MEDICATIONS IN HUMAN MILK

By Uma Yakandawala

Thesis submitted to the Faculty of Graduate Studies at the University of Manitoba in partial fulfillment of the requirements of the degree

Master of Science

College of Pharmacy
Rady Faculty of Health Sciences
University of Manitoba
Winnipeg, MB, Canada

THESIS ABSTRACT

Many people require the use of medications during lactation to treat acute or chronic health conditions. One identified barrier to continued breastfeeding is medication use due to concerns of drug exposure risks to the infant through milk. Currently, there are no consistent and standardized practices for the collection and drug analysis in human milk. This thesis consists of two complementary studies.

In the first study, a systematic review was conducted to understand collection methods and analytical techniques used to study medications in human milk. The systematic review included 224 studies on 186 medications belonging to 46 different therapeutic categories. The five therapeutic categories most reported include antidepressants (N=58), anti-retroviral agents (N=43), antibiotics (N=16), non-steroidal anti-inflammatory drugs (N=14), and opioids (N=14). The most used sampling method was multiple collection time points within a 24-hour period (N=55,24.6%). There were 45 different assay methods used, the most common being high-performance liquid chromatography (HPLC) used in a third of the studies (N=74,33.0%).

The second study used a mixed-methods research design to understand parents' and healthcare providers (HCP) preferences, decision-making and knowledge around medication use during lactation. A scoping review was conducted to inform the design of the survey study. There were 149 parents and 47 HCP participants. The majority of the parents in this study used medication during postpartum (N=138/146,94.5%). Over half (N=68/124,54.8%) of the parents found decision-making on medication use while nursing to be difficult and very few parents felt certain about what to do when making decisions (N=11/124,8.8%). Parents ranked the leading factor impeding decision-making to be lacking information about options, benefits, and risks of medications. HCPs listed their professional training on medication use during lactation as below average (N=9/29,31.0%) and extremely poor (N=9/29,31.0%). HCPs stated reliable resources, improved patient resources, more education on medication safety would help better support parents' decision-making.

Results from the studies have identified medications of interest, that can be used to develop standardized protocols for future prospective studies. Future studies could focus on assessing decisional needs around commonly used medications by postpartum parents to develop a decision aid that can be used in clinical practice.

ACKNOWLEDGEMENTS

I would like to thank,

My supervisors, Dr.Christine Leong and Dr.Lauren Kelly for their utmost support and guidance. I have learned so much throughout this program and I sincerely appreciate all your support and encouragement.

My advisory committee members, Dr.Turcotte and Dr.Zelenitsky..

Steering committee members, Angela Blouin, Dr. Katherine Kearns, Dr. Christina Raimondi, Dr. Karine Toupin-April and Laurie Proulx.

Lab members in the Clinical Pharmacology Lab.

Pharmacoepidemiology group at the College of Pharmacy.

My friends and family for their encouraging words and support throughout my studies.

Centre for Health Innovation (CHI) for awarding the PREPPP award which funded the parent engagement interviews and support with recruitment.

Rady Innovation Fund for making it possible to do this important research.

DEDICATION

This thesis is dedicated to my parents

Ammi and Thathi,

You have instilled the love of learning and nurtured my passion for science.

Thank you for always supporting and encouraging me in everything I do.

THESIS PREFACE

This thesis project consists of two complementary studies and is presented using a grouped manuscript style. Three research papers are intended for peer-reviewed journal publication.

Chapter 1: Introduction/Background

Study 1

Chapter 2: A systematic review of collection methods and analytical techniques used to study medications in human milk (research paper)

Study 2

Chapter 3: Parent and healthcare providers' preference factors, decision-making and knowledge on medication use during lactation: scoping review (research paper)

Chapter 4: Parent engagement interviews

Chapter 5: Parent and healthcare providers preference factors, decision-making and knowledge on medication use during lactation: a Canada-wide survey study (research paper)

Chapter 6: Conclusions/future directions - pilot protocols, decision aid

Contributions of Authors

Uma Yakandawala: Completed study 1 and 2 including literature review, conducting all methods, data analysis, writing manuscript and finalizing this thesis

Dr.Christine Leong: Supervisor

Dr.Lauren Kelly: Co-supervisor

Youstina Soliman: assisted with study 1 systematic review article screening

Even Frost: assisted with study 2 scoping review article screening

Dr. Christina Raimondi, Dr. Katherine Kearns, Angela Blouin, Dr. Karine Toupin April, Laurie Proulx: steering committee members for study 2 contributed to inform and develop the study design

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

CHAPTER 1. INTRODUCTION/BACKGROUND

1.1 HUMAN BREAST MILK

Human breast milk is a biological fluid that is widely understood to be the best source of nutrition for all infants.[1] Human milk contains all the necessary nutrients needed for the growth and development of an infant in the first six months of life and is an important source of nutrients beyond this point.[2] The main components in breast milk include macronutrients (proteins, fats and carbohydrates), micronutrients (vitamins and minerals) and other trace elements.[1] Additionally, breast milk contains other components such as hormones, digestive enzymes, bioactive molecules such as stem cells, immune cells and growth factors. The average nutritional composition of mature human breast milk is 87% water, 7% lactose, 3-5% fat and 1% protein. However, the composition of human milk does vary to some extent due to factors such as maternal genes, body composition of the mother, diet of the mother, infant factors and duration of lactation.[2,3]

Ninety percent of the total energy in breast milk is provided by fat (50%) and lactose (40%). Breast milk contains about 22 calories per 1 fluid ounce.[4] The protein content in breast milk is 0.9 g per 100 ml.[5] The main protein in breast milk is casein and whey. During the course of lactation, there are changes to the protein content in breast milk. The casein content is lower during the early stages of lactation and increases at the later stages. Whey protein content, however, remains high and stable during the entire period of lactation.[1] The carbohydrate content in breast milk is about 7 g per 100ml and is another important source of energy proving about 40% of calories.[5] The main carbohydrate in breast milk is lactose, a disaccharide.[6] It also contains small quantities of oligosaccharides, fructose and galactose. Lactose content during the start of lactation is low but starts to increase during the first few weeks of life and the concentration remains stable throughout the stages of lactation.[7,8] Lactose is beneficial for calcium absorption and the oligosaccharides may help to maintain beneficial gut bacterial flora.[9] Fat content in breast milk is about 3.5g per 100 ml and provides about 50% of the calories.[5] The fat content in human breast milk contains long-chain polyunsaturated fatty acids (docosahexaenoic acid or DHA, and arachidonic acid or ARA) that are not provided by other types of milk and are important for the neurological development of the infant. The fat content is

also an essential part of the cell membrane particularly in the brain and eye and may have benefits for visual and mental acuity.[10]

1.2 Anatomy of the breast

The human breast includes the following structures: areola, nipple, mammary tissue, nerves, connective tissues, fat, blood and lymphatic vessels.[11,12] The breast in both females and males contains special glands called mammary glands. Mammary glands are a type of exocrine gland which is an enlarged and modified sweat gland that can produce and eject milk. In females, they develop around the time of puberty and in men they do not get fully developed.[12] Before pregnancy, the mammary glands do not make up a large percentage of a woman's breast. However, during pregnancy, these glands expand and branch out in response to stimulation by hormones such as estrogen and prolactin. Surrounding the mammary glands are cells called myoepithelial cells, or muscle cells. These are special cells that not only line the outside of the mammary glands, also contract down on these glands to assist with milk extraction along the duct. Milk is drained toward the nipple through ducts called lactiferous ducts and the milk is ejected out through the nipple. [12]

1.3 Physiology of lactation

Lactation is the process where milk is made and ejected from the mammary glands inside the female breasts. There are a few hormones involved in the process of lactation, these include estrogen, progesterone, prolactin, and oxytocin.[13] During pregnancy there is an increase in estrogen and progesterone, which are released by the placenta during pregnancy. Together, they have two major roles, which include increasing the size and number of milk ducts in the breast and preventing the breast from producing large amounts of breast milk until the baby is delivered.[13] Throughout pregnancy, there is also the continuous increase of the hormone, prolactin, which is essential for the initiation of lactation. Prolactin in the blood increases during pregnancy and contributes to the development and growth of the mammary tissues necessary for lactation.[14] However, high levels of both estrogen and progesterone during pregnancy inhibit the action of prolactin on mammary tissue by blocking the prolactin receptor therefore milk production does not occur.

Once the infant is delivered and the placenta is removed, the hormones estrogen and progesterone decrease, which disinhibits the prolactin receptor. This decrease in estrogen and progesterone signals the body that it is now time to produce milk. The suckling action of the baby is the primary stimulus for increased levels of prolactin, ultimately increasing milk production.[15] As the infant feeds, the hormone oxytocin is released which stimulates milk expulsion from the breast. This release causes myoepithelial cells to contract which causes milk to squeeze out of the alveoli into the ducts and out of the nipple. This process is called the "let-down reflex" or "milk ejection reflex."[16]

1.4 Phases of Milk

There are three phases of breast milk production, these include colostrum, transitional milk, and mature milk.

Phase 1: Colostrum. The first milk that is produced during lactation is called colostrum. Production begins during pregnancy and continues for several days after the delivery of the baby.[17] Colostrum is yellow and creamy in colour and has a thicker consistency compared to milk that is produced later in lactation.[19] Colostrum has more protein, fat-soluble vitamins and minerals compared to breast milk produced later.[13] Colostrum is also rich in white cells and antibodies called immunoglobulins, providing important passive immunity for the baby which is necessary for protection from viral and bacterial infections.[18]

Phase 2: Transitional Milk. Colostrum will be replaced by transitional milk at around four days after delivery and will continue for about two weeks. Transitional milk has a higher calorie content compared to colostrum and includes high levels of lactose, fat and water-soluble vitamins.[18]

Phase 3: Mature milk. The final phase of milk that is produced is called mature milk and starts at around two weeks and continues until breastfeeding is discontinued. The content of mature milk is about 90% water important for the baby's hydration and the other 10% is contains mostly proteins, carbohydrates and fats.[18]

1.5 BENEFITS OF BREASTFEEDING

Human milk is the optimal nutrition for infant growth and development, and a source of antibodies that promote the child's innate immune system.[20] "Among the most common reasons breastfeeding infants receive supplements is the concern that the infant is not getting enough milk and mothers' lack of breastfeeding self-efficacy." [21,22] There are differences in health outcomes for both mother and infants between human milk versus formula feeding "compared with breastfed infants, formula-fed infants face higher risks of infectious morbidity in the first year of life." [23] Some data suggest the benefits are greater in low-/middle-income countries than high-income countries.[24]

There are numerous benefits of breastfeeding for both the infant and mother. Some of these benefits are shown in Table 1.1.

Table 1.1 Benefits of breastfeeding for infants and mother

Benefits for the infant	**Benefits for the mother**
Optimal nutrition for infant[20]	Skin to skin contact which promotes bonding between mother and baby[28]
Protection from environmental exposures [19]	Accelerated uterine recovery [27]
Promotes development of the child's innate immune system[27]	Saves money on formula for the infant[29]
Prevention of illness: gastroenteritis and diarrhea, respiratory disease[25], sudden infant death syndrome (SIDS) [26], lower risk of otitis media, lower respiratory tract infections (LRTI), diabetes, atopic dermatitis, asthma and neurodevelopment [23,24]	Long-term benefits include reduction in risk of breast cancer, ovarian cancer, endometrial cancer, cardiovascular disease and developing type 2 diabetes [29]
Long-term benefits by reducing risk for several chronic diseases [27]	Earlier return to pre-pregnant weight[29]

1.6 Challenges of breastfeeding

Parents may face various challenges during breastfeeding. Among Canadian mothers, the main reasons for breastfeeding for less than six months included perception of insufficient breast milk quantity and challenges with breastfeeding techniques.[30] Additional challenges and barriers parents face during breastfeeding are displayed in Table 1.2.

Table 1.2 Challenges and barriers to breastfeeding

Challenges and barriers	**Examples**
Physical feeding challenges	Low milk supply[32] Nipple pain, irritation, engorgement, sensitivity and soreness[31] Mastitis[31] Baby not latching properly[34] Pumping challenges: time commitment, lack of access to breast pumps, lack of time or places to pump in public/work/school[36,37]
Perceptions, views, and knowledge on breastfeeding	Concerns for medication use on milk supply or milk quality[32] and infant health outcomes[35] Parents' level of self-efficacy and confidence[42] Cultural barriers[47]
Parents' health and other needs	Physical disabilities[38] Emotional stress[33] Fatigue or burnout[33] Contraindicated medications or medical procedures e.g., radioisotopes, chemotherapy[39] Illicit drug use[39] Medical conditions breastfeeding is contraindicated: active HIV, HTLV-1, HTLV-2 infection, active untreated tuberculosis, suspected or confirmed Ebola virus disease[39]
Infants' health needs	Failure to gain weight[40] Weight loss[41] Medical conditions breastfeeding is contraindicated: metabolic disorder of classic galactosemia[39]
External factors	Lack of social support[42] Time constraints due to return to work and/or school[43,44]

Efforts should be made to find ways to mitigate challenges faced during breastfeeding. In a qualitative study by Francis et al. mothers reported in-home lactation consultant services helped mitigate and addressed key breastfeeding challenges.[45]In this study, an International Board-Certified Lactation Consultant (IBCLC) helped teach parents how to breastfeed "providing physical support included hands-on guidance with hand expression, latching, positioning, engorgement, and blocked ducts…enhance their breastfeeding self-efficacy…encouraging attitude of the IBCLC and emotional support provided." Another study by Francis et al. examined an enhanced postnatal lactation support program for vulnerable women which showed "high uptake by clients and corresponding high rates of breastfeeding." Breastfeeding was initiated by all participants and continued for 6 months by 84%.[46]

Although it is well understood that breastfeeding for six months is optimal, challenges like the ones presented often lead to reduced breastfeeding duration.[30] It is therefore essential that healthcare professionals offer continuous support throughout this process. Types of support available for Canadian parents include public health nurses, lactation consultants, breastfeeding support groups, breastfeeding doctors, and provincial online and phone support.

In Manitoba, there are numerous breastfeeding resources and supports for parents, including:

- A toll-free line, operated by Manitoba's Health Links, support parents' challenges with breastfeeding, fatigue, and emotional stress.
- Breastfeeding hotline with 24-hour nursing phone support
- Breastfeeding clinics for individual and group support, are provided by the Winnipeg Regional Health Authority.
- Healthy Baby Community Support programs offer various prenatal and postpartum support services and resources, including breastfeeding support. Parents can connect with other parents, families, and health professionals.
- Youville Community Health Resource Centre (St. Vital) has lactation consultants by appointment and breastfeeding support drop-in.

1.7 Medications and breastfeeding

Although most drugs transfer into the breastmilk in small amounts, the impact on the infant can vary greatly depending on the drug. There have been case reports of infant morbidity

and even fatalities following exposure to medications in breastmilk.[48] Many mothers require the use of medications during lactation to treat acute or chronic health conditions which may be crucial for their clinical care and maternal well-being. One identified barrier for parents to continue breastfeeding is medication use, due to concerns of drug exposure risks to the child through milk.[35] Mothers requiring medications may be left ill-informed about the risks of nursing while taking medications given a historical exclusion from research and drug development. It is important to assess the risk (including the risks of not breastfeeding) and benefits for both mother and child when advising on medication decisions while breastfeeding. Mothers may take an absolute risk avoidance approach and stop breastfeeding or discontinue taking necessary medications to avoid possible (unknown) adverse effects on their children. Sixty-four percent of women who are pregnant received at least one prescription medication based on administrative data from Manitoba and British Columbia.[49,50] Roughly the same proportion at 63% receive a prescription medication 0-3 months postpartum.[50] Given these significant statistics, it is critical that healthcare professionals offer advice based on scientific evidence and clear that more research is needed in this area.

A survey from the Netherlands by Schirm et al. reported that breastfeeding women (BFW) used drugs (65.9%) less frequently compared to non-breastfeeding women (NBFW) (79.6%).[51] Non-breastfeeding women used drugs such as iron preparations, oral contraceptives, medications to treat peptic ulcers, and psychotropic drugs more frequently compared to BFW.[51] Additionally, a prospective cohort study (Soliman Y, Yakandawala U, unpublished data, February 2022) examining the use of prescription and non-prescription health products of breastfeeding Canadian mothers report almost half (41.9%) used at least one prescription medication during the first three months postpartum. The five most used prescription medication by BFW at 3 months postpartum were domperidone (9.0%), norethisterone (5.0%), levothyroxine (4.3%), cephalexin (3.7%), amoxicillin (2.7%).

Currently, to determine the risk of medication use during breastfeeding, parents and health providers have access to evidence-based resources such as “Medications and Mothers Milk”[52] by Hale, and “Drugs in Pregnancy and Lactation” [53] by Briggs and Freeman. To better assess the safety of drugs transferred through human milk, more information is urgently needed on the mechanism, variability, and quantity of drug exposure in the infant. There is a large

knowledge gap on the quantity of drug transferred into milk and how this affects infants which are not considered during drug development.

1.8 Transfer of drugs and therapeutics into breastmilk

Drugs are transferred from maternal plasma to breast milk primarily through passive diffusion. Low maternal plasma protein binding, small molecular weight and high lipid solubility have the greatest potential for drug transfer.[54] When determining the risk to infants it is important to consider drug properties, the volume of milk consumed and how genetic polymorphisms in drug metabolism may influence overall exposure or pharmacodynamics.

