lactation in Otolaryngology Patients Through Medication Optimization, Radiology Considerations, and More: A Literature Review. JAMA otolaryngology-- head & neck surgery. 2022;148(10):973-980. doi:10.1001/jamaoto.2022.2286

Abstract:

Importance: The benefits of breastfeeding are well established, with the American Academy of Pediatrics and Canadian guidelines recommending exclusive breastfeeding for the first 6 months of life. However, maternal hospitalization, illness, medication use, and poor support can result in early termination of breastfeeding. Caring for breastfeeding patients in otolaryngology is a challenge because of the lack of literature regarding otolaryngology-specific medication safety, patient concerns, and inadequate education among otolaryngologists. This review highlights recent literature regarding lactation in otolaryngology patients, including medication, radiologic imaging, perioperative considerations, and subspecialty-specific considerations for lactating patients.

Observations: The majority of common medications used in general otolaryngology are safe for breastfeeding patients, including antihistamines, mucolytics, antitussives, antifungals, and decongestants. Certain analgesics and anti-inflammatories, such as tramadol, are not preferred in breastfeeding individuals. Some subspeciality-specific medications such as biologics (dupilumab) and methotrexate should be avoided. Lactating patients require special perioperative attention to ensure that optimal patient care is provided, such as managing supply, considering length of surgery, managing postoperative pain, and determining the safe amount of time until an infant can be fed.

Conclusions and Relevance: Most medications can be safely used with lactating patients. If physicians are unsure about a medication's safety, they should consult appropriate resources prior to recommending breastfeeding cessation or to discard pumped milk.

- This article is a clinical literature review, not a systematic review, but it was still chosen because it directly addresses all of the key outcomes in my PICO question, including infant sedation, effects on milk supply, and overall clinical recommendations. It was also published in JAMA Otolaryngology, which adds credibility and relevance to current clinical practice. This article clearly compares first-generation and second-generation antihistamines in breastfeeding. It helps connect the pharmacologic data to real-world decision-making when choosing safer antihistamines for breastfeeding patients as well as include other drugs and its safety in breast feeding which I thought was great to share.

Key Findings:

- First-generation antihistamines (such as diphenhydramine, chlorpheniramine, and dimenhydrinate) may decrease milk supply when used in higher doses or over a prolonged period and can cause irritability or sedation in infants. However, small and occasional doses are less likely to cause significant adverse effects. Timing strategies, such as taking the medication at bedtime, may help reduce infant exposure.
- Second-generation antihistamines (such as loratadine and cetirizine) are recommended as the preferred option during breastfeeding. They have lower levels in breast milk and are associated with less sedation. Infant effects are minimal, with possible drowsiness only at higher doses or prolonged use.

- Systemic decongestants, especially pseudoephedrine, can decrease milk supply and may cause irritability in infants, while topical decongestants are safer due to minimal systemic absorption.
- Intranasal corticosteroids are safe and preferred in breastfeeding, and systemic corticosteroids are generally safe, though timing breastfeeding 3-4 hours after high doses may reduce infant exposure.
- Most analgesics are safe in breastfeeding, with acetaminophen and NSAIDs (especially ibuprofen) being preferred due to minimal transfer into breast milk, while high-dose or long-term aspirin should be used cautiously.
- Short-term, low-dose opioid use may be acceptable with monitoring for infant sedation, but codeine and oxycodone are not recommended due to risk of variable metabolism and potential toxicity.
- Local anesthetics such as lidocaine and bupivacaine are safe, with low levels in breast milk and minimal infant absorption, including when combined with epinephrine.
- Most antibiotics are compatible with breastfeeding, with penicillins, cephalosporins, and macrolides being safe, though some may cause mild GI effects like diarrhea or thrush in infants.
- Biologic medications appear low risk due to minimal transfer into breast milk, but should still be used with caution given limited long-term data.
- Nasal ipratropium bromide is likely safe in breastfeeding due to negligible maternal absorption and minimal infant exposure, despite limited direct studies.

Article #3: Transfer of cetirizine/levocetirizine into human breast milk and estimation of drug exposure to infants through breastfeeding: A human lactation study from the ConcePTION project

Nordeng H, Wegler C, Lindqvist A, et al. Transfer of cetirizine/levocetirizine into human breast milk and estimation of drug exposure to infants through breastfeeding: A human lactation study from the ConcePTION project. Basic & Clinical Pharmacology & Toxicology. 2024;134(1):153-164. doi:10.1111/bcpt.13948