Most drugs and supplements enter breastmilk primarily through passive diffusion (crossing membranes down a concentration gradient from high concentrations in maternal blood to low concentrations in milk). Some drugs pass by carrier-mediated diffusion and some agents are actively transported.[52]

Medications must generally pass through both bilayer lipid membranes of the alveolar cell to penetrate milk. Equilibrium may be established between maternal plasma and breast milk. As drug concentrations in the mother decrease, a higher drug concentration in the milk will promote transfer back into the maternal circulation. Almost all the drugs that a mother ingests will be present to some extent in her breastmilk.[52]

1.9 Drug properties affecting the concentration of drugs in milk

Maternal Plasma Concentration

Maternal plasma concentration is an important determinant of drug penetration into milk. Drugs move through passive diffusion from the maternal serum and enter the breast milk. When the medication level in the mother's plasma increases, the concentration in milk will subsequently increase as well.[52]

Size of a Drug molecule

Drugs that are low in molecular weight can transfer more readily compared to larger molecules. Most drug molecules are small enough to penetrate breast milk such as caffeine,

alcohol and nicotine. Some drugs have high-molecular weights, therefore, do not enter breast milk, such as heparin and insulin.[56]

Maternal Plasma Protein Binding

Drugs binding to plasma proteins influence the extent of transfer into breast milk. Free unbound drugs diffuse readily while highly protein-bound drugs are unable to enter breastmilk in significant amounts.[52]

Degree of Ionization

Drugs generally cross the plasma membrane and enter breastmilk in an un-ionized form. Breast milk is slightly more acidic at pH 7.2 compared to the mothers' plasma at pH 7.4, attracting weak organic bases. Therefore, weakly basic drugs will become ionized and stay in the milk compartment.[56]

Lipid Solubility

Lipid soluble drugs can penetrate breast milk in higher concentrations. The mammary epithelium is a lipid membrane, making lipid-soluble drugs more likely to enter breast milk. Additionally, drugs that easily cross the blood-brain barrier usually enter breast milk more readily.[52]

1.10 FACTORS THAT INFLUENCE EFFECTS ON THE INFANT

Timing of dose

Timing of dose is impacted by factors such as pharmacokinetics, dosing frequency, whether a drug is used as needed or regular dosing. For drugs with a short half-life to minimize medication transfer to the infant through breast milk, feeding the infant before taking a medication will result in the infant receiving the lowest possible dose.[56]

Metabolism

Infants that were born prematurely and neonates may have a lower capacity to metabolize and excrete drugs and this may lead to prolonged exposure to agents.[56]

Oral Bioavailability

Oral bioavailability refers to the amount of a drug that reaches the circulation of the individual. Therefore, although a drug may be found present in breast milk it does not indicate the infant will have significant exposure to the drug. The stomach of the infant is quite acidic and can degrade and destroy drugs and some drugs are not well absorbed through the gut.[56]

Volume of Breastmilk

The quantity of breast milk an infant receives varies due to many factors. Some mothers may choose to exclusively breastfeed their child while others may choose to breastfeed as well as formula feed. The amount of breastmilk the baby receives during a feed may vary as well. Additionally, an infant that is 2 months old that is exclusively breastfeeding will be receiving more breast milk compared to an older infant that is being started on solid food that only nurses for comfort and bonding. Therefore, those infants that are receiving a greater volume of breastmilk will be exposed to medications in breastmilk at higher levels.[56]

Age of the Infant

Most adverse events from drug exposure through breast milk occur in infants under two months.[57] Reports document that about 75% of adverse events occur in infants under two months and rarely occur in those older than six months.[57] Compared to a 7-8-month-old baby, a newborn infant's metabolism and excretion ability are only about one-third. Additionally, newborns may consume larger doses of a drug in comparison to their weight and are also more likely to be exclusively breastfed compared to older infants.[56]

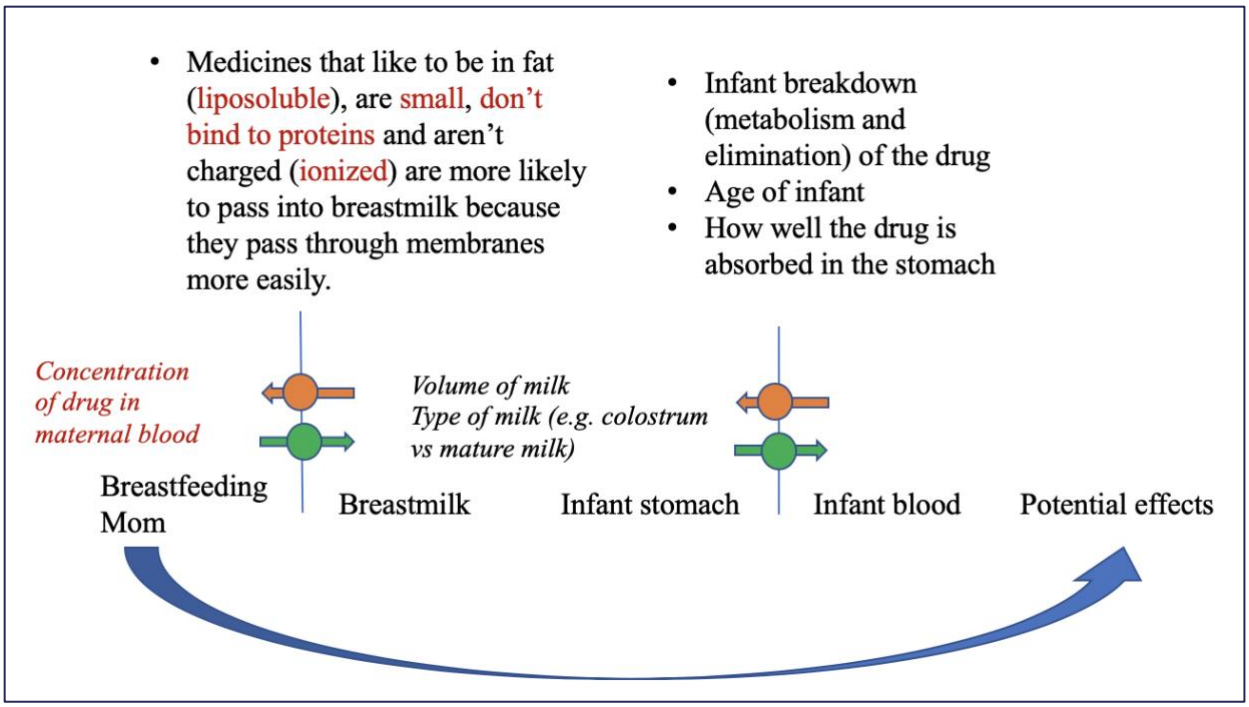


Figure 1.1 Properties that influence the concentration of drugs in breast milk and adverse effects on the infant

1.11 METHODS FOR ESTIMATING INFANT DRUG EXPOSURE

Relative Infant Dose (RID)

$$RID = \frac{\text{Dose in infant } \frac{\text{mg}}{\text{kg}}}{\text{Dose in mother } \frac{\text{mg}}{\text{kg}}}$$

Relative infant dose (RID) approximates how much of the maternal medication dose the infant is receiving. Relative infant dose provides an estimate of weight-normalized dose relative to the mother's dose. The infants' dose is calculated from the drug concentration in the breast milk and multiplied by the total volume of milk that is ingested by the infant. In this calculation, babies are estimated to consume 150 mL/kg/day of breastmilk. The RID is expressed as a percentage of the maternal dose. RIDs less than 10% are considered clinically insignificant for most medications, although this also depends on the type of drug taken.

Some drugs, such as acetaminophen, have RIDs above the 10% threshold, however, because the drug itself is quite non-toxic, there is no adverse effect on the infant.[54]

Milk to plasma ratio (M/P)

Another value used to estimate infant exposure to drugs through human milk is the milk to plasma ratio (M/P). This is the ratio of the concentration of drugs in the mother's milk divided by the concentration in the mother's plasma and is indicative of the extent to which a medication crosses from the mother's plasma into her breast milk.[58] It is a description of a relationship, unlike the RID which gives an estimate of the actual amount of drug transferred. If the M/P ratio is high (greater than 1-5) it can be an indicator that the drug may sequester at high levels in breast milk. If the M/P ratio is low (less than 1), a minimal level of drug is transferred into the milk, which is the preferred scenario.[58] Although it is better to select drugs with low M/P ratios, the level of drug transferred is also dependent on the level of drug in the mother plasma. The amount of medication that is transferred can still be small with a high M/P ratio and low maternal plasma levels.[55]

1.12 Drugs contraindicated during breastfeeding

Overall, there are very few drugs that are absolutely contraindicated while breastfeeding. Some of these agents include[56]

- Chemotherapeutic/antineoplastic agents
- Radioactive pharmaceuticals
- Oral retinoids
- Illicit drugs (e.g., phencyclidine or cocaine)

1.13 Human milk Recommendations

Breastfeeding has numerous important health benefits for both mother and child, as previously discussed. Exclusive breastfeeding is recommended for the first six months of life by The American Academy of Pediatrics[59], the World Health Organization[60], and Health Canada.[61] Consensus also acknowledges that breastfeeding continues to benefit the nutritional, emotional and immunologic health of the child up to two years of age.[62] Human milk provides children

with necessary nutrients, contains antibodies that help support the baby's immune system and facilitates maternal-infant bonding.[30]

1.14 Rates of breastfeeding

A 2021 study by Neves et al, examining breastfeeding practices worldwide between 2000 and 2019 shows that due to the promotion of optimal breastfeeding practices worldwide there has been an increase in breastfeeding rates over time. Specifically exclusive breastfeeding at 6 and 12 months in upper-middle- and high-income countries.[64] Breastfeeding initiation rates are high among Canadian parents with 90% attempting to breastfeed in 2015/2016, which has increased since 1965 when rates were less than 25%.[39]

Around 25% of parents stopped breastfeeding by the time their infant was one month. Over half (57%) of parents who breastfed continued some breastfeeding past six months and 19% beyond one year (2011/12).[63] Over a third (32%) of parents breastfed exclusively for six months.[30] The main reasons parents state for stopping breastfeeding at less than six months are "'not enough milk' (44%) and 'difficulty with breastfeeding technique' (18%)."[30]As well, rates of breastfeeding initiation vary across provinces with the rate of 96% in British Columbia and Yukon to 57% in Newfoundland and Labrador (2011/2012).[63]

1.15 Decision-making around medication use and breastfeeding

Making decisions around medication use during lactation can often be a challenge for parents due to limited evidence-based information. The decisions to be made can be more complex than deciding to take or not to take a medication.

Decisions could look like this:

'Do I breastfeed exclusively? Mix feed? Or provide formula only?'

'Do I continue taking my medication? What will happen to my baby?'

'Do I stop taking my medication? What will happen to my condition?'

'Do I need to change medications, even if I am doing well on my current medicine?'

'Do I need to change the timing of medication administration and/or pump breast milk?'

Various factors can contribute to decision-making; therefore, it is important to better understand parents' lived experiences, preferences, values, and concerns around medication use during lactation when providing recommendations. Shared decision-making involves patients

and their clinicians sharing the best available evidence when faced with the task of making health decisions.[65] Patients are encouraged and supported to consider different options and to weigh the benefit and risks of the choices. Shared decision-making allows patients to be involved and better informed about their healthcare decisions and to relay their preferences to the clinicians. Shared decision-making is essential for good patient-centred care and has benefits for patients such as increased confidence in their decisions, active involvement, and improved knowledge.[66]

Decision aid tools can be used to help facilitate shared decision-making based on parents' priorities and values as well as research evidence. "Decision aids are evidence-based tools that help people become involved in decision making by making explicit the decision that needs to be made, providing information about the options and outcomes, and by clarifying personal values."[67] These tools are not a replacement for healthcare providers' counseling but are meant to facilitate meaningful interaction and patient involvement in their health decisions.

Currently, there is a decision aid for parents considering whether or not to breastfeed their child.[68] However, there do not exist any decision aid tools to assist parents in making decisions around medication use during breastfeeding.

1.16 Project Overview

Critical questions around what medications are commonly used during breastfeeding in Canada, how milk samples should be collected, what analysis methods should be implemented, and what factors related to medication taking are important from the perspective of breastfeeding people require rigorous answers. The current thesis project aims to determine the best methodologies and tools needed for studying medications in human milk

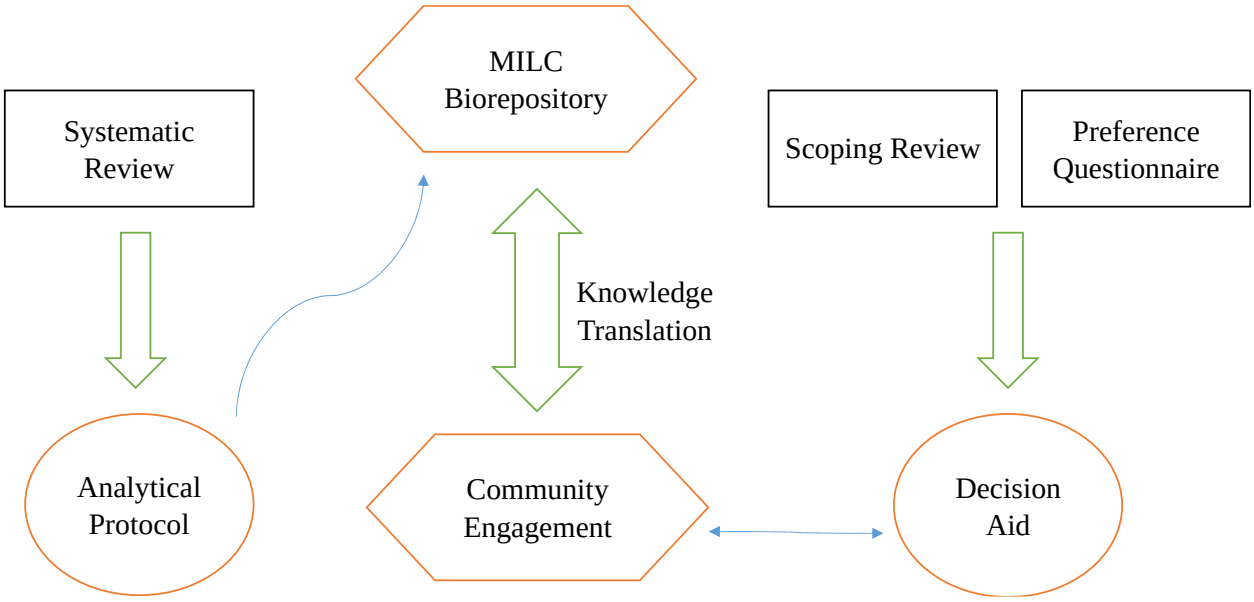


Figure 1.2 Overview of the thesis project

Study 1: A systematic review of collection methods and analytical techniques used to study medications in human milk

Chapters included:

*Chapter 2: A systematic review of collection methods and analytical techniques used to study medications in human milk (research paper)

*Intended for publication in a peer-reviewed scientific journal

Literature on optimal breast milk collection and analysis procedures for studying drugs in breastmilk is limited, and there are no standardized protocols that have been established. A systematic review was conducted to better understand the collection methods and analytical

techniques used to study medications used during breastfeeding. The historical changes in collection and analysis methods over time are currently unknown therefore it is of interest to examine how analytical techniques have changed over time, as well as the advantages and disadvantages of different methods. In the future, this information can be used to develop validated collection methods and analytical techniques to quantify the levels of medications excreted in breast milk.

Study 2: Parent and healthcare providers' preferences, decision making and knowledge on medication use during lactation

Chapters included

*Chapter 3: Parent and healthcare providers preference factors, decision making and knowledge on medication use during lactation: scoping review (research paper)
Chapter 4: Parent engagement interviews
*Chapter 5: Parent and healthcare providers preference factors, decision making and knowledge on medication use during lactation: a Canada-wide survey study (research paper)
* Chapters 3 and 5 are intended for publication in a peer-reviewed scientific journal

Ethics approval

The study has been reviewed and approved by the Health Research Ethics Board (HREB) of the University of Manitoba, approval number HS24663 (H2021:069).

Overview of research design

Existing literature on parent preferences and decision-making around medication use during lactation is limited. A mixed-methods study design was employed to understand parents' and healthcare providers' preference factors, decision making and knowledge around medication use during breastfeeding. This study included a scoping review, parent interviews and parent and healthcare provider surveys.

The International Patient Decision Aid Standards (IPDAS) and Ottawa Decision Support Framework (ODSF) were used as the framework to guide question development for the surveys in this study. ODFP "conceptualizes the support needed by patients, families, and their practitioners for 'difficult' decisions with multiple options whose features are valued differently.

It guides practitioners and researchers to assess participants' decisional needs, provide decision support interventions (clinical counselling, patient decision tools, decision coaching) and evaluate their effects on decisional outcomes".[69] The primary investigator completed the Ottawa Patient Decision Aid Development eTraining[70] at the start of the study to prepare for study development. Decisional needs assessment in populations[71], a workbook for assessing patients' and practitioners' decision-making needs, was used to develop the methodology of this study.

A scoping review was conducted to understand the current literature on parent and health care providers' preferences factors and decision making around medication use during breastfeeding. The current findings and gaps in the literature helped inform the development and direction of the preference survey. Qualitative interviews of mothers and birthing parents identified concepts important to the research outcomes. The survey was also pilot tested, and feedback was provided which further developed items for the survey. Quantitative questionnaires were developed based on the scoping review findings, advice from the advisory steering committee, and revised based on the feedback from the parent interviews.

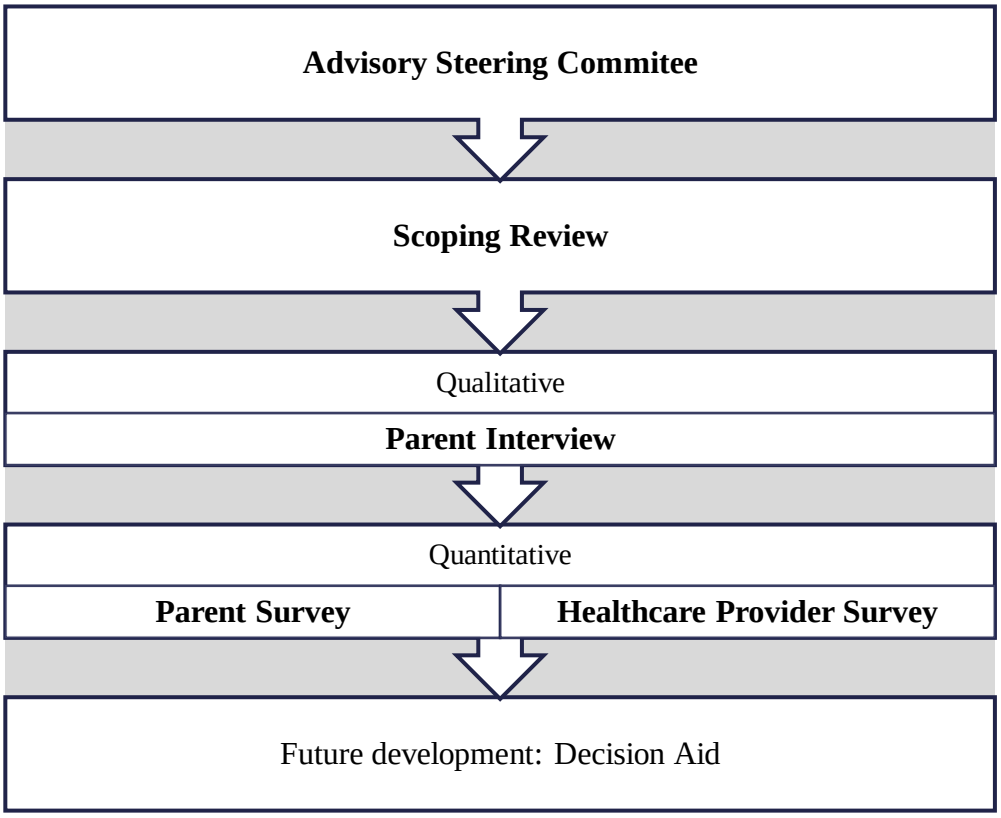


Figure 1.3 Study 2 research study design

Advisory steering committee

The first step was to assemble an advisory steering committee of parents with lived experience, physicians, pharmacists, researchers, nurses who have an interest in research related to medication in breast milk that help to guide this study. The steering committee has allowed us to understand what key concerns parents have regarding decision-making around medication use during breastfeeding. They have helped inform the scoping review strategy and provided input for the preference questionnaire development.

The advisory steering committee gathered for 3 meetings

- Meeting 1 (Winter 2021)– Meeting to discuss scoping review content and design of preferences questionnaire
- Meeting 2 (Spring 2021) – Review of preferences questionnaire and planning for recruitment
- Meeting 3 (Spring 2022)- Share and interpret results from scoping review and questionnaire

Scoping review

The second step involved conducting a scoping review of the available literature to understand mothers/birthing parents and health care professionals' preference factors and knowledge that contribute to decision making around medication use during lactation.

Parent engagement interviews

The third step involved qualitative interviews of mothers/birthing parents. We facilitated meaningful engagement sessions in the form of individual structured interviews of mothers/birthing parents to better understand their lived experiences, preferences, values, and concerns around medication use during lactation. The participants also pilot tested and provided feedback on the parent questionnaire which helped further develop and better meet the study objectives and identify parent important outcomes.

Parent and healthcare provider survey

The final step was to administer the parent survey and healthcare provider survey online. All these activities together will inform the future development of a decision aid related to medication use during breastfeeding. Future studies plan to collaborate with mothers and birthing parents in the decision-making process, priority setting and outcome selection for the design of a

parent-informed decision aid that can help guide decision-making around medication use while breastfeeding.

Future development: Decision Aid

Findings from the scoping review and survey will help inform the future development of a shared decision-aid around medication use during lactation for parents and healthcare providers to use in clinical practice.

1.17 REFERENCES

1. Stam J, Sauer PJ, Boehm G. Can we define an infant's need from the composition of human milk? *Am J Clin Nutr*. 2013;98(2):521S-528S.
2. Jensen RG. Lipids in human milk. Lipids 1999;34:1243–71.
3. Qian J, Chen T, Lu W, Wu S, Zhu J. Breast milk macro-and micronutrient composition in lactating mothers from suburban and urban Shanghai. J Paediatr Child Health 2010;46:115–20
4. Saarela T, Kokkonen J, Koivisto M. Macronutrient and energy contents of human milk fractions during the first six months of lactation. Acta Paediatr 2005;94:1176–81.
5. Infant and Young Child Feeding: Model Chapter for Textbooks for Medical Students and Allied Health Professionals. Geneva: World Health Organization; 2009. SESSION 2, The physiological basis of breastfeeding.
6. Mitoulas LR, Kent JC, Cox DB, Owens RA, Sherriff JL, Hartmann PE. Variation in fat, lactose and protein in human milk over 24 h and throughout the first year of lactation. Br J Nutr 2002;88:29–37.
7. Coppa GV, Gabrielli O, Pierani P, Catassi C, Carlucci A, Giorgi PL. Changes in carbohydrate composition in human milk over 4 months of lactation. Pediatrics 1993;91:637–41.
8. Thurl S, Munzert M, Henker J, Boehm G, Mu¨ller-Werner B, Jelinek J, Stahl B. Variation of human milk oligosaccharides in relation to milk groups and lactational periods. Br J Nutr 2010;104:1261–71.
9. Bode L. Human milk oligosaccharides: prebiotics and beyond. Nutr Rev 2009;67(suppl 2):S183–91.
10. Bouwens M, van de Rest O, Dellschaft N, Bromhaar MG, de Groot LC, Geleijnse JM, Mu¨ller M, Afman LA. Fish-oil supplementation induces antiinflammatory gene expression profiles in human blood mononuclear cells. Am J Clin Nutr 2009;90:415–24.
11. WHO. Breastfeeding counselling: a training course. Trainer's guide (Session 3: How breastfeeding works); and Overhead figures (Figure 3/1). Geneva, World Health Organization, 1993 (WHO/ CDR/93.4 and WHO/CDR/93.6).
12. Edgar A. Anatomy of a working breast. New Beginnings [La Leche League International], 2005 March–April.
13. Lawrence RA and Lawrence RM. Breastfeeding: a guide for the medical profession. 6th Edition. London, Mosby, 2005.
14. Hartmann PE et al. Breast development and the control of milk synthesis. Food and Nutrition Bulletin, 1996, 17(4):292–302.
15. Glasier A, McNeilly AS, Howie PW. The prolactin response to suckling. Clinical Endocrinology, 1984, 21:109–116.
16. Ramsay DT et al. Ultrasound imaging of milk ejection in the breast of lactating women. Pediatrics, 2004, 113:361–367.
17. Casey Cet al. Nutrient intake by breastfed infants during the first five days after birth. American Journal of Diseases of Childhood, 1986, 140: 933–936.
18. Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. Pediatr Clin North Am. 2013;60(1):49-74. doi:10.1016/j.pcl.2012.10.002
19. Heinig MJ, Dewey KG. Health advantages of breastfeeding for infants: a critical review. Nutr Res Rev 1996; 9: 89–110.

20. Martin CR, Ling PR, Blackburn GL. Review of Infant Feeding: Key Features of Breast Milk and Infant Formula. *Nutrients*. 2016;8(5):279. Published 2016 May 11. doi:10.3390/nu8050279
21. Chan S, Nelson E, Leung S, Li C. Breastfeeding failure in a longitudinal post-partum maternal nutrition study in Hong Kong. J Paediatr Child Health. 2000;36(5):466-71.
22. Semenic S, Loiselle C, Gottlieb L. Predictors of the duration of exclusive breastfeeding among first-time mothers. Res Nurs Health. 2008;31(5):428-41.
23. Stuebe A. The risks of not breastfeeding for mothers and infants. *Rev Obstet Gynecol*. 2009;2(4):222-231.
24. Victora CG, Bahl R, Barros AJ, et al. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet*. 2016;387(10017):475-490. doi:10.1016/S0140-6736(15)01024-7
25. Blaymore BJA, Oliver T, Ferguson A, Vohr BF. Human milk reduces outpatient upper respiratory symptoms in premature infants during their first year of life. J Perinatol 2002; 22(5): 354–9.
26. McVea KL, Turner PD, Peppler DK. The role of breastfeeding in sudden infant death syndrome. J Hum Lact 2000; 16(1): 13–20.
27. Allen, J., & Hector, D. (2005). Benefits of breastfeeding. *New South Wales Public Health Bulletin, 16*(4), 42–46. https://doi.org/10.1071/NB05011
28. Hart S, Boylan LM, Carroll S, Musick YA, Lampe RM. Brief report: Breast-fed one-week olds demonstrate superior neurobehavioural organisation. J Pediatr Psychol 2003; 28:529–34.
29. Rea, MF. Benefits of breastfeeding and women's health. J Pediatr (Rio J) 2004; 80(5 Suppl): S142–S146
30. Gionet L. Breastfeeding trends in Canada. Health at a glance. Statistics Canada Catalogue No. 820624-X. Ottawa, ON: Statistics Canada; 2015.
31. Qureshi AM, Oche OM, Sadiq UA, Kabiru S. Using community volunteers to promote exclusive breastfeeding in Sokoto State, Nigeria. Pan Afr Med J. 2011;10:8.
32. Redshaw M, Henderson J. Learning the hard way: expectations and experiences of infant feeding support. Birth. 2012;39:21–9.
33. Dewey KG. Maternal and fetal stress are associated with impaired lactogenesis in humans. J Nutr. 2001;131:3012S–5.
34. Peacock-Chambers, E., Dicks, K., Sarathy, L., Brown, A. A., Boynton-Jarrett, R. (2017). Perceived maternal behavioral control, infant behavior, and milk supply: A qualitative study. Journal of Developmental & Behavioral Pediatrics, 38, 401-408.
35. Wang J, Johnson T, Sahin L, et al. Evaluation of the Safety of Drugs and Biological Products Used During Lactation: Workshop Summary. *Clin Pharmacol Ther*. 2017;101(6):736-744.
36. Holmes, A. V., Chin, N. P., Kaczorowski, J., & Howard, C. R. (2009). A barrier to exclusive breastfeeding for WIC enrollees: limited use of exclusive breastfeeding food package for mothers. *Breastfeed Med, 4,* 25-30.
37. Johnson, S., Williamson, I., Lyttle, S., & Leeming, D. (2009). Expressing yourself: a feminist analysis of talk around expressing breast milk. *Social Science & Medicine, 69,* 900-907.
38. Wambach K, Riordan J. Breastfeeding and human lactation. 5th ed. Burlington (MA): Jones & Bartlett Learning; 2016.
39. Chapter 6: Breastfeeding: Public Health Agency of Canada. Family-Centred Maternity and Newborn Care: National Guidelines. Ottawa (ON): PHAC; 2018. Available:

https://www.canada.ca/en/public-health/services/publications/healthy-living/breastfeeding-infographic.html
40. Flower, K. B., Willoughby, M., Cadigan, R. J., Perrin, E. M., Randolph, G., & Family Life Project Investigative Team (2008). Understanding breastfeeding initiation and continuation in rural communities: a combined qualitative/quantitative approach. *Maternal & Child Health Journal, 12,* 402-414.
41. Lewallen, L. P., Dick, M. J., Flowers, J., Powell, W., Zickefoose, K. T., Wall, Y. G. et al. (2006). Breastfeeding support and early cessation. *JOGNN - Journal of Obstetric, Gynecologic, & Neonatal Nursing, 35,* 166-172.
42. Barona-Vilar, C., Escriba-Aguir, V., & Ferrero-Gandia, R. (2009). A qualitative approach to social support and breast-feeding decisions. *Midwifery, 25,* 187-194.
43. Gatrell, C. J. (2007). Secrets and lies: Breastfeeding and professional paid work. *Social Science & Medicine, 65,* 393-404.
44. Stolzer, J. M. (2010). Breastfeeding and WIC Participants: A Qualitative Analysis. *Journal of Poverty, 14,* 423-442.
45. Francis, J, Mildon, A, Stewart, S, et al. Vulnerable mothers' experiences breastfeeding with an enhanced community lactation support program. *Matern Child Nutr*. 2020; 16:e12957. https://doi.org/10.1111/mcn.12957
46. Francis, J., Mildon, A., Stewart, S. *et al.* Breastfeeding rates are high in a prenatal community support program targeting vulnerable women and offering enhanced postnatal lactation support: a prospective cohort study. *Int J Equity Health* **20,** 71 (2021). https://doi.org/10.1186/s12939-021-01386-6
47. Twamley, K., Puthussery, S., Harding, S., Baron, M., & Macfarlane, A. (2011). UK-born ethnic minority women and their experiences of feeding their newborn infant. Midwifery, 27, 595-602.
48. Cohen M, Morley S,Coombs R. Acta Paediatrica, Maternal use of methadone and risk of sudden neonatal death. *International Journal of Paediatrics* 2015;104 (9):883-887.
49. Leong C, Chateau D, Dahl M, et al. Prescription medication use during pregnancies that resulted in births and abortions (2001-2013): A retrospective population-based study in a Canadian population. *PLoS One.* 2019;14(3):e0211319.
50. Smolina K, Hanley GE, Mintzes B, Oberlander TF, Morgan S. Trends and Determinants of Prescription Drug Use during Pregnancy and Postpartum in British Columbia, 2002-2011: A Population-Based Cohort Study. *PLoS One.* 2015;10(5):e0128312
51. Schirm, E., Schwagermann, M., Tobi, H. et al. Drug use during breastfeeding. A survey from the Netherlands. Eur J Clin Nutr 58, 386–390 (2004). https://doi.org/10.1038/sj.ejcn.1601799
52. Hale TW. Medications and Mothers' Milk. 17th ed. New York: Springer Publishing Company; 2017.
53. Briggs GG, Freeman RK. *Drugs in Pregnancy and Lactation.* 10. Lippincott Williams & Wilkins; Philadelphia: 2014.
54. Spencer JP, Gonzalez Iii LS, Barnhart DJ. Medications in the Breast-Feeding Mother.(which to use). *American Family Physician*. 2001;64(1):119.
55. Rowe H, Baker T, Hale TW. Maternal medication, drug use, and breastfeeding. *Child Adolesc Psychiatr Clin N Am*. 2015;24(1):1-20. doi:10.1016/j.chc.2014.09.005
56. Hotham N, Hotham E. Drugs in breastfeeding [published correction appears in Aust Prescr. 2016 Feb;39(1):27]. *Aust Prescr*. 2015;38(5):156–159. doi:10.18773/austprescr.2015.056

57. Anderson PO, Pochop SL, Manoguerra AS. Adverse drug reactions in breastfed infants: less than imagined. *Clin Pediatr(Phila)* 2003;42:325
58. Ilett KF, Kristensen JH, Wojnar-Horton RE, Begg EJ. Drug distribution in human milk. Aust Prescr 1997;20:35-40.
59. Section on B. Breastfeeding and the use of human milk. *Pediatrics.* 2012;129(3): e827-841.
60. World Health Organization. The optimal duration of exclusive breastfeeding: Report of an expert consultation. World Health Organization, 2001.
61. Health Canada. Breastfeeding duration: 2004 health Canada recommendation. Ottawa, ON, Canada: Author.
62. World Health Organization. *Global strategy for infant and young child feeding*. Geneva: WHO; 2003. Available from: www.who.int/nutrition/publications/gs_infant_feeding_text_eng.pdf.
63. Health Canada, Canadian Paediatric Society, Dietitians of Canada, Breastfeeding Committee for Canada. Nutrition for healthy term infants: recommendations from six to 24 months [Internet]. Ottawa (ON): HC; 2014
64. Neves, Paulo & Vaz, Juliana & Maia, Fatima & Baker, Phillip & Gatica-Domínguez, Giovanna & Piwoz, Ellen & Rollins, Nigel & Victora, Cesar. (2021). Rates and time trends in the consumption of breastmilk, formula, and animal milk by children younger than 2 years from 2000 to 2019: analysis of 113 countries. The Lancet Child & Adolescent Health. 5. 10.1016/S2352-4642(21)00163-2.
65. Elwyn G, Laitner S, Coulter A, Walker E, Watson P, Thomson R. Implementing shared decision making in the NHS. *BMJ*. 2010;341:c5146. Published 2010 Oct 14. doi:10.1136/bmj.c5146
66. Stacey D, Bennett C, Barry M, Col N, Eden K, Holmes-Rovner, M Llewellyn-Thomas, H Lyddiatt A, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database of Systematic Reviews. 2011;as well as(10):CD001431.
67. Jacobsen MJ, O'Connor AM, Stacey D. Decisional needs assessment in populations. 1999 [updated 2013].
68. Healthwise Staff. Breastfeeding: Should I Breastfeed My Baby? *Patient decision AIDS - Ottawa Hospital Research Institute*. Retrieved February 23, 2022,
69. Stacey D, Légaré F, Boland L, et al. 20th Anniversary Ottawa Decision Support Framework: Part 3 Overview of Systematic Reviews and Updated Framework. Med Decis Making. 2020;40(3):379-398. doi:10.1177/0272989X20911870
70. Patient Decision Aid Development Training: O'Connor A, Stacey D, Saarimaki A, et al. Ottawa Patient Decision Aid Development eTraining. Web. Free login to e-training.
71. Jacobsen MJ, O'Connor AM, Stacey D. Decisional needs assessment in populations. 1999 [updated 2013].

STUDY 1 INTRODUCTION

This study includes the following chapters:

Chapter 2: A systematic review of collection methods and analytical techniques used to study medications in human milk

This paper is intended for publication in a peer-reviewed scientific journal

CHAPTER 2 MANUSCRIPT

A systematic review of collection methods and analytical techniques used to study medications in human milk

Uma Yakandawala[1], Youstina Soliman[2], Christine Leong[1], Lauren E Kelly[2]

1. College of Pharmacy, Rady Faculty of Health Science, University of Manitoba, Winnipeg, Manitoba, Canada
2. Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba, Canada

To be submitted to journal (undecided)

Corresponding author:
Christine Leong, BSc (Gen), BSc (Pharm), PharmD
750 McDermot Avenue,Winnipeg, MB, Canada R3E 0T5
Tel: 204-318-5276
Email: christine.leong@umanitoba.ca

Running title: Medication in human milk collection and analysis techniques

Funding sources: Rady Innovation Fund

Key words: breastmilk, human milk, medication, preferences, decision making, parents, breastfeeding, lactation

CHAPTER 2. A SYSTEMATIC REVIEW OF COLLECTION METHODS AND ANALYTICAL TECHNIQUES USED TO STUDY MEDICATIONS IN HUMAN MILK

2.1 ABSTRACT

Background: Rigorous studies are needed to fill in the large knowledge gaps on the amount of medication transferred into human milk and the impact on infants, which are not considered during drug development.

Objectives: To understand sample collection procedures and analytical techniques used to study medications in human milk.

Methods: Studies reporting on collection methods and analytical techniques used to assess prescription and over-the-counter medications used by lactating parents were included. Studies were included irrespective of study design, type, or year of publication. No restrictions on country and geographic location and only English-language studies were included. The following databases were searched: MEDLINE (OVID, EMBASE (OVID), PsycINFO (OVID), International Pharmaceutical Abstracts (Ovid), and the Cochrane Library Databases (Wiley), Global Health (Ovid), and Scopus.

Results: The current systematic review included 224 studies published between 1969 and 2020. Studies were conducted in 38 different countries with the largest number of studies conducted in the United States (N= 49), and Australia (N= 31). Over half (N = 113) of the studies were observational studies, with 73 being cross-sectional. There were 186 medications belonging to 46 different therapeutic categories in the included studies. The five therapeutic categories most reported include antidepressants (N=58), anti-retroviral agents (N=43), antibiotics (N=16), non-steroidal anti-inflammatory drugs (NSAIDs) (N=14), and opioids (N=14). The top ten most frequently reported medications in the included studies are antidepressants Fluoxetine, sertraline, paroxetine, citalopram, and venlafaxine; the anti-retroviral HIV medications nevirapine, lamivudine and tenofovir disoproxil; the opioid agonist methadone; and the antimalarial drug chloroquine. Human milk samples were collected at various post-partum ages ranging from day of delivery to 26.5 months postpartum. Mature milk exclusively was collected the most among all the articles (N=86) followed by colostrum (N=41). Collection of samples at multiple time points within a time interval was employed by over half (N=114, 55.4%) of the studies. Overall,

the most used sampling method was multiple collection time points within a 24-hour period (N=55, 24.6%). Less than half of the included articles provided details on the volume of milk collected at each collection point (N=104) and mode of collection (N=103). A little over half the studies (N=116) reported on the temperature of sample storage. There were 45 different assay methods used, with the most common being high-performance liquid chromatography (HPLC) used in almost a third of the studies (N=74, 33.0%). Followed by high-performance liquid chromatography-UV (HPLC-UV) and liquid chromatography with tandem mass spectrometry (LC-MS-MS) both being used in 18 studies.

Conclusion: This review provides guidance for future studies to directly compare the different methodologies and develop standardized protocols for each medication of interest. Our review further supports the need for standardized protocols and recommendations for best practices in human milk research.

2.2 Introduction

Breastfeeding has numerous important health benefits for both parent and child. Exclusive breastfeeding is recommended for the first six months of life by The American Academy of Pediatrics[1], the World Health Organization[2], and Health Canada.[3] Breast milk provides children with necessary nutrients, contains antibodies that help support the baby's immune system and facilitates parent-infant bonding.[4] While Canadian rates of breastfeeding initiation in-hospital are high (90% in 2015/16), rates of breastfeeding post-discharge are much lower as only 32% of mothers breastfed exclusively for six months or more.[4] It is evident that support and encouragement for mothers who wish to breastfeed is an important public health initiative.

Many people require the use of medications during lactation to treat acute or chronic health conditions. Sixty-four percent of women who are pregnant received at least one prescription medication based on administrative data from Manitoba and British Columbia.[5,6] Roughly the same proportion (63%) receive a prescription medication 0-3 months postpartum.[6] According to our previous study which looked at the use of prescription medications and non-prescription health products by breastfeeding mothers using the Canadian Healthy Infant Longitudinal Development (CHILD) cohort, 52.9% of women have used prescription medications while breastfeeding and they used significantly more medications than women used while not

breastfeeding is 44.3% (unpublished data). Medications are crucial for postpartum clinical care and maternal well-being. One identified barrier to continued breastfeeding is medication use due to concerns of drug exposure risks to the infant through milk.[7] Most drugs transfer into milk in small amounts.[8] Given the historical exclusion of pregnant and breastfeeding women from research and drug development, mothers requiring medications and their healthcare providers may be ill-informed about the risks of nursing while taking medications. In some cases, mothers may take an absolute risk avoidance approach due to understudied medications and stop breastfeeding or discontinue taking necessary medications to avoid possible (unknown) adverse effects on their child. It is important to know the risks (including the risks of not breastfeeding) and benefits for both mother and child when advising on medication decisions during breastfeeding, while also considering the preferences and experiences of the mother before, during and after pregnancy.

To assess the safety of drugs transferred through human milk more information is urgently needed on the mechanism, variability, and quantity of drug exposure in the infant.[9] There is a large knowledge gap on the amount of drug transferred into milk and how this may impact the infant, as these details are generally not considered during drug development. In order to analyze medication transfer through human milk, it is important to use optimal milk collection and analysis procedures. Currently, there are no set standardized approaches for collecting, storing, and analyzing drugs in human milk. Therefore, a review of the literature is necessary to gather information on the most frequently presented medications and therapeutic categories in previous studies, highlight the different sampling procedures and analytical assays used. This information will be valuable for future studies to prioritize medications of interest and develop validated protocols to quantify levels of medications excreted in human milk.

2.3 Objectives

The specific purpose of this systematic review will be to examine the literature on:

1. The collection methods and analytical techniques used to study medications in human milk.
2. Historical changes in human milk collection and drug analysis procedures throughout time.
3. Gaps in research specific to human milk collection and analysis methods and determine where further research is needed.

2.4 METHODS

Protocol

The comprehensive search strategy was developed, and peer-reviewed by an experienced health sciences librarian at the University of Manitoba. The full version of the protocol and search strategy can be found in Appendix 2.1. This systematic review was registered at PROSPERO as CRD42020179723.