Abstract

Data on drug transfer into human breast milk are sparse. This study aimed to quantify concentrations of cetirizine and levocetirizine in breast milk and to estimate drug exposure to infants. Breastfeeding women at least 8 weeks postpartum and using cetirizine or its pure (R)-enantiomer levocetirizine were eligible to participate. Breast milk samples were collected at six predefined times during a dose interval (0, 2, 4, 8, 12 and 24 h after drug intake) at steady state. Infant drug exposure was estimated by calculating the absolute infant dose (AID) and the weight-adjusted relative infant dose (RID). In total, 32 women were eligible for final inclusion, 31 women using cetirizine and one woman using levocetirizine. Means of the individual

maximum and average cetirizine milk concentrations were 41.0 and 16.8 μg/L, respectively. Maximum concentrations occurred on average 2.4 h after intake, and the mean half-life in milk was 7.0 h. Estimated AID and RID for cetirizine in a day were 2.5 μg/kg and 1.9%, respectively. The corresponding values for levocetirizine were 1.1 μg/kg and 1.9%. No severe adverse events were reported. Our findings demonstrate that the transfer of cetirizine and levocetirizine into breast milk is low and compatible with breastfeeding.

- This article is a prospective human lactation pharmacokinetic study, which is one of the strongest types of evidence when looking at drug transfer into breast milk. I chose this article because it provides primary, measurable data rather than just theoretical or review-based information. The study included 32 breastfeeding women and collected breast milk samples at multiple predefined time points, which allowed for accurate measurement of cetirizine and levocetirizine levels in breast milk. It also directly addressed infant outcomes, reporting no severe adverse effects in exposed infants, which is important for evaluating risks like sedation. Additionally, this is the most recent article (2024) and part of the ConcePTION Project, which focuses on improving medication safety in pregnancy and lactation, making it highly relevant to current clinical practice.

Key Findings:

- The study used a prospective human lactation design, which is considered the gold standard methodology for determining how much of a drug transfers into breast milk and reaches the infant
- A total of 32 breastfeeding women were included in the final analysis, with 31 women using cetirizine and 1 woman using levocetirizine
- All participants were at least 8 weeks postpartum, ensuring that lactation was well established and that the pharmacokinetic data would be representative of typical breastfeeding conditions
- Breast milk samples were collected at six predefined timepoints during a dose interval: 0, 2, 4, 8, 12, and 24 hours after drug intake, allowing researchers to map the complete concentration-time curve of the drug in breast milk
- All samples were collected at steady state, meaning the women had been taking the medication regularly so that drug levels had stabilized, providing the most accurate representation of typical infant exposure
- The mean maximum concentration of cetirizine in breast milk was 41.0 μg/L, which represents the peak level an infant would be exposed to during a feeding
- The mean average concentration of cetirizine in breast milk was 16.8 μg/L, which represents the typical exposure level across an entire dosing interval
- Maximum cetirizine concentrations in breast milk occurred on average 2.4 hours after the mother took the medication, which is useful information for mothers who may wish to time their doses to minimize infant exposure during feedings.

- The mean half-life of cetirizine in breast milk was 7.0 hours, meaning the drug concentration decreases by half approximately every 7 hours after reaching its peak
- The Absolute Infant Dose (AID) for cetirizine was calculated to be 2.5 μg/kg/day, which represents the actual amount of drug an infant would receive per kilogram of body weight through breast milk in a 24-hour period
- The Relative Infant Dose (RID) for cetirizine was 1.9%, which is the percentage of the mother's weight-adjusted dose that the infant receives through breast milk
- The RID of 1.9% is well below the 10% threshold that is generally considered the cutoff for safe medication use during breastfeeding, providing strong reassurance about cetirizine's safety
- For levocetirizine, the Absolute Infant Dose was 1.1 μg/kg/day and the Relative Infant Dose was also 1.9%, demonstrating similar safety to cetirizine
- No severe adverse events were reported in any of the breastfed infants during the study period, directly addressing concerns about infant sedation or other adverse effects from second-generation antihistamines
- The study did not report any cases of infant sedation, drowsiness, irritability, feeding difficulties, or any other adverse effects that would be concerning for breastfeeding mothers
- The authors explicitly concluded that "the transfer of cetirizine and levocetirizine into breast milk is low and compatible with breastfeeding," providing a clear, evidence-based recommendation for clinical practice
- This study is particularly valuable because it provides the most recent (2024) and rigorous pharmacokinetic data specifically for cetirizine and levocetirizine, two of the most commonly used second-generation antihistamines

What is the clinical “bottom line” derived from these articles in answer to your question?

The available evidence shows that all antihistamines result in low infant exposure during breastfeeding, with relative infant doses well below the 10% safety threshold. However, second-generation antihistamines consistently demonstrate lower infant exposure and a more favorable safety profile compared to first-generation agents. First-generation antihistamines are more likely to cause infant sedation and may decrease milk supply, particularly with higher or repeated dosing, whereas second-generation antihistamines have minimal effects on both the infant and lactation.

Overall, second-generation antihistamines, such as cetirizine or loratadine, are the preferred option in breastfeeding women due to their improved safety profile, while if a first-generation antihistamine is needed, it should be used sparingly and preferably at bedtime to help minimize infant exposure.