Eligibility criteria

Inclusion: Studies were eligible for inclusion if they were evaluating prescription medication, non-prescription medications and non-medicinal (cannabis, alcohol, tobacco) products used by lactating parents. The study reports on the collection methods used for human milk. The study reports on the analytical techniques used to analyze medications in the milk. Milk samples must have been collected for the purpose of drug analysis. Studies were included irrespective of study design, type, or year of publication. There was no restriction on the country and geographic location.

Exclusion: Eligibility was limited to studies in humans; animal or in vitro studies were not included. Studies examining vitamins, minerals, supplements, natural health products or food products were excluded. Studies assessing experimental or illicit drugs were also excluded. Studies not reported in the English language or those that included only abstracts were not included.

Database sources and search strategy

Several relevant electronic databases: MEDLINE (OVID, EMBASE (OVID), PsycINFO (OVID), International Pharmaceutical Abstracts (Ovid), and the Cochrane Library Databases (Wiley), Global Health (Ovid), and Scopus were searched using a combination of controlled vocabulary and keywords. The article search did not have any date range restrictions and the last search was conducted on April 24, 2020.

Selection process

To meet the aims of this systematic review, article selection for inclusion in this study was comprehensive. Article screening was conducted in a duplicate and involve an iterative process using Rayyan software. The screening was conducted in two phases, (1) title and abstract and (2) full-text review. Title and abstract screening were independently screened by two investigators (UY and YS) to determine if they met the broad eligibility criteria. Next, full-text screening was conducted by the same investigators and any discrepancies between reviewers concerning inclusion were resolved by consensus through discussion with Drs. Leong and Kelly.

Data extraction

Once the full-text screening was completed, articles that were case studies (N=138) and studies that examined non-medicinal products (N=19) were not included for data extraction for this review. One investigator (UY) independently extracted data from each included article (N=224). Data were extracted using pre-piloted, standardized data extraction forms. Data extracted included information on the parent population, study setting, study type and medication(s) analyzed (including medication name, the dose administered, the timing of the dose, if applicable). Methodological details included breast milk collection procedures (including mode of expression (hand expression, breast pump, or both), collection time relative to drug administration, frequency of collection, stage of lactation/postpartum age, sample storage procedures, the volume of milk collected, and the number of samples collected per participant). Drug analysis techniques include (assay methods and equipment). The data collection form is included in Appendix 2.2.

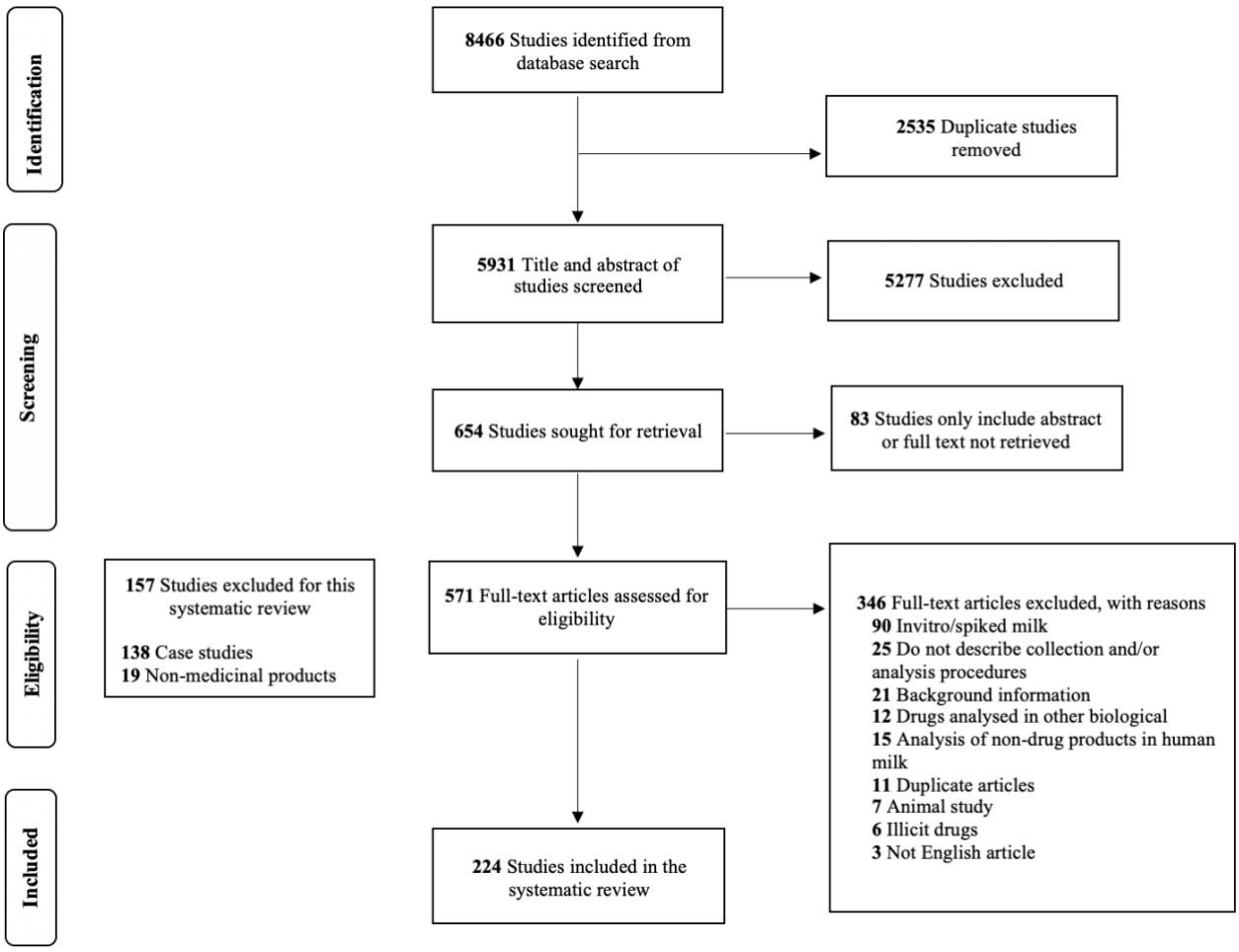


Figure 2.1 PRISMA flow diagram depicting the process of article inclusion and exclusion

2.5 RESULTS

Summary of studies

Our search strategy identified a total of 8466 publications, of which 224 were included in this systematic review. A summary of the included studies is presented in Table 2.1.

There is a wide range of publication dates for the studies included in this review, between 1969 and 2020. Between 2011 to 2020[11-74] consisted of 64 studies, from 2001 to 2010[75-130] there were 56 articles were published, 1991 to 2000[131-170] included 40 articles were published, 1981 to 1990[171-220] included 50 articles, and between 1969 to 1980[221-234] there were 14 articles published.

The included studies were conducted in 38 different countries. The country that conducted the largest number of studies was the United States (N= 49), followed by Australia (N= 31). Over half (N = 113) of the studies were observational studies, with 73 being cross-sectional, 25 were prospective cohorts, nine were longitudinal, five were case-control and one article was a retrospective cohort in design. Almost half (N=110) of the articles were interventional studies (N=110), with six being randomized controlled trials. There was one systematic review included.

Population characteristics

The sample size of participants in the included studies (N=223) ranged from two to 273 with a mean of 16.2. The participants' ages also varied from 17 to 44 years,[225] with most studies including participants in their 20's and 30's. Human milk samples were collected across a wide range of postpartum ages, from the day of delivery to 26.5 months postpartum.[118] Twenty studies collected milk samples at different time points over a few weeks or months from participants which implied collecting samples at more than one stage of lactation. [38, 42, 43, 51, 53, 54, 62, 65, 67, 77, 78, 80, 86, 105, 113, 119, 133, 160, 172, 214]

Table 2.1 Characteristics of publications sampled for systematic review (N=224)

Characteristic	No. of articles	%
Study methodology		
Observational studies	113	50.45%
Cross sectional	73	32.59%
Prospective cohort	25	11.16%
Longitudinal	9	4.02%
Case-control	5	2.23%
Retrospective cohort	1	0.45%
Interventional studies	110	49.11%
Randomized controlled trial	6	2.68%
Systematic Review	1	0.45%
Year of publication		
2020-2011	64	28.57%
2010-2001	56	25.00%
2000-1991	40	17.86%
1990-1981	50	22.32%
1980-1969	14	6.25%
Study Location		
USA	49	21.88%
Australia	31	13.84%
Sweden	20	8.93%
UK	18	8.04%
Japan	9	4.02%
France	8	3.57%
Canada	7	3.13%
India	7	3.13%
Germany	6	2.68%
Finland	5	2.23%
Italy	5	2.23%
Denmark	4	1.79%
Israel	4	1.79%
Nigeria	4	1.79%
Turkey	4	1.79%
Argentina	3	1.34%
Brazil	3	1.34%
Egypt	3	1.34%

Malawi	3	1.34%
Papua New Guinea	3	1.34%
Chile	2	0.89%
Iran	2	0.89%
Kenya	2	0.89%
Norway	2	0.89%
Tanzania	2	0.89%
The Netherlands	2	0.89%
Ugandan	2	0.89%
Belgium	1	0.45%
China	1	0.45%
Czech Republic	1	0.45%
Gambia	1	0.45%
Greece	1	0.45%
Mexico	1	0.45%
Mozambique	1	0.45%
New Zealand	1	0.45%
Poland	1	0.45%
Switzerland	1	0.45%
Multi-site*	4	1.79%

*Multi-site includes: Kenya/Uganda(n=1), Nigeria/Uganda (n=1), Sweden/Austria (n=1) and USA/Canada/Switzerland/The Netherlands (n=1)

Summary of medical conditions and illnesses

Many of the studies in this review included medications that treated chronic and other illnesses of the study participants. There were 46 medical conditions/illnesses that were studied across all the included articles. Thirty-two studies included healthy participants with no specific medical condition or illness. The most common medical condition among the participants was depression, studied in 36 articles. Both human immunodeficiency virus (HIV) and postpartum pain were the second most common conditions reviewed, cited in 16 articles each. Other common conditions included hypertension (N=13), medications used for contraception (N=12), epilepsy (N=11) and opioid use disorder (N=9). A list of medical conditions and illnesses of the participants in the included studies is included in Appendix 2.3.

Summary of medications

The majority of the studies (N=197) included measured one medication. The remaining articles reported the following number of medications: two (N=9), three (N=5), five (N=3), nine (N=1), combination medications (N=8), and review articles (N=11) which included 13 medications.

There were 186 medication types belonging to 46 different therapeutic categories in this review. All the medications included are prescription medications and eight medications are also available over the counter (OTC). These include acetaminophen (Tylenol®) (N=1), acetylsalicylic acid (Aspirin®) (N=3), cimetidine (N=1), loratadine (N=1), pseudoephedrine (N=1), bisacodyl (Dulcolax®) (N=1), sodium picosulfate (Dulcolax Pico Liquid®) (N=1), and ibuprofen (N=2).

The five therapeutic categories most reported include antidepressants (N=58), anti-retroviral agents (N=43), antibiotics (N=16), non-steroidal anti-inflammatory drugs (NSAIDs) (N=14), and opioids (N=14).

The top 10 most frequently reported medications are shown in Table 2.2. Fluoxetine, sertraline, paroxetine, citalopram, and venlafaxine are all antidepressants. Nevirapine, lamivudine and tenofovir disoproxil are anti-retroviral agent to treat HIV. Methadone is an opioid agonist medication used in opioid maintenance therapy and chloroquine is an antimalarial drug. A list of all medications and therapeutic categories is included in Appendix 2.4.

Table 2.2 Top 10 medications reported in the studies with corresponding therapeutic categories

Medication	Therapeutic category	No. of studies
Fluoxetine	Antidepressant	11
Sertraline	Antidepressant	8
Nevirapine	Anti-retroviral agent (HIV)	8
Paroxetine	Antidepressant	7
Lamivudine	Anti-retroviral agent (HIV)	7
Methadone	Opioid	6
Citalopram	Antidepressant	5
Venlafaxine	Antidepressant	5
Chloroquine	Antimalarial	5
Tenofovir Disoproxil	Anti-retroviral agent (HIV)	5

Stage of lactation

Human milk samples were collected at various post-partum ages ranging from day of delivery to 26.5 months postpartum.[118] Type of human milk produced by participants was determined by categorizing the postpartum ages reported in the studies into the following lactation stages: colostrum (day of delivery to four days postpartum), transitional milk (five days to two weeks postpartum) and mature milk (two weeks and onwards), as displayed in Figure 2.2. Mature milk exclusively was collected the most among all the articles (N=86) and was also collected along with transitional milk and colostrum in 13 and 11 articles respectively. Colostrum exclusively was collected in 41 studies; it was also collected along with transitional milk in 15 studies. Transitional milk was collected exclusively in 12 studies. Fifteen studies included the collection of milk samples at any lactation stage from colostrum to mature milk. Six studies included the collection of milk samples from each participant at every lactation stage. Twenty-six studies did not report postpartum age or type of milk collected therefore lactation stage could not be determined.

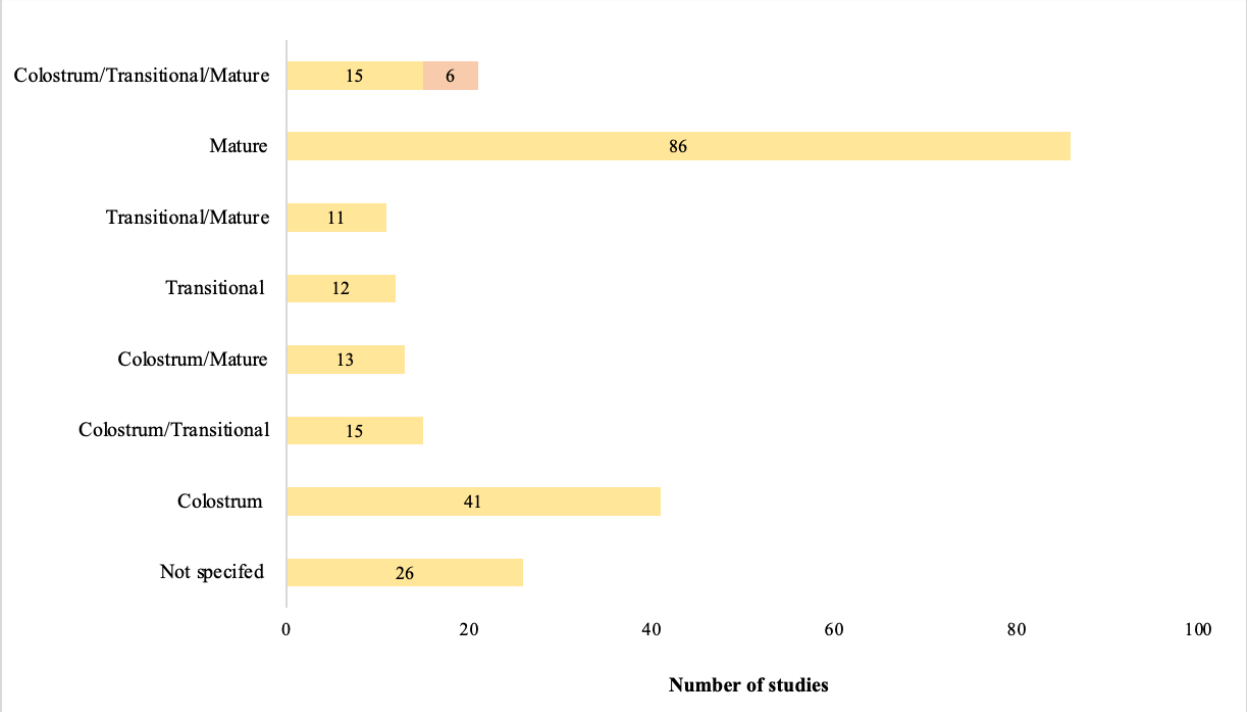


Figure 2.2 Distribution of included studies based on lactation stage: colostrum, transitional and mature milk (N=224)

Note: Category colostrum/transitional/mature milk divided into two parts, 15 articles included sample collection from participants at any lactation stage from colostrum to mature milk. Six studies included samples from participants at each lactation stage.

Summary of collection methods

There was a broad range of human milk collection methods used across all the included studies. Direct comparison between specific collection methods across studies is difficult due to the variation in collection time, range and number of samples retrieved. Therefore, collection methods were divided into five broad categories and those methods that did not fit into any of the categories were listed as not specified and articles describing multiple methods were included in the category various. Within each category studies using similar methods were further subdivided. The number of studies that applied each human milk collection method along with sub-categorization is displayed in Appendix 2.5. Four studies applied two different collection methods, three articles used the time interval method and collection at a specific time point [58, 149, 176] and one article used the time interval method and collection at a specific time range.[153]

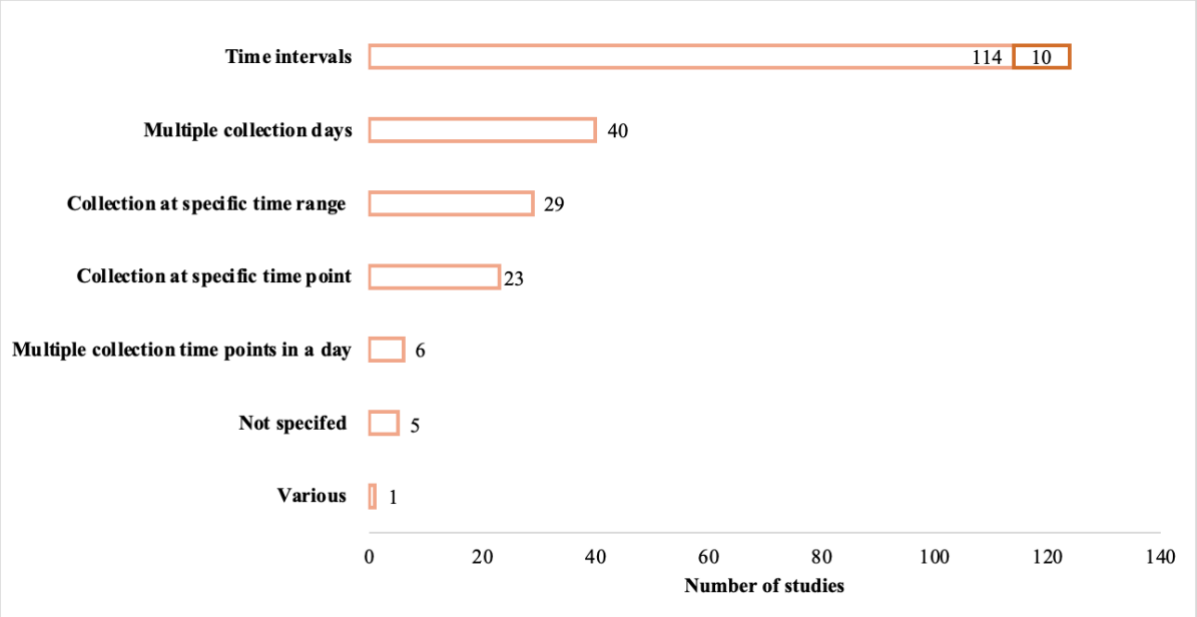


Figure 2.3 Number of studies applying each human milk collection method (N=224)
Note: collection method time interval is divided into two parts 114 articles collected human milk during one collection cycle, ten studies used the time interval collection method over multiple collection cycles.

1. Time intervals were the most used collection method employed by 124 studies; ten studies applied time intervals over multiple collection time points. Time interval categories included studies where samples were collected at specified time points over a certain number of hours. Studies were categorized based on the period of time samples were collected regardless of the number of sample collection points within a period. For example, collection of samples over

a 24-hour period (0, 2,4,6,8,12,14, 24h). There were 29 different time intervals used to collect milk samples, ranging from 3-hour to 227-hour period. The most used time intervals include a 24-hour period (N=55), followed by a 12-hour period (N=17), an 8-hour period (N=13) and a 48-hour period (N=10). Eight studies applied two different time intervals and two studies used three different time intervals.

2. Multiple collection days included studies (N=40) that collected multiple human milk samples on different days. Studies were subdivided into three groups which include, collection over a specified interval (N=27), consecutive days (N=10) and a specific range of days (N=3). Specified intervals included studies that collected samples on specified days over a certain period of days, weeks, or months. Studies were categorized based on the time-period samples were collected regardless of the number of collection days within the period. For example, collection of samples over 17 days (1, 2, 3 to 5, 7 to 11, and 14 to 17 days).[53] There were 16 different intervals used to collect human milk samples these ranged from 4 days to 24 months. One article included two different intervals (14 days and 28 days).[38] Consecutive days included sample collection on back-to-back days, studies included a collection for two, three, four, five, seven and nine consecutive days. The specific range of days includes studies that collected samples on multiple days within a specified range of days but does not provide detail on which days samples were collected.

3. Collection at a specific time range includes studies (N=29) that collected human milk samples at one collection time between a specific range of time. Studies were subdivided into ranges in hours (N=19), days (N=7), and months (N=3). One study included also applied the time interval collection method (24 hour-period) along with a time range of 8 to 12 hours after dose administration.[153]

4. Collection at a specific time point includes studies (N=23) that collect human milk samples at specified time points, which included samples at specified hours, days, or weeks. Fifteen studies collected samples at one-time point, six studies collected samples at two-time points and two studies collected at three-time points. Three articles also included a time interval collection method along with one specified collection time. [58, 149, 176]

5. Multiple collection time points in a day include studies (N=6) that collected multiple samples in a day but did not specify the time points. Articles included two,[170] three to five,[28] six,[177] nine,[123] and collection at every pre and post feed. [152,171]

6. Not specified included studies (N=5) that did not report details on sample collection method. These articles did not report on the number of samples collected per participant or time points of collection. [31,60,83,104,215]

7. Various includes the one systematic review which reports several different collection methods used in the articles included in the review.[49]

Human milk collection techniques

Less than half of the included articles provided details on the volume of milk collected at each collection point (N=104) and mode of collection (N=103). A little over half of the studies reported on the storage procedures (N=116) which include sample storage temperature before analysis. Figure 2.4 displays the sample collection techniques of the included studies in this review.

The volume of human milk samples. One hundred and four studies reported on the amount of milk collected at each sampling session. The volume of samples ranged from 1mL to 100mL. Common sampling volumes include 5mL (N=15), 10mL (N=17), 15mL (N=11), 20 mL (N=4) and nine studies collected full milk expression from either one or both breasts. Studies also collected a range of milk samples such as between 10 to 20mL, because there was a large variety of ranges included for ease of reporting some ranges were reported as up to x mL which was the maximum volume of milk collected in that range. Two additional articles reported on the overall daily milk volume collected which is 340 mL[18] and 70 to 540 mL.[19]

Mode of human milk expression. Mode of milk expression was included in 103 studies and reported on the method of human milk expression, including using a breast pump (manual or electric), manual expression using their hand or using both methods in each study. A breast pump was used in 61 studies, and it was the most used method of expression among the studies reported. Manual hand expression was used in 23 studies and both manual and pump were employed in 19 studies.

Human milk storage procedures. Over half (N=116) of the included studies reported on the storage procedures used before sample analysis. Details were collected on the temperature samples were stored at and were later categorized into the storage location. Among the studies that provided detailed deep freezer at -20°C was the most stored at temperature (N=65), followed by ultra-low temperature freeze at -80°C (N=30).

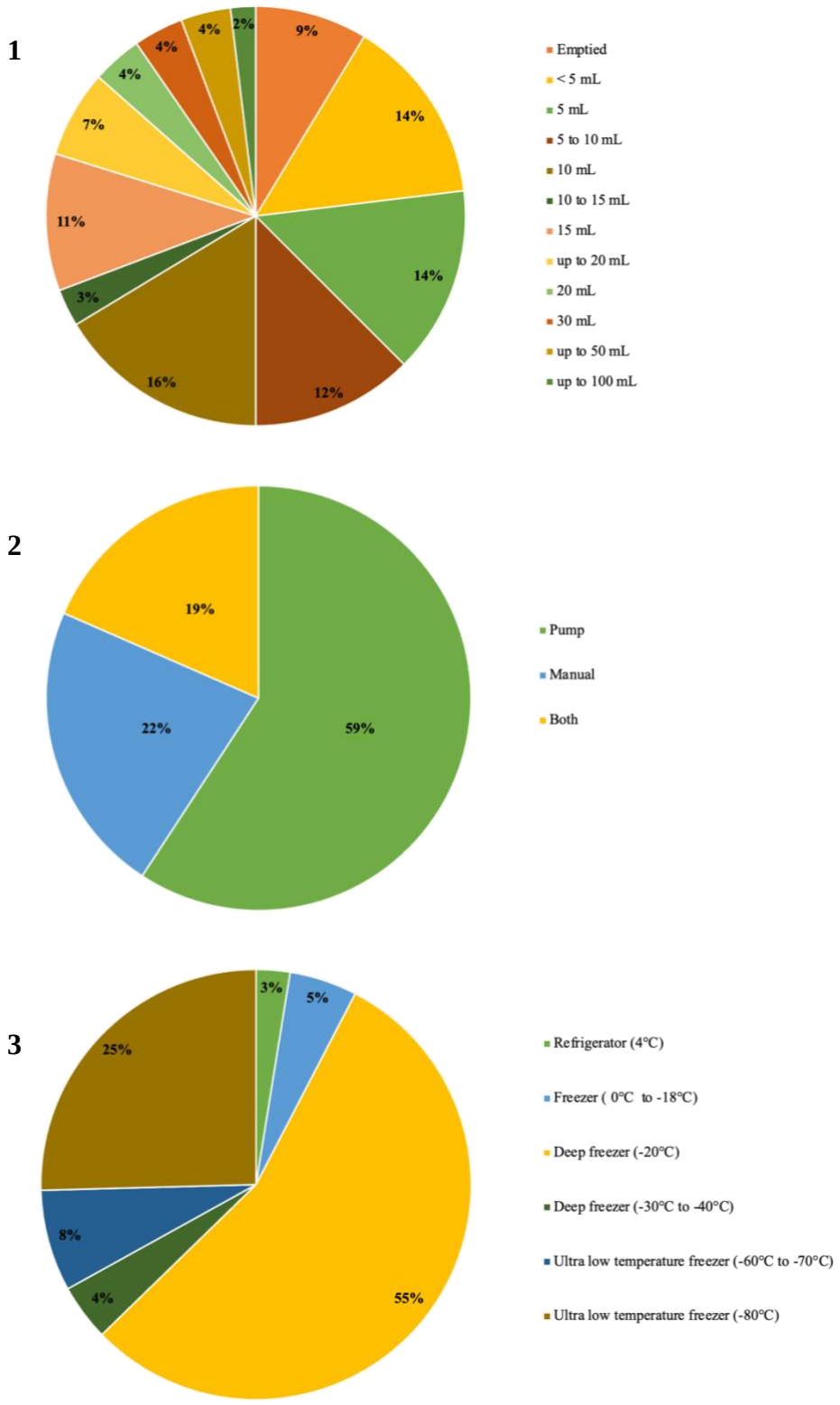


Figure 2.4 Human milk collection techniques of included studies: 1. volume of milk collected per sample (N=104), 2. mode of sample collection (pump, manual expression, both) (N=103), 3. milk sample storage location and temperature (N=116)

Summary of analytical techniques

There was a broad range of techniques used to analyze medications in human milk, displayed in Appendix 2.6. There were 45 different assay methods used, with the most common being high-performance liquid chromatography (HPLC), applied in 74 studies, followed by high-performance liquid chromatography-UV (HPLC-UV), and liquid chromatography with tandem mass spectrometry (LC-MS/MS) both being used in 18 studies. Other common methods include liquid chromatography-mass spectrometry (LC-MS), used in 13 studies, radioimmunoassay (RIA) in 12 studies and gas chromatography (GC), used in 9 studies. Many of the other methods include variations to HPLC and LC with additions such as MS, MS/MS, UV, reverse phase (RP), ion pair (IP), fluorescence detection (FLD), diode array detector (DAD), electron capture detection (ECD), negative chemical ionization mode (NCI) etc. Direct comparison between studies is difficult due to the variability in the analysis methods used for each medication.

.

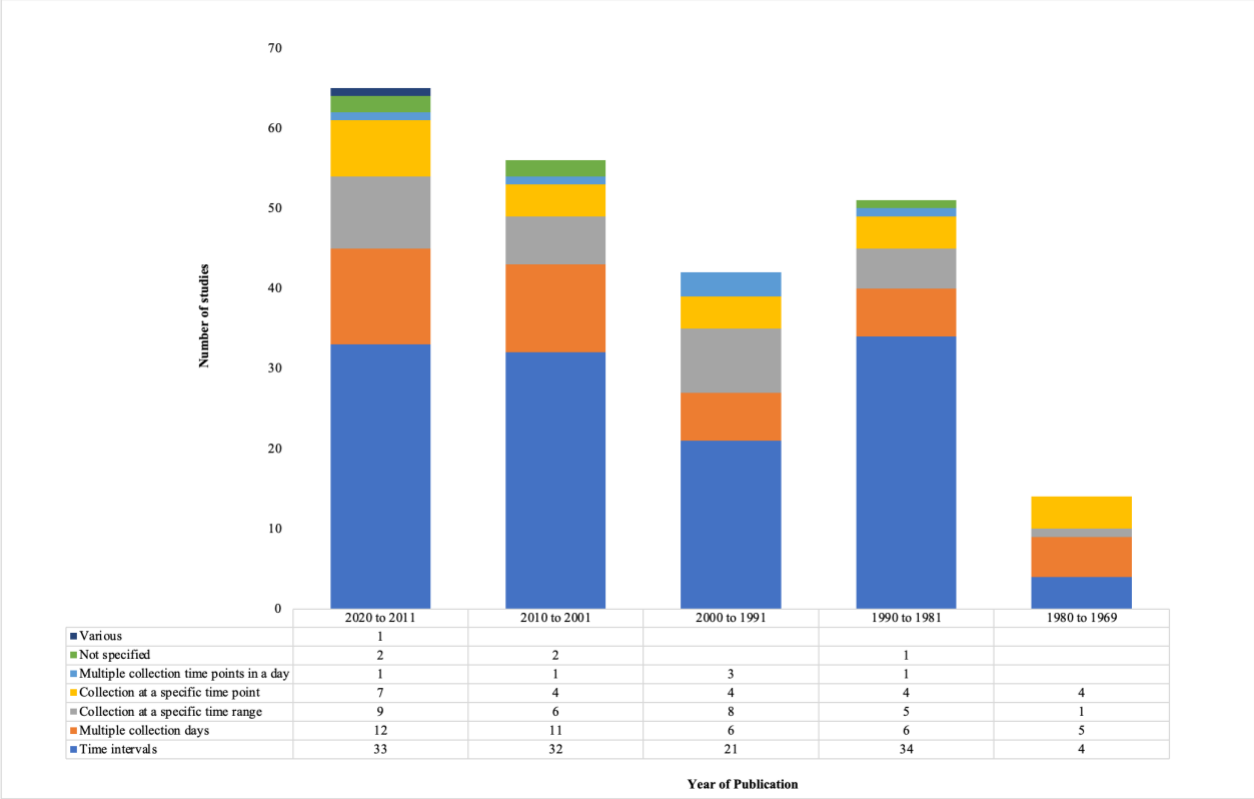
Table 2.3 Assay methods used for the top 10 medications of the included studies

Medication	**Therapeutic category**	**Assay methods used (N)**
Fluoxetine	Antidepressant	LC-MS RP-HPLC-UV GC-ECD GC-MS LC-MS/MS HPLC (2) HPLC-UV (2) GLC GC HPLC-MS/MS
Sertraline	Antidepressant	HPLC-UV (2) HPLC-MS/MS HPLC (3) LC-MS GC
Nevirapine	Anti-retroviral agent (HIV)	LC-MS (2) EIA (ARK NVP-test) (2) HPLC-MS/MS LC-MS/MS RP-HPLC-UV

Paroxetine	Antidepressant	HPLC-MS/MS HPLC-UV (2) GC-MS HPLC (2) LC-MS
Lamivudine	Anti-retroviral agent (HIV)	LC-MS/MS (4) LC-MS RP-HPLC-UV
Methadone	Opioid	GC GC-EI-MS LC-APCI-MS/MS HPLC-UV HPLC GLC
Citalopram	Antidepressant	RP-HPLC-FLD HPLC HPTLC LC-MS HPLC-MS/MS
Venlafaxine	Antidepressant	LC-MS HPLC-MS/MS HPLC (2) HPLC-UV
Chloroquine	Antimalarial	HPLC (2) ELISA TLC-MS IP-HPLC-UV
Tenofovir Disoproxil	Anti-retroviral agent (HIV)	LC-MS/MS (4)

Historical changes in human milk collection methods and analytical techniques

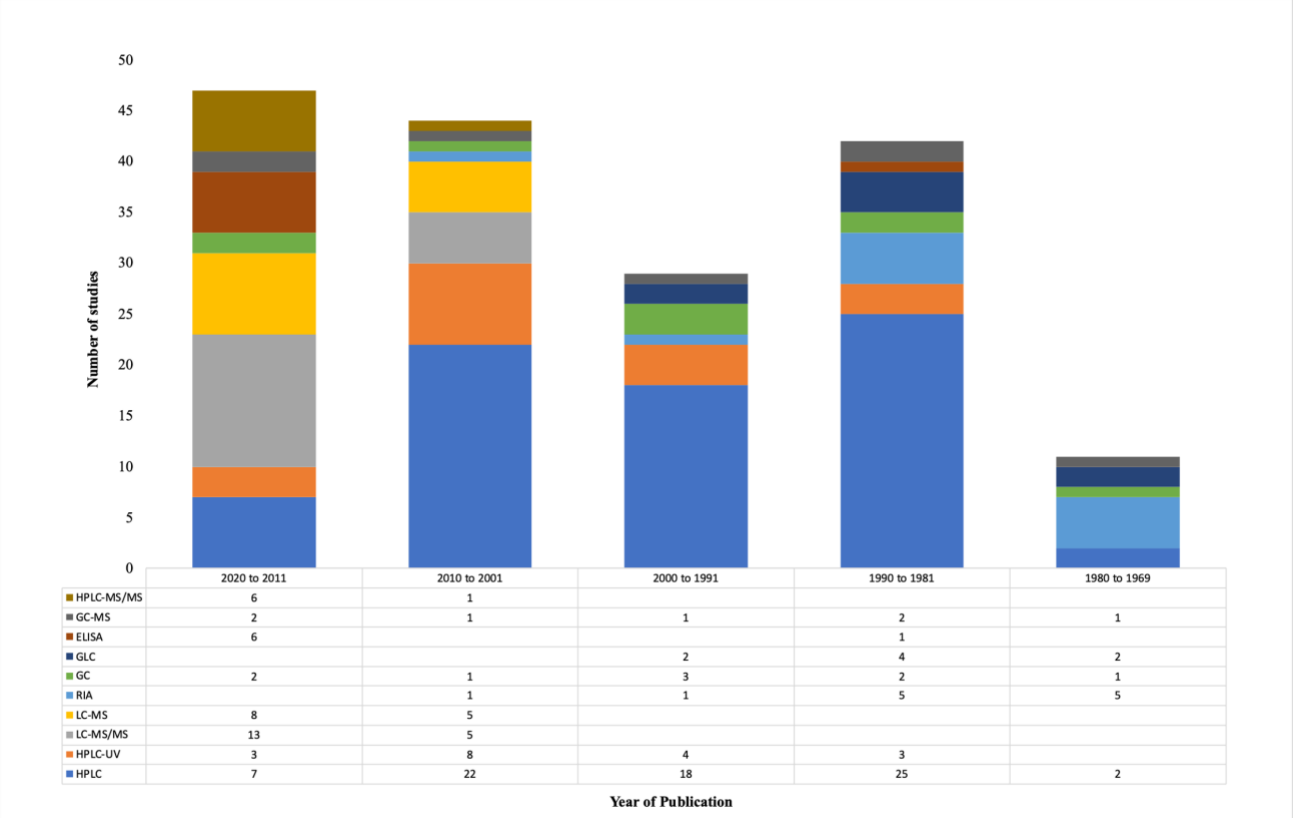
Changes in collection methods and analytical techniques over time were analyzed and presented in Figures 2.5 and 2.6 respectively. Time intervals collection methods were the most frequently used in all publication year groupings except for the years 1980 to 1969 where multiple collection days (N=5) were used more frequently. Time interval collection methods accounted for over half of the methods used within the publication years 2020 to 2011 (51.6%), 2010 to 2001 (57.1%), 2000 to 1991 (52.5%) and 1990 to 1981(68.0%). For the years 1980 to 1969 multiple collection days were used in 35.7% of studies followed by time intervals and collection at a specific time point both with 28.6% and collection at a specific time range with 7.1%. Multiple collection days were the second most frequently used method followed by collection at a specific time range in the included studies within the publication groupings 2020 to 2011 (18.8%,14.1%), 2010 to 2001 (19.6%,10.7%) and 1990 to 1981(12.0%,10.0%). Multiple collection time points in a day were the least used collection method in all publication years.



	2020 to 2011	2010 to 2001	2000 to 1991	1990 to 1981	1980 to 1969
Various	1				
Not specified	2	2		1	
Multiple collection time points in a day	1	1	3	1	
Collection at a specific time point	7	4	4	4	4
Collection at a specific time range	9	6	8	5	1
Multiple collection days	12	11	6	6	5
Time intervals	33	32	21	34	4

Figure 2.5 Collection methods used in the included studies across years of publication (N=224)
Note: Four studies applied two different collection methods

There was a large number of analytical techniques (45) used in the included studies with over half (24) only being used in one study. Therefore, the top 10 most commonly used assay methods were compared across publication years and were present in 167 studies. The most common assay method HPLC was used in 74 studies and was the most frequently used analytical method in the years 2010 to 2001 (N=22), 2000 to 1991(N=18) and 1990 to 1981 (N=25), while from 1980 to 1969 it was only used in two studies. From 2020 to 2011 LC-MS/MS was the most used technique (N=13) followed by LC-MS (N=8) and HPLC (N=7). HPLC-UV was used the most in the years 2010 to 2001 (N=8) followed by 2000 to 1991 (N=4). HPLC-MS/MS was only used from 2020 to 2011 (N=6) and 2010 to 2001 (N=1). ELISA was mainly used from 2020 to 2011 (N=6) and in one study from 1990 to 1981. RIA was the most used method from 1980 to 1969 (N=5).



	2020 to 2011	2010 to 2001	2000 to 1991	1990 to 1981	1980 to 1969
HPLC-MS/MS	6	1			
GC-MS	2	1	1	2	1
ELISA	6			1	
GLC			2	4	2
GC	2	1	3	2	1
RIA		1	1	5	5
LC-MS	8	5			
LC-MS/MS	13	5			
HPLC-UV	3	8	4	3	
HPLC	7	22	18	25	2

Figure 2.6 Top 10 analytical techniques presented across years of publication (N=167)
Note: Five studies used two and one study used three different analytical techniques.

2.6 Discussion

The current systematic review is to our knowledge the first evaluation of collection methodologies and analytical techniques used in studies about medication levels in human milk. This review evaluated a total of 224 articles highlighting the wide range of methodologies used for drug analysis in human milk, as well as the variation between studies as it related to factors such as stage of lactation, sample collection, and analytical techniques applied to measure drug levels in milk. We found an almost equal distribution of observational (N=113) to interventional (N=110) study designs. Specifically, a cross-sectional study design was used in over one-third of the studies (N=73, 32.6%). We included a study by Waitt et. al: Is infant exposure to antiretroviral drugs during breastfeeding quantitatively important? A systematic review and meta-analysis of pharmacokinetic studies[49], briefly summarizes methods to obtain and process human milk samples from antiretroviral drug exposure. Another review conducted by Fríguls et al.: A comprehensive review of assay methods to determine drugs in breast milk and the safety of breastfeeding when taking drugs,[235] reports on the analytical techniques developed to detect different drugs in human milk. This review reported on primarily non-medicinal (nicotine, caffeine, alcohol and cannabis) and illicit drugs (cocaine, amphetamines, opioids). They also included licit opioids (methadone, buprenorphine, codeine, morphine, and tramadol), benzodiazepines, antidepressants, and antipsychotic medications. This review however lacks detail on participant information, stage of lactation and collection procedures.

There were 186 different medications belonging to 46 therapeutic categories in the included studies. The five therapeutic categories most reported include antidepressants (N=58), anti-retroviral agents (N=43), antibiotics (N=16), non-steroidal anti-inflammatory drugs (NSAIDs) (N=14), and opioids (N=14). The top 10 reported medications include fluoxetine, sertraline, paroxetine, citalopram, and venlafaxine which are all antidepressants. Nevirapine, lamivudine and tenofovir disoproxil are anti-retroviral agents to treat HIV. Methadone is an opioid agonist medication used in opioid maintenance therapy and chloroquine which is an antimalarial drug. This corresponds to the medical conditions/illnesses of the participants included in the studies. The most common medical condition among the participants was depression (N=36), followed by HIV (N=16) and postpartum pain (N=16). It is important to note that there were only eight OTC medications among the included studies. These include

acetaminophen (Tylenol), acetylsalicylic acid (Aspirin), cimetidine, loratadine, pseudoephedrine, bisacodyl (Dulcolax), sodium picosulfate (Dulcolax Pico Liquid) and ibuprofen (Advil).

This review provides a comprehensive summary of the methodologies used to analyze prescription and over-the-counter medication in human milk across a wide range of publication years, study designs, and geographical areas. We also included studies with participants of any demographic group and across a large range of post-partum ages, from the day of delivery to over two years postpartum. Because of the large range of post-partum ages included across studies the stage of lactation is an important aspect to consider when selecting sampling methods. Many of the studies did not report on the type of milk that was collected therefore this was determined in our analysis based on the postpartum ages that were reported of the included participants. The majority of the studies (N=139, 62.1%) collected samples exclusively from one stage of lactation. Mature milk was collected in the largest number of studies (N=86, 38.4%), followed by colostrum (N=41, 18.3%) and transitional milk (N=12, 5.4%). Almost a fourth (N=54, 24.1%) of the articles included participants of various postpartum ages that collected samples from more than one lactation stage. Only a small number of studies (N=6, 2.7%) collected milk samples from each participant at every lactation stage. Postpartum ages were not reported in 26 of the included articles.

The included studies consisted of a large range of sample collection methods. There were variations in collection time, number of samples collected per sampling point, and number of samples collected per participant. Therefore, collection methods were divided into broader categories, shown in Figure 2.3. Collection of samples at multiple time points within a time interval was employed by over half (N=114, 55.4%) of the studies. Overall, the most used sampling method was multiple collection time points within a 24-hour period (N=55, 24.6%). Researchers in the field consider this as the "'gold standard' approach of collecting complete breast expressions for a 24-hour period and analyzing a representative (composite) sample". [236] Rationale for using this method is that it is thought to be representative of infant milk consumption.[237]Although this is considered the "gold standard" collection method it requires considerable demand of the research participants to express milk fully at each collection time point, requires an alternative feeding method for the infant and may not be feasible for certain demographics.

Details on milk collection techniques were limited, less than half the included articles provided details on the volume of milk collected at each collection point (N=104) and mode of collection (N=103). A little over half the studies (N=116) reported on the temperature of sample storage before analysis. There was a large variation in the volume of milk collected from 1 mL to 100 mL samples. Common sample volumes include full expression, 5, 10, 15 and 20 mL at each sampling time point. Details were limited on the time of day of sample collection and if the samples were collected pre-or post-feed and breastfeeding status (exclusive, partial, not providing human milk). The breast pump was the mode of milk expression utilized the most in the reported studies (N=61) compared to manual hand expression (N=23). Both pumps and manual expression were used in 19 studies. Milk samples were stored before analysis consisted of using a deep freezer at -20°C being the most used (N=65), followed by an ultra-low temperature freeze at -80°C (N=30). Details were limited on the handling of samples after collection, transportation, sample treatment, duration of storage before analysis and freeze-thaw cycles. These factors may impact the integrity of the milk samples and impact the results of drug analysis; therefore, studies should report on these details and future studies should assess the impact of these factors on the drug composition in milk and provide parameters in collection protocols.[238,239,240]

Universal and standardized collection protocols currently do not exist for human milk sampling. The review conducted by Leghi et al.: A Systematic Review of Collection and Analysis of Human Milk for Macronutrient Composition,[241] reports on collection methods and analytical techniques used for macronutrient composition in human milk. Although this review investigates a macronutrient composition in human milk, it provides an insightful synthesis of human milk collection procedures and recommendations. The study recommendations include using the same sampling procedures for all participants in a study, standardizing factors such as collection time of day, collection mode, collection breast and time since last feed or expression. These recommendations ring true to the findings from our review. Additionally, studies should aim to collect milk samples at the same after medication administration for all participants. It would also be beneficial to collect samples from participants that have taken the medication for the same length of time, dose and frequency and are maintained at a steady-state. Due to the large variation in sampling protocols across all studies and the large number of medications included, further investigation is warranted to compare different collection protocols with

specific medications or medication classes to determine the most practical and feasible method that can also provide a representative sampling of infant consumption.

There was a broad range of analytical techniques used to determine medications in human milk. There were 45 different assay methods used, with the most common being high-performance liquid chromatography (HPLC) used in almost a third of the studies (N=74, 33.0%). Followed by high-performance liquid chromatography-UV (HPLC-UV) and liquid chromatography with tandem mass spectrometry (LC-MS-MS) both being used in 18 studies. Many of the assay methods included variations to HPLC and LC. It was not possible to directly compare analysis methods used across all studies due to the great number of medications included and the differences in properties between medication classes. The assay methods used for the top 10 most reported medications are included in Table 2.3. Tenofovir disoproxil was the only medication that used the same assay method (LC-MS/MS) between studies. The other medications used between three (Lamivudine) to ten (Fluoxetine) different assay methods between studies. The variation between studies in the assay methods that are used to quantify medication levels in milk makes it a challenge to interpret results and compare results. There is also a lack of detail on how samples are handled during analysis, the amount of breastmilk used for analysis, the number of samples analyzed and if methods were validated for human milk. Future studies along with standardized sample collection procedures should aim to use standardized analytical methods. Analytical techniques should use human milk standards when possible and methods should be validated for human milk. Future studies can aim to develop standardized assay methods by comparing the previously used assay methods for each medication to determine the most reliable technique to quantify the medication in milk samples.

Historical trends in human milk collection methods revealed that time-interval collection methods were the most frequently used and accounted for over half of the methods used within all publication year groupings excluding 1980 to 1969. While for the years 1980 to 1969 multiple collection days were the most used collection method followed by time intervals. This finding was not surprising because the “gold standard” approach for sample collection is the use of multiple collection time points within a 24-hour period. There was not much variation in the use of the other collection methods over time. Across all publication years, multiple collection time points in a day were the least used.

Over half (24 out of 45) of the assay methods used were present in only one study therefore comparison was limited to the top 10 most commonly used techniques included in 167 studies. The changes in analytical techniques over time are interesting to note. The most used assay method HPLC was used in 74 studies and was the most frequently used method between the years 2010 to 1981 accounting for 65 studies and was used less frequently in earlier and more recent years 1980 to 1969 it was only used in two studies and between 2020 to 2011 it was used in seven studies. LC-MS/MS was only used in recent years between 2020 to 2001 and was the most frequently used method from 2020 to 2011 (N=13). Similarly, LC-MS was also only used between 2020 to 2001 (N=13). HPLC-UV was used the most in the years 2010 to 2001 (N=8) and less frequently either three or four times in the other publication years. RIA was the most used method from 1980 to 1969 (N=5) and was used less frequently over time up till 2010. Techniques such as ELISA and HPLC-MS/MS were mainly used in more recent years. ELISA was used in six studies from 2020 to 2011 and in only one study from 1990 to 1981. Similarity HPLC-MS/MS was only used between 2020 to 2001, with the majority of studies in 2020 to 2011 (N=6) and one study between 2010 to 2001. The trends show a shift towards using assay methods such as LC-MS/MS, LC-MS, HPLC-MS/MS and ELISA in recent years and a decrease in using methods such as RIA.

Although a comprehensive search protocol was developed and reviewed some articles may have not been captured during our search. This may be due to the databases chosen to be included, search terms used and only including articles in the English language. We also did not extract data from case reports in this review or search grey literature therefore unpublished studies were not identified. Due to feasibility, we did not collect data on infant outcomes such as infant gestational age, blood sample collection, drug levels in infant blood and any reported adverse events. The primary strength of this review is comprehensive details on sample collection procedures and analytical methods used for 186 medications. Findings from this systematic review can help identify medications of interest and be used to inform the development and validation of analytical techniques to quantify the levels of medication excreted in human milk.

2.6 Conclusion

The current systematic review evaluated 224 studies on methodological processes used in medication quantification in human milk. We were able to identify the most studied medications and therapeutic categories and highlight the different sampling procedures and analytical assays used. This study provides guidance for future studies to prioritize medications of interest and directly compare the different collection procedures and assay methods used to validate and standardized practices. Our review further supports the need for standardized protocols and recommendations for best practices in human milk research.

2.8 REFERENCES

1. The section on B. Breastfeeding and the use of human milk. *Pediatrics.* 2012;129(3): e827-841.
2. World Health Organization. The optimal duration of exclusive breastfeeding: Report of an expert consultation. World Health Organization, 2001.
3. Health Canada. Breastfeeding duration: 2004 health Canada recommendation. Ottawa, ON, Canada:
4. Gionet L. Breastfeeding trends in Canada. Health at a glance. Statistics Canada Catalogue No. 820624-X. Ottawa, ON*: Statistics Canada*; 2015.
5. Leong C, Chateau D, Dahl M, et al. Prescription medication use during pregnancies that resulted in births and abortions (2001-2013): A retrospective population-based study in a Canadian population. *PLoS One.* 2019;14(3):e0211319.
6. Smolina K, Hanley GE, Mintzes B, Oberlander TF, Morgan S. Trends and Determinants of Prescription Drug Use during Pregnancy and Postpartum in British Columbia, 2002-2011: A Population-Based Cohort Study. *PLoS One.* 2015;10(5):e0128312.
7. Wang J, Johnson T, Sahin L, et al. Evaluation of the Safety of Drugs and Biological Products Used During Lactation: Workshop Summary. *Clin Pharmacol Ther*. 2017;101(6):736-744.
8. Hale TW. Maternal medications during breastfeeding. *Clin Obstet Gynecol*. 2004;47(3):696-711. doi:10.1097/01.grf.0000135653.56778.3f
9. Spencer JP, Gonzalez Iii LS, Barnhart DJ. Medications in the Breast-Feeding Mother.(which to use). *American Family Physician*. 2001;64(1):119.
10. Subbarao P, Anand SS, Becker AB, et al. The Canadian Healthy Infant Longitudinal Development (CHILD) study: Examining developmental origins of allergy and asthma.
11. Ayuk P, Kampouraki E, Truemann A, et al. Investigation of dabigatran secretion into breast milk: Implications for oral thromboprophylaxis in post-partum women. *American Journal of Hematology.* 2020;95(1):E10-E13.
12. Krysko KM, LaHue SC, Anderson A, et al. Minimal breast milk transfer of rituximab, a monoclonal antibody used in neurological conditions. *Neurology(R) neuroimmunology & neuroinflammation.* 2020;7(1).
13. Leggett C, Lwin EMP, Ritchie U, et al. Perindopril in Breast Milk and Determination of Breastfed Infant Exposure: A Prospective Observational Study. *Drug design, development and therapy.* 2020;14:961-967.
14. Malfara BN, Benzi JRdL, de Oliveira Filgueira GC, et al. ABCG2 c.421C>A polymorphism alters nifedipine transport to breast milk in hypertensive breastfeeding women. *Reproductive toxicology (Elmsford, NY).* 2019;85:1-5.
15. Peng W, Liu R, Zhang L, Fu Q, Mei D, Du X. Breast milk concentration of hydroxychloroquine in Chinese lactating women with connective tissue diseases. *European journal of clinical pharmacology.* 2019;75(11):1547-1553.
16. Saito J, Yakuwa N, Kaneko K, et al. Clinical application of the dried milk spot method for measuring tocilizumab concentrations in the breast milk of patients with rheumatoid arthritis. *International journal of rheumatic diseases.* 2019;22(6):1130-1137.
17. Datta P, Rewers-Felkins K, Kallem RR, Baker T, Hale TW. Determination of Mesalamine levels in Human Milk as a Function of Dose. *Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine.* 2019;14(2):98-101.
18. Ware J, Marahatta A, McElhinney K, Dong M, Vinks A, Ware R. Hydroxyurea exposure in lactation-a pharmacokinetics study (HELPS). *Breastfeeding Medicine.* 2019;14:S-2.
19. Pogliani L, Baldelli S, Cattaneo D, et al. Selective serotonin reuptake inhibitors' passage into human milk of lactating women. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians.* 2019;32(18):3020-3025.
20. Iwasa C, Zaima K, Metori K, et al. Transfer of epinastine to infants through human breast milk. *Die Pharmazie.* 2019;74(12):732-736.

21. Kacirova I, Grundmann M, Brozmanova H. Valproic acid concentrations in nursing mothers, mature milk, and breastfed infants in monotherapy and combination therapy. *Epilepsy & behavior : E&B.* 2019;95:112-116.
22. Lwin EMP, Gerber C, Leggett C, et al. Estimation of Atenolol Transfer Into Milk and Infant Exposure During Its Use in Lactating Women. *Journal of human lactation : official journal of International Lactation Consultant Association.* 2018;34(3):592-599.
23. Aoki H, Ito N, Kaniwa N, et al. Low Levels of Amlodipine in Breast Milk and Plasma. *Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine.* 2018;13(9):622-626.
24. Kociszewska-Najman B, Mazanowska N, Pietrzak B, et al. Low Transfer of Tacrolimus and Its Metabolites into Colostrum of Graft Recipient Mothers. *Nutrients.* 2018;10(3).
25. Proschmann U, Thomas K, Thiel S, Hellwig K, Ziemssen T. Natalizumab during pregnancy and lactation. *Multiple sclerosis (Houndmills, Basingstoke, England).* 2018;24(12):1627-1634.
26. Morgan JL, Kogutt BK, Meek C, et al. Pharmacokinetics of amlodipine besylate at delivery and during lactation. *Pregnancy hypertension.* 2018;11:77-80.
27. Waitt C, Olagunju A, Nakalema S, et al. Plasma and breast milk pharmacokinetics of emtricitabine, tenofovir and lamivudine using dried blood and breast milk spots in nursing African mother-infant pairs. *The Journal of antimicrobial chemotherapy.* 2018;73(4):1013-1019.
28. Delaney SR, Malik PRV, Stefan C, Edginton AN, Colantonio DA, Ito S. Predicting Escitalopram Exposure to Breastfeeding Infants: Integrating Analytical and In Silico Techniques. *Clinical pharmacokinetics.* 2018;57(12):1603-1611.
29. Ryu RJ, Easterling TR, Caritis SN, et al. Prednisone Pharmacokinetics During Pregnancy and Lactation. *Journal of clinical pharmacology.* 2018;58(9):1223-1232.
30. Yazdani-Brojeni P, Tanoshima R, Taguchi N, et al. Quetiapine Excretion Into Human Breast Milk. *Journal of clinical psychopharmacology.* 2018;38(4):362-364.
31. Ramirez-Ramirez A, Sanchez-Serrano E, Loaiza-Flores G, et al. Simultaneous quantification of four antiretroviral drugs in breast milk samples from HIV-positive women by an ultra-high performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) method. *PloS one.* 2018;13(1):e0191236.
32. Jalilian N, Ahmadi F, Farhadi E. Two phase solvent extraction method for analysis of methadon in immature human milk, a breast feeding recommendation in early postpartum period. *Journal of Reports in Pharmaceutical Sciences.* 2018;7(1):9-19.
33. Lahat A, Shitrit ABG, Naftali T, et al. Vedolizumab Levels in Breast Milk of Nursing Mothers With Inflammatory Bowel Disease. *Journal of Crohn's & colitis.* 2018;12(1):120-123.
34. Nakanishi R, Yoshimura M, Suno M, et al. Detection of dexmedetomidine in human breast milk using liquid chromatography-tandem mass spectrometry: Application to a study of drug safety in breastfeeding after Cesarean section. *Journal of chromatography B, Analytical technologies in the biomedical and life sciences.* 2017;1040:208-213.
35. Barker EC, Puchowicz M, Letterio J, Higgins K, Sharkey KM. GHB levels in breast milk of women with narcolepsy with cataplexy treated with sodium oxybate. *Sleep medicine.* 2017;36:172-177.
36. Yoshimura M, Kunisawa T, Suno M, et al. Intravenous dexmedetomidine for cesarean delivery and its concentration in colostrum. *International journal of obstetric anesthesia.* 2017;32:28-32.
37. Boz C, Terzi M, Karahan SZ, et al. Methylprednisolone concentrations in breast milk and serum in patients with multiple sclerosis treated with IV pulse methylprednisolone. *Multiple Sclerosis Journal.* 2017;23(3):462.
38. Clowse MEB, Forger F, Hwang C, et al. Minimal to no transfer of certolizumab pegol into breast milk: Results from cradle, a prospective, postmarketing, multicenter, pharmacokinetic study. *Annals of the Rheumatic Diseases.* 2017;76:548-549.
39. Boz C, Terzi M, Karahan SZ, Sen S, Sarac Y, Mavis M. Safety of IV pulse methylprednisolone therapy during breastfeeding in patients with multiple sclerosis. *European Journal of Neurology.* 2017;24:490.

40. Datta P, Rewers-Felkins K, Kallem RR, Baker T, Hale TW. Transfer of Low Dose Aspirin Into Human Milk. *Journal of human lactation : official journal of International Lactation Consultant Association.* 2017;33(2):296-299.
41. Datta P, Rewers-Felkins K, Baker T, Hale TW. Transfer of Montelukast into Human Milk During Lactation. *Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine.* 2017;12:54-57.
42. Palombi L, Pirillo MF, Marchei E, et al. Concentrations of tenofovir, lamivudine and efavirenz in mothers and children enrolled under the Option B-Plus approach in Malawi. *The Journal of antimicrobial chemotherapy.* 2016;71(4):1027-1030.
43. Jansson LM, Spencer N, McConnell K, et al. Maternal Buprenorphine Maintenance and Lactation. *Journal of human lactation : official journal of International Lactation Consultant Association.* 2016;32(4):675-681.
44. Lockwood PA, Pauer L, Scavone JM, et al. The Pharmacokinetics of Pregabalin in Breast Milk, Plasma, and Urine of Healthy Postpartum Women. *Journal of human lactation : official journal of International Lactation Consultant Association.* 2016;32(3):NP1-NP8.
45. Mugwanya KK, Hendrix CW, Mugo NR, et al. Pre-exposure Prophylaxis Use by Breastfeeding HIV-Uninfected Women: A Prospective Short-Term Study of Antiretroviral Excretion in Breast Milk and Infant Absorption. *PLoS medicine.* 2016;13(9):e1002132.
46. McFarland TJ, Rhoads AD, Hartzell M, Emerson GG, Bhavsar AR, Stout JT. Bevacizumab Levels in Breast Milk after Long-Term Intravitreal Injections. *Retina (Philadelphia, Pa).* 2015;35(8):1670-1673.
47. Padro JM, Pellegrino Vidal RB, Echevarria RN, Califano AN, Reta MR. Development of an ionic-liquid-based dispersive liquid-liquid microextraction method for the determination of antichagasic drugs in human breast milk: Optimization by central composite design. *Journal of separation science.* 2015;38(9):1591-1600.
48. Olagunju A, Bolaji OO, Amara A, et al. Development, validation and clinical application of a novel method for the quantification of efavirenz in dried breast milk spots using LC-MS/MS. *The Journal of antimicrobial chemotherapy.* 2015;70(2):555-561.
49. Waitt CJ, Garner P, Bonnett LJ, Khoo SH, Else LJ. Is infant exposure to antiretroviral drugs during breastfeeding quantitatively important? A systematic review and meta-analysis of pharmacokinetic studies. *Journal of Antimicrobial Chemotherapy.* 2015;70(7):1928-1941.
50. Garcia-Bournissen F, Moroni S, Marson ME, et al. Limited infant exposure to benznidazole through breast milk during maternal treatment for Chagas disease. *Archives of disease in childhood.* 2015;100(1):90-94.
51. Salado-Rasmussen K, Theilgaard ZP, Chiduo MG, et al. Nevirapine, sodium concentration and HIV-1 RNA in breast milk and plasma among HIV-infected women receiving short-course antiretroviral prophylaxis. *PloS one.* 2015;10(3):e0121111.
52. Sutton AL, Acosta EP, Larson KB, Kerstner-Wood CD, Tita AT, Biggio JR. Perinatal pharmacokinetics of azithromycin for cesarean prophylaxis. *American journal of obstetrics and gynecology.* 2015;212(6):812.e811-816.
53. Moore BR, Salman S, Benjamin J, et al. Pharmacokinetics of piperaquine transfer into the breast milk of Melanesian mothers. *Antimicrobial agents and chemotherapy.* 2015;59(7):4272-4278.
54. Salman S, Davis TME, Page-Sharp M, et al. Pharmacokinetics of Transfer of Azithromycin into the Breast Milk of African Mothers. *Antimicrobial agents and chemotherapy.* 2015;60(3):1592-1599.
55. Bolat E, Bestas A, Bayar MK, Ozcan S, Erhan OL, Ustundag B. Evaluation of levobupivacaine passage to breast milk following epidural anesthesia for cesarean delivery. *International journal of obstetric anesthesia.* 2014;23(3):217-221.
56. Rigourd V, de Villepin B, Amirouche A, et al. Ibuprofen concentrations in human mature milk--first data about pharmacokinetics study in breast milk with AOR-10127 "Antalait" study. *Therapeutic drug monitoring.* 2014;36(5):590-596.

57. Mirochnick M, Taha T, Kreitchmann R, et al. Pharmacokinetics and safety of tenofovir in HIV-infected women during labor and their infants during the first week of life. *Journal of acquired immune deficiency syndromes (1999).* 2014;65(1):33-41.
58. Bramham K, Chusney G, Lee J, Lightstone L, Nelson-Piercy C. Breastfeeding and tacrolimus: serial monitoring in breast-fed and bottle-fed infants. *Clinical journal of the American Society of Nephrology : CJASN.* 2013;8(4):563-567.
59. El-Gindy A, Nassar MW, Attia KAS, Abu-Seada HH, El-Ghandour M. High-performance liquid chromatographic determination of ethamsylate in human breast milk. *Journal of Liquid Chromatography and Related Technologies.* 2013;36(14):1915-1930.
60. Marson ME, Padro JM, Reta MR, Altcheh J, Garcia-Bournissen F, Mastrantonio G. A simple and efficient HPLC method for benznidazole dosage in human breast milk. *Therapeutic drug monitoring.* 2013;35(4):522-526.
61. Whitmore TJ, Trengove NJ, Graham DF, Hartmann PE. Analysis of insulin in human breast milk in mothers with type 1 and type 2 diabetes mellitus. *International journal of endocrinology.* 2012;2012:296368.
62. Palombi L, Pirillo MF, Andreotti M, et al. Antiretroviral prophylaxis for breastfeeding transmission in Malawi: drug concentrations, virological efficacy and safety. *Antiviral therapy.* 2012;17(8):1511-1519.
63. Ilett KF, Hackett LP, Gower S, Doherty DA, Hamilton D, Bartu AE. Estimated dose exposure of the neonate to buprenorphine and its metabolite norbuprenorphine via breastmilk during maternal buprenorphine substitution treatment. *Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine.* 2012;7:269-274.
64. Drake AL, Roxby AC, Kiarie J, et al. Infant safety during and after maternal valacyclovir therapy in conjunction with antiretroviral HIV-1 prophylaxis in a randomized clinical trial. *PloS one.* 2012;7(4):e34635.
65. Aizire J, McConnell MS, Mudiope P, et al. Kinetics of nevirapine and its impact on HIV-1 RNA levels in maternal plasma and breast milk over time after perinatal single-dose nevirapine. *Journal of acquired immune deficiency syndromes (1999).* 2012;60(5):483-488.
66. Nakamichi T, Yawata A, Hojo H, Kagaya H, Kobayashi S, Chikuma T. Monitoring of methylergometrine in human breast milk by solid-phase extraction and high-performance liquid chromatography with fluorimetric detection. *Die Pharmazie.* 2012;67(6):482-484.
67. Fogel JM, Taha TE, Sun J, et al. Stavudine concentrations in women receiving postpartum antiretroviral treatment and their breastfeeding infants. *Journal of acquired immune deficiency syndromes (1999).* 2012;60(5):462-465.
68. Paech MJ, Salman S, Ilett KF, O'Halloran SJ, Muchatuta NA. Transfer of parecoxib and its primary active metabolite valdecoxib via transitional breastmilk following intravenous parecoxib use after cesarean delivery: a comparison of naive pooled data analysis and nonlinear mixed-effects modeling. *Anesthesia and analgesia.* 2012;114(4):837-844.
69. Friedrich C, Richter E, Trommeshauser D, 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. *Drug metabolism and pharmacokinetics.* 2011;26(5):458-464.
70. Ben-Horin S, Yavzori M, Kopylov U, et al. Detection of infliximab in breast milk of nursing mothers with inflammatory bowel disease. *Journal of Crohn's & colitis.* 2011;5(6):555-558.
71. Rampono J, Teoh S, Hackett LP, Kohan R, Ilett KF. Estimation of desvenlafaxine transfer into milk and infant exposure during its use in lactating women with postnatal depression. *Archives of women's mental health.* 2011;14(1):49-53.
72. Korth-Bradley JM, Parks V, Chalon S, et al. Excretion of moxidectin into breast milk and pharmacokinetics in healthy lactating women. *Antimicrobial agents and chemotherapy.* 2011;55(11):5200-5204.

73. Salado-Rasmussen K, Theilgaard ZP, Chiduo M, Pedersen C, Gerstoft J, Katzenstein TL. Good performance of an immunoassay based method for nevirapine measurements in human breast milk. *Clinical chemistry and laboratory medicine.* 2011;49(7):1171-1175.
74. Salman S, Sy SKB, Ilett KF, Page-Sharp M, Paech MJ. Population pharmacokinetic modeling of tramadol and its O-desmethyl metabolite in plasma and breast milk. *European journal of clinical pharmacology.* 2011;67(9):899-908.
75. Saav I, Fiala C, Hamalainen JM, Heikinheimo O, Gemzell-Danielsson K. Medical abortion in lactating women--low levels of mifepristone in breast milk. *Acta obstetricia et gynecologica Scandinavica.* 2010;89(5):618-622.
76. Abdel-tawab AM, Bradley M, Ghazaly EA, Horton J, el-Setouhy M. Albendazole and its metabolites in the breast milk of lactating women following a single oral dose of albendazole. *British journal of clinical pharmacology.* 2009;68(5):737-742.
77. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrobial agents and chemotherapy.* 2009;53(3):1170-1176.
78. Davis MF, Miller HS, Nolan PE, Jr. Bupropion levels in breast milk for 4 mother-infant pairs: More answers to lingering questions. *The Journal of Clinical Psychiatry.* 2009;70(2):297-298.
79. Matsota PK, Markantonis SL, Fousteri MZF, et al. Excretion of ropivacaine in breast milk during patient-controlled epidural analgesia after cesarean delivery. *Regional anesthesia and pain medicine.* 2009;34(2):126-129.
80. Kunz A, Frank M, Mugenyi K, et al. Persistence of nevirapine in breast milk and plasma of mothers and their children after single-dose administration. *The Journal of antimicrobial chemotherapy.* 2009;63(1):170-177.
81. Lindemalm S, Nydert P, Svensson JO, Stahle L, Sarman I. Transfer of buprenorphine into breast milk and calculation of infant drug dose. *Journal of human lactation : official journal of International Lactation Consultant Association.* 2009;25(2):199-205.
82. Newport DJ, Ritchie JC, Knight BT, Glover BA, Zach EB, Stowe ZN. Venlafaxine in human breast milk and nursing infant plasma: determination of exposure. *The Journal of clinical psychiatry.* 2009;70(9):1304-1310.
83. Nikolaou PD, Papoutsis II, Maravelias CP, et al. Development and validation of an EI-GC-MS method for the determination of methadone and its major metabolites (EDDP and EMDP) in human breast milk. *Journal of analytical toxicology.* 2008;32(7):478-484.
84. Newport DJ, Pennell PB, Calamaras MR, et al. Lamotrigine in breast milk and nursing infants: determination of exposure. *Pediatrics.* 2008;122(1):e223-231.
85. Lobo ED, Loghin C, Knadler MP, et al. Pharmacokinetics of duloxetine in breast milk and plasma of healthy postpartum women. *Clinical pharmacokinetics.* 2008;47(2):103-109.
86. Law I, Ilett KF, Hackett LP, et al. Transfer of chloroquine and desethylchloroquine across the placenta and into milk in Melanesian mothers. *British journal of clinical pharmacology.* 2008;65(5):674-679.
87. Singh N, Golani A, Patel Z, Maitra A. Transfer of isoniazid from circulation to breast milk in lactating women on chronic therapy for tuberculosis. *British Journal of Clinical Pharmacology.* 2008;65(3):418-422.
88. Ilett KF, Paech MJ, Page-Sharp M, et al. Use of a sparse sampling study design to assess transfer of tramadol and its O-desmethyl metabolite into transitional breast milk. *British journal of clinical pharmacology.* 2008;65(5):661-666.
89. Sau A, Clarke S, Bass J, Kaiser A, Marinaki A, Nelson-Piercy C. Azathioprine and breastfeeding: is it safe? *BJOG : an international journal of obstetrics and gynaecology.* 2007;114(4):498-501.
90. Jansson LM, Choo RE, Harrow C, et al. Concentrations of methadone in breast milk and plasma in the immediate perinatal period. *Journal of human lactation : official journal of International Lactation Consultant Association.* 2007;23(2):184-190.

91. Goncalves PVB, Cavalli RC, da Cunha SP, Lanchote VL. Determination of pindolol enantiomers in amniotic fluid and breast milk by high-performance liquid chromatography: applications to pharmacokinetics in pregnant and lactating women. *Journal of chromatography B, Analytical technologies in the biomedical and life sciences.* 2007;852(1):640-645.
92. Jacqz-Aigrain E, Serreau R, Boissinot C, et al. Excretion of ketoprofen and nalbuphine in human milk during treatment of maternal pain after delivery. *Therapeutic drug monitoring.* 2007;29(6):815-818.
93. Falt A, Bengtsson T, Kennedy BM, et al. Exposure of infants to budesonide through breast milk of asthmatic mothers. *The Journal of allergy and clinical immunology.* 2007;120(4):798-802.
94. Gainer E, Massai R, Lillo S, et al. Levonorgestrel pharmacokinetics in plasma and milk of lactating women who take 1.5 mg for emergency contraception. *Human reproduction (Oxford, England).* 2007;22(6):1578-1584.
95. Viguera AC, Newport DJ, Ritchie J, et al. Lithium in breast milk and nursing infants: clinical implications. *The American journal of psychiatry.* 2007;164(2):342-345.
96. Tomson T, Palm R, Kallen K, et al. Pharmacokinetics of levetiracetam during pregnancy, delivery, in the neonatal period, and lactation. *Epilepsia.* 2007;48(6):1111-1116.
97. Giuliano M, Guidotti G, Andreotti M, et al. Triple antiretroviral prophylaxis administered during pregnancy and after delivery significantly reduces breast milk viral load: a study within the Drug Resource Enhancement Against AIDS and Malnutrition Program. *Journal of acquired immune deficiency syndromes (1999).* 2007;44(3):286-291.
98. Nitsun M, Szokol JW, Saleh HJ, et al. Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. *Clinical pharmacology and therapeutics.* 2006;79(6):549-557.
99. Gardiner SJ, Doogue MP, Zhang M, Begg EJ. Quantification of infant exposure to celecoxib through breast milk. *British Journal of Clinical Pharmacology.* 2006;61(1):101-104.
100. Kim J, Riggs KW, Misri S, et al. Stereoselective disposition of fluoxetine and norfluoxetine during pregnancy and breast-feeding. *British journal of clinical pharmacology.* 2006;61(2):155-163.
101. Rampono J, Hackett LP, Kristensen JH, Kohan R, Page-Sharp M, Ilett KF. Transfer of escitalopram and its metabolite demethylescitalopram into breastmilk. *British journal of clinical pharmacology.* 2006;62(3):316-322.
102. Hackett LP, Ilett KF, Rampono J, Kristensen JH, Kohan R. Transfer of reboxetine into breastmilk, its plasma concentrations and lack of adverse effects in the breastfed infant. *European journal of clinical pharmacology.* 2006;62(8):633-638.
103. Briggs GG, Ambrose PJ, Nageotte MP, Padilla G, Wan S. Excretion of metformin into breast milk and the effect on nursing infants. *Obstetrics and gynecology.* 2005;105(6):1437-1441.
104. Silverman DA, Ford J, Shaw I, Probert CSJ. Is mesalazine really safe for use in breastfeeding mothers? 5. *Gut.* 2005;54(1):170-171.
105. Johannessen SI, Helde G, Brodtkorb E. Levetiracetam concentrations in serum and in breast milk at birth and during lactation. *Epilepsia.* 2005;46(5):775-777.
106. Hellgren M, Johansson S, Eriksson UG, Wahlander K. The oral direct thrombin inhibitor, ximelagatran, an alternative for anticoagulant treatment during the puerperium and lactation. *BJOG : an international journal of obstetrics and gynaecology.* 2005;112(5):579-583.
107. Ohman I, Vitols S, Tomson T. Pharmacokinetics of gabapentin during delivery, in the neonatal period, and lactation: does a fetal accumulation occur during pregnancy? *Epilepsia.* 2005;46(10):1621-1624.
108. Feig DS, Briggs GG, Kraemer JM, et al. Transfer of glyburide and glipizide into breast milk. *Diabetes care.* 2005;28(8):1851-1855.
109. Berle JO, Steen VM, Aamo TO, Breilid H, Zahlsen K, Spigset O. Breastfeeding during maternal antidepressant treatment with serotonin reuptake inhibitors: infant exposure, clinical symptoms, and cytochrome p450 genotypes. *The Journal of clinical psychiatry.* 2004;65(9):1228-1234.
110. Amsden GW, Nicolau DP, Whitaker AM, et al. Characterization of the penetration of garenoxacin into the breast milk of lactating women. *Journal of clinical pharmacology.* 2004;44(2):188-192.

111. Hostetter AL, Stowe ZN, Cox M, Ritchie JC. A novel system for the determination of antidepressant concentrations in human breast milk. *Therapeutic drug monitoring.* 2004;26(1):47-52.
112. Edwards JE, Rudy AC, Wermeling DP, Desai N, McNamara PJ. Hydromorphone transfer into breast milk after intranasal administration. *Pharmacotherapy.* 2003;23(2):153-158.
113. Heikkinen T, Ekblad U, Palo P, Laine K. Pharmacokinetics of fluoxetine and norfluoxetine in pregnancy and lactation. *Clinical pharmacology and therapeutics.* 2003;73(4):330-337.
114. Stowe ZN, Hostetter AL, Owens MJ, et al. The pharmacokinetics of sertraline excretion into human breast milk: determinants of infant serum concentrations. *The Journal of clinical psychiatry.* 2003;64(1):73-80.
115. Abdel-Aleem H, Villar J, Gulmezoglu AM, et al. The pharmacokinetics of the prostaglandin E1 analogue misoprostol in plasma and colostrum after postpartum oral administration. *European journal of obstetrics, gynecology, and reproductive biology.* 2003;108(1):25-28.
116. Aljazaf K, Hale TW, Ilett KF, et al. Pseudoephedrine: effects on milk production in women and estimation of infant exposure via breastmilk. *British journal of clinical pharmacology.* 2003;56(1):18-24.
117. Gardiner SJ, Kristensen JH, Begg EJ, et al. Transfer of olanzapine into breast milk, calculation of infant drug dose, and effect on breast-fed infants. *The American journal of psychiatry.* 2003;160(8):1428-1431.
118. Kristensen JH, Hackett LP, Kohan R, Paech M, Ilett KF. The amount of fluvoxamine in milk is unlikely to be a cause of adverse effects in breastfed infants. *Journal of human lactation : official journal of International Lactation Consultant Association.* 2002;18(2):139-143.
119. Heikkinen T, Ekblad U, Kero P, Ekblad S, Laine K. Citalopram in pregnancy and lactation. *Clinical pharmacology and therapeutics.* 2002;72(2):184-191.
120. Baka NE, Bayoumeu F, Boutroy MJ, Laxenaire MC. Colostrum morphine concentrations during postcesarean intravenous patient-controlled analgesia. *Anesthesia and analgesia.* 2002;94(1):184-contents.
121. Ilett KF, Kristensen JH, Hackett LP, Paech M, Kohan R, Rampono J. Distribution of venlafaxine and its O-desmethyl metabolite in human milk and their effects in breastfed infants. *British journal of clinical pharmacology.* 2002;53(1):17-22.
122. Suri R, Stowe ZN, Hendrick V, Hostetter A, Widawski M, Altshuler LL. Estimates of nursing infant daily dose of fluoxetine through breast milk. *Biological psychiatry.* 2002;52(5):446-451.
123. Croke S, Buist A, Hackett LP, Ilett KF, Norman TR, Burrows GD. Olanzapine excretion in human breast milk: estimation of infant exposure. *The international journal of neuropsychopharmacology.* 2002;5(3):243-247.
124. Kawada K, Itoh S, Kusaka T, Isobe K, Ishii M. Pharmacokinetics of zonisamide in perinatal period. *Brain & development.* 2002;24(2):95-97.
125. Hale TW, Kristensen JH, Hackett LP, Kohan R, Ilett KF. Transfer of metformin into human milk. *Diabetologia.* 2002;45(11):1509-1514.
126. Gerk PM, Kuhn RJ, Desai NS, McNamara PJ. Active transport of nitrofurantoin into human milk. *Pharmacotherapy.* 2001;21(6):669-675.
127. Giuliani M, Grossi GB, Pileri M, Lajolo C, Casparrini G. Could local anesthesia while breast-feeding be harmful to infants? *Journal of pediatric gastroenterology and nutrition.* 2001;32(2):142-144.
128. Begg EJ, Malpas TJ, Hackett LP, Ilett KF. Distribution of R- and S-methadone into human milk during multiple, medium to high oral dosing. *British journal of clinical pharmacology.* 2001;52(6):681-685.
129. Richter C, Sitzmann J, Lang P, Weitzel H, Huch A, Huch R. Excretion of low molecular weight heparin in human milk. *British journal of clinical pharmacology.* 2001;52(6):708-710.
130. Hendrick V, Stowe ZN, Altshuler LL, et al. Fluoxetine and norfluoxetine concentrations in nursing infants and breast milk. *Biological psychiatry.* 2001;50(10):775-782.

131. Rampono J, Kristensen JH, Hackett LP, Paech M, Kohan R, Ilett KF. Citalopram and demethylcitalopram in human milk; distribution, excretion and effects in breast fed infants. *British journal of clinical pharmacology.* 2000;50(3):263-268.
132. Kubik-Huch RA, Gottstein-Aalame NM, Frenzel T, et al. Gadopentetate dimeglumine excretion into human breast milk during lactation. *Radiology.* 2000;216(2):555-558.
133. Ohman I, Vitols S, Tomson T. Lamotrigine in pregnancy: pharmacokinetics during delivery, in the neonate, and during lactation. *Epilepsia.* 2000;41(6):709-713.
134. Shimoyama R, Ohkubo T, Sugawara K. Monitoring of carbamazepine and carbamazepine 10,11-epoxide in breast milk and plasma by high-performance liquid chromatography. *Annals of clinical biochemistry.* 2000;37:210-215.
135. Stowe ZN, Cohen LS, Hostetter A, Ritchie JC, Owens MJ, Nemeroff CB. Paroxetine in human breast milk and nursing infants. *The American journal of psychiatry.* 2000;157(2):185-189.
136. Misri S, Kim J, Riggs KW, Kostaras X. Paroxetine levels in postpartum depressed women, breast milk, and infant serum. *The Journal of clinical psychiatry.* 2000;61(11):828-832.
137. Dodd S, Stocky A, Buist A, Burrows GD, Maguire K, Norman TR. Sertraline in paired blood plasma and breast-milk samples from nursing mothers. *Human Psychopharmacology, Clinical and Experimental.* 2000;15(4):261-264.
138. Kristensen JH, Ilett KF, Hackett LP, Yapp P, Paech M, Begg EJ. Distribution and excretion of fluoxetine and norfluoxetine in human milk. *British journal of clinical pharmacology.* 1999;48(4):521-527.
139. Ortega D, Viviand X, Lorec AM, Gamerre M, Martin C, Bruguerolle B. Excretion of lidocaine and bupivacaine in breast milk following epidural anesthesia for cesarean delivery. *Acta anaesthesiologica Scandinavica.* 1999;43(4):394-397.
140. Ohman R, Hagg S, Carleborg L, Spigset O. Excretion of paroxetine into breast milk. *Journal of Clinical Psychiatry.* 1999;60(8):519-523.
141. Begg EJ, Duffull SB, Saunders DA, et al. Paroxetine in human milk. *British journal of clinical pharmacology.* 1999;48(2):142-147.
142. Kristensen JH, Ilett KF, Dusci LJ, et al. Distribution and excretion of sertraline and N-desmethylsertraline in human milk. *British journal of clinical pharmacology.* 1998;45(5):453-457.
143. Ilett KF, Hackett LP, Dusci LJ, et al. Distribution and excretion of venlafaxine and O-desmethylvenlafaxine in human milk. *British journal of clinical pharmacology.* 1998;45(5):459-462.
144. Yoshida K, Smith B, Craggs M, Kumar RC. Fluoxetine in breast-milk and developmental outcome of breast-fed infants. *The British journal of psychiatry : the journal of mental science.* 1998;172:175-178.
145. Shimoyama R, Ohkubo T, Sugawara K, et al. Monitoring of phenytoin in human breast milk, maternal plasma and cord blood plasma by solid-phase extraction and liquid chromatogr
146. Yoshida K, Smith B, Craggs M, Kumar R. Neuroleptic drugs in breast-milk: a study of pharmacokinetics and of possible adverse effects in breast-fed infants. *Psychological medicine.* 1998;28(1):81-91.
147. Buist A, Dennerstein L, Maguire KP, Norman TR. Plasma and human milk concentrations of moclobemide in nursing mothers. *Human Psychopharmacology.* 1998;13(8):579-582.
148. Borgatta L, Jenny RW, Gruss L, Ong C, Barad D. Clinical significance of methohexital, meperidine, and diazepam in breast milk. *Journal of clinical pharmacology.* 1997;37(3):186-192.
149. Spigset O, Carleborg L, Öhman R, Norström Å. Excretion of citalopram in breast milk. *British Journal of Clinical Pharmacology.* 1997;44(3):295-298.
150. Venkatesan K, Mathur A, Girdhar A, Girdhar BK. Excretion of clofazimine in human milk in leprosy patients. *Leprosy review.* 1997;68(3):242-246.
151. Yoshida K, Smith B, Craggs M, Kumar RC. Investigation of pharmacokinetics and of possible adverse effects in infants exposed to tricyclic antidepressants in breast-milk. *Journal of affective disorders.* 1997;43(3):225-237.

152. Wojnar-Horton RE, Kristensen JH, Yapp P, Ilett KF, Dusci LJ, Hackett LP. Methadone distribution and excretion into breast milk of clients in a methadone maintenance programme. *British journal of clinical pharmacology.* 1997;44(6):543-547.
153. Stowe ZN, Owens MJ, Landry JC, et al. Sertraline and desmethylsertraline in human breast milk and nursing infants. *The American journal of psychiatry.* 1997;154(9):1255-1260.
154. Wojnar-Horton RE, Hackett LP, Yapp P, Dusci LJ, Paech M, Ilett KF. Distribution and excretion of sumatriptan in human milk. *British journal of clinical pharmacology.* 1996;41(3):217-221.
155. Taddio A, Ito S, Koren G. Excretion of fluoxetine and its metabolite, norfluoxetine, in human breast milk. *Journal of clinical pharmacology.* 1996;36(1):42-47
156. Oo CY, Kuhn RJ, Desai N, McNamara PJ. Active transport of cimetidine into human milk. *Clinical pharmacology and therapeutics.* 1995;58(5):548-555.
157. Gupta RC, Paliwal JK, Nityanand S, Asthana OP, Lal J. Centchroman: a new non-steroidal oral contraceptive in human milk. *Contraception.* 1995;52(5):301-305.
158. Toddywalla VS, Patel SB, Betrabet SS, Kulkarni RD, Saxena BN. Is time-interval between mini-pill ingestion and breastfeeding essential? *Contraception.* 1995;51(3):193-195.
159. Daniel Lucas Jr B, Purdy CY, Scarim SK, Benjamin S, Abel SR, Hilleman DE. Terfenadine pharmacokinetics in breast milk in lactating women. *Clinical Pharmacology and Therapeutics.* 1995;57(4):398-402.
160. Tomson T, Villen T. Ethosuximide enantiomers in pregnancy and lactation. *Therapeutic drug monitoring.* 1994;16(6):621-623.
161. Paliwal JK, Grover PK, Asthana OP, Nityanand S, Gupta RC. Excretion of centchroman in breast milk. *British journal of clinical pharmacology.* 1994;38(5):485-486.
162. Celiloglu M, Celiker S, Guven H, Tuncok Y, Demir N, Erten O. Gentamicin excretion and uptake from breast milk by nursing infants. *Obstetrics and gynecology.* 1994;84(2):263-265.
163. Ogbuokiri JE, Ozumba BC, Okonkwo PO. Ivermectin levels in human breast milk 1. *European Journal of Clinical Pharmacology.* 1994;46(1):89-90.
164. Heintz RC, Stebler T, Lunell NO, Mueller S, Guentert TW. Excretion of tenoxicam and 5'-hydroxy-tenoxicam into human milk. *Journal of Pharmaceutical Medicine.* 1993;3(2):57-64.
165. Dan M, Weidekamm E, Sagiv R, Portmann R, Zakut H. Penetration of fleroxacin into breast milk and pharmacokinetics in lactating women. *Antimicrobial agents and chemotherapy.* 1993;37(2):293-296.
166. Buist A, Norman TR, Dennerstein L. Plasma and breast milk concentrations of dothiepin and northiaden in lactating women. *Human Psychopharmacology.* 1993;8(1):29-33.
167. Shyu WC, Shah VR, Campbell DA, et al. Excretion of cefprozil into human breast milk. *Antimicrobial agents and chemotherapy.* 1992;36(5):938-941.
168. Ilett KF, Lebedevs TH, Wojnar-Horton RE, et al. The excretion of dothiepin and its primary metabolites in breast milk. *British journal of clinical pharmacology.* 1992;33(6):635-639
169. Lebedevs TH, Wojnar-Horton RE, Yapp P, et al. Excretion of indomethacin in breast milk. *British journal of clinical pharmacology.* 1991;32(6):751-754.
170. Manninen AK, Juhakoski A. Nifedipine concentrations in maternal and umbilical serum, amniotic fluid, breast milk and urine of mothers and offspring. *International journal of clinical pharmacology research.* 1991;11(5):231-236.
171. Bald R, Bernbeck-Betthauser EM, Spahn H, Mutschler E. Excretion of azapropazone in human breast milk. *European journal of clinical pharmacology.* 1990;39(3):271-273.
172. Witte AM, Klever HJ, Brabin BJ, Eggelte TA, Van der Kaay HJ, Alpers MP. Field evaluation of the use of an ELISA to detect chloroquine and its metabolites in blood, urine and breast-milk. *Transactions of the Royal Society of Tropical Medicine and Hygiene.* 1990;84(4):521-525.
173. McQuinn RL, Pisani A, Wafa S, et al. Flecainide excretion in human breast milk. *Clinical pharmacology and therapeutics.* 1990;48(3):262-267.
174. Lahteenmaki PL, Diaz S, Miranda P, Croxatto H, Lahteenmaki P. Milk and plasma concentrations of the progestin ST-1435 in women treated parenterally with ST-1435. *Contraception.* 1990;42(5):555-562.

175. Pons G, Schoerlin MP, Tam YK, et al. Moclobemide excretion in human breast milk. *British journal of clinical pharmacology.* 1990;29(1):27-31.
176. Wischnik A, Manth SM, Lloyd J, Bullingham R, Thompson JS. The excretion of ketorolac tromethamine into breast milk after multiple oral dosing. *European journal of clinical pharmacology.* 1989;36(5):521-524.
177. Smith IJ, Hinson JL, Johnson VA, et al. Flurbiprofen in post-partum women: plasma and breast milk disposition. *Journal of clinical pharmacology.* 1989;29(2):174-184.
178. Dailland P, Cockshott ID, Lirzin JD, et al. Intravenous propofol during cesarean section: placental transfer, concentrations in breast milk, and neonatal effects. A preliminary study. *Anesthesiology.* 1989;71(6):827-834.
179. Pons G, Francoual C, Guillet P, et al. Zolpidem excretion in breast milk. *European journal of clinical pharmacology.* 1989;37(3):245-248.
180. Hilbert J, Radwanski E, Affrime MB, Perentesis G, Symchowicz S, Zampaglione N. Excretion of loratadine in human breast milk. *Journal of clinical pharmacology.* 1988;28(3):234-239.
181. Hartmann D, Lunell NO, Friedrich G, Rane A. Excretion of tiapamil in breast milk. *British journal of clinical pharmacology.* 1988;26(2):183-186.
182. Matheson I, Samseth M, Loberg R, Faegri A, Prentice A. Milk transfer of phenoxymethylpenicillin during puerperal mastitis. *British Journal of Clinical Pharmacology.* 1988;25(1):33-40.
183. Ette EI, Essien EE, Ogonor JI, Brown-Awala EA. Chloroquine in human milk. *Journal of clinical pharmacology.* 1987;27(7):499-502.
184. Andersen LW, Qvist T, Hertz J, Mogensen F. Concentrations of thiopentone in mature breast milk and colostrum following an induction dose. *Acta anaesthesiologica Scandinavica.* 1987;31(1):30-32.
185. Ogunbona FA, Onyeji CO, Bolaji OO, Torimiro SE. Excretion of chloroquine and desethylchloroquine in human milk. *British journal of clinical pharmacology.* 1987;23(4):473-476.
186. Cox SR, Forbes KK. Excretion of flurbiprofen into breast milk. *Pharmacotherapy.* 1987;7(6):211-215.
187. Liu DT, Savage JM, Donnell D. Nefopam excretion in human milk. *British journal of clinical pharmacology.* 1987;23(1):99-101.
188. Roex AJ, van Loenen AC, Puyenbroek JI, Arts NF. Secretion of cefoxitin in breast milk following short-term prophylactic administration in caesarean section. *European journal of obstetrics, gynecology, and reproductive biology.* 1987;25(4):299-302.
189. Edstein MD, Veenendaal JR, Newman K, Hyslop R. Excretion of chloroquine, dapsone and pyrimethamine in human milk. *British Journal of Clinical Pharmacology.* 1986;22(6):733-735.
190. Zylber-Katz E, Linder N, Granit L, Levy M. Excretion of dipyrone metabolites in human breast milk. *European journal of clinical pharmacology.* 1986;30(3):359-361.
191. Olsson B, Bolme P, Dahlstrom B, Marcus C. Excretion of noscapine in human breast milk. *European journal of clinical pharmacology.* 1986;30(2):213-215.
192. Lamont RF, Elder MG. Transfer of hydralazine across the placenta and into breast milk. *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology.* 1986;7(1):47-48.
193. Aaes-Jorgensen T, Bjorndal F, Bartels U. Zuclopenthixol levels in serum and breast milk. *Psychopharmacology.* 1986;90(3):417-418.
194. White WB, Andreoli JW, Cohn RD. Alpha-methyldopa disposition in mothers with hypertension and in their breast-fed infants. *Clinical pharmacology and therapeutics.* 1985;37(4):387-390.
195. Pond SM, Kreek MJ, Tong TG, Raghunath J, Benowitz NL. Altered methadone pharmacokinetics in methadone-maintained pregnant women. *The Journal of pharmacology and experimental therapeutics.* 1985;233(1):1-6.
196. Witter FR, Smith RV. The excretion of pentoxifylline and its metabolites into human breast milk. *American journal of obstetrics and gynecology.* 1985;151(8):1094-1097.
197. Cooke ID, Back DJ, Shroff NE. Norethisterone concentration in breast milk and infant and maternal plasma during ethynodiol diacetate administration. *Contraception.* 1985;31(6):611-621.

198. Ost L, Wettrell G, Bjorkhem I, Rane A. Prednisolone excretion in human milk. *The Journal of pediatrics.* 1985;106(6):1008-1011.
199. Foulds G, Miller RD, Knirsch AK, Thrupp LD. Sulbactam kinetics and excretion into breast milk in postpartum women. *Clinical pharmacology and therapeutics.* 1985;38(6):692-696.
200. Evaldson GR, Lindgren S, Nord CE, Rane AT. Tinidazole milk excretion and pharmacokinetics in lactating women. *British journal of clinical pharmacology.* 1985;19(4):503-507.
201. Weissenbacher ER, Adams D, Gutschow K, Peters-Welte C, Luehr HG. Clinical results and concentrations of cefmenoxime in serum, amniotic fluid, mother's milk, and umbilical cord. *The American journal of medicine.* 1984;77(6):11-12.
202. Townsend RJ, Benedetti TJ, Erickson SH, et al. Excretion of ibuprofen into breast milk. *American journal of obstetrics and gynecology.* 1984;149(2):184-186.
203. Kunka RL, Venkataramanan R, Stern RM, Ladik CF. Excretion of propoxyphene and norpropoxyphene in breast milk. *Clinical pharmacology and therapeutics.* 1984;35(5):675-680.
204. Hilbert JM, Gural RP, Symchowicz S, Zampaglione N. Excretion of quazepam into human breast milk. *Journal of clinical pharmacology.* 1984;24(10):457-462.
205. Lou MA, Wu YH, Jacob LS, Pitkin DH. Penetration of cefonicid into human breast milk and various body fluids and tissues. *Reviews of infectious diseases.* 1984;6:S816-820.
206. Lindberg C, Boreus LO, de Chateau P, Lindstrom B, Lonnerholm G, Nyberg L. Transfer of terbutaline into breast milk. *European journal of respiratory diseases Supplement.* 1984;134:87-91.
207. Heisterberg L, Branebjerg PE. Blood and milk concentrations of metronidazole in mothers and infants. *Journal of perinatal medicine.* 1983;11(2):114-120.
208. Kuhnz W, Jager-Roman E, Rating D, et al. Carbamazepine and carbamazepine-10,11- epoxide during pregnancy and postnatal period in epileptic mother and their nursed infants: pharmacokinetics and clinical effects. *Pediatric pharmacology (New York, NY).* 1983;3(3):199-208.
209. Smith MT, Livingstone I, Hooper WD, Eadie MJ, Triggs EJ. Propranolol, propranolol glucuronide, and naphthoxylactic acid in breast milk and plasma. *Therapeutic drug monitoring.* 1983;5(1):87-93.
210. Chaikin P, Chasin M, Kennedy B, Silverman BK. Suprofen concentrations in human breast milk. *Journal of clinical pharmacology.* 1983;23(8):385-390.
211. Dresse A, Lambotte R, Dubois M, Delapierre D, Kramp R. Transmammary passage of cefoxitin: additional results. *Journal of clinical pharmacology.* 1983;23(10):438-440.
212. Steen B, Rane A. Clindamycin passage into human milk. *British Journal of Clinical Pharmacology.* 1982;13(5):661-664.
213. Johansen K, Andersen AN, Kampmann JP, Hansen JM, Mortensen HB. Excretion of methimazole in human milk. *European Journal of Clinical Pharmacology.* 1982;23(4):339-341.
214. Heikkila M, Haukkamaa M, Luukkainen T. Levonorgestrel in milk and plasma of breast-feeding women with a levonorgestrel-releasing IUD. *Contraception.* 1982;25(1):41-49.
215. Hoskins JA, Holliday SB, Budden GC, Clark DC. Methyldopa in breast milk and its relation to maternal plasma levels. *Journal of Obstetrics and Gynaecology.* 1982;3(2):109-111.
216. Krause W, Stoppelli I, Milia S, Rainer E. Transfer of mepindolol to newborns by breast-feeding mothers after single and repeated daily doses. *European journal of clinical pharmacology.* 1982;22(1):53-55.
217. Findlay JWA, DeAngelis RL, Kearney MF. Analgesic drugs in breast milk and plasma. *Clinical Pharmacology and Therapeutics.* 1981;29(5):625-633.
218. Erickson SH, Oppenheim GL, Smith GH. Metronidazole in breast milk. *Obstetrics and gynecology.* 1981;57(1):48-50.
219. Devlin RG, Duchin KL, Fleiss PM. Nadolol in human serum and breast milk. *British journal of clinical pharmacology.* 1981;12(3):393-396.
220. Jamali F, Keshavarz E. Salicylate excretion in breast milk. *International Journal of Pharmaceutics.* 1981;8:285-290.
221. Berlin CM, Jr., Yaffe SJ, Ragni M. Disposition of acetaminophen in milk, saliva, and plasma of lactating women. *Pediatric pharmacology (New York, NY).* 1980;1(2):135-141.

222. Stec GP, Greenberger P, Ruo TI, et al. Kinetics of theophylline transfer to breast milk. *Clinical Pharmacology and Therapeutics.* 1980;28(3):404-408.
223. Sandstrom B, Regardh C. Metoprolol excretion into breast milk. *British Journal of Clinical Pharmacology.* 1980;9(5):518-519.
224. Toddywalla VS, Mehta S, Virkar KD, Saxena BN. Release of 19-nor-testosterone type of contraceptive steroids through different drug delivery systems into serum and breast milk of lactating women. *Contraception.* 1980;21(3):217-223.
225. O'Hare MF, Murnaghan GA, Russell CJ, Leahey WJ, Varma MP, McDevitt DG. Sotalol as a hypotensive agent in pregnancy. *British journal of obstetrics and gynaecology.* 1980;87(9):814-820.
226. Rey E, Giraux P, d'Athis P, Turquais JM, Chavinie J, Olive G. Pharmacokinetics of the placental transfer and distribution of clorazepate and its metabolite nordiazepam in the feto-placental unit and in the neonate. *European journal of clinical pharmacology.* 1979;15(3):181-185.
227. Bhaskar A, Schulze PE, Acksteiner B, Laumas KR. Quantitative analysis of norethindrone in milk using deuterated carrier and gas chromatography-mass spectrometry. *Journal of steroid biochemistry.* 1979;11(3):1323-1328.
228. Nilsson S, Nygren KG, Johansson EDB. Ethinyl estradiol in human milk and plasma after oral administration. *Contraception.* 1978;17(2):131-139.
229. Erkkola R, Kanto J, Allonen H, Kleimola T, Mantyla R. Excretion of methylergometrine (methylergonovine) into the human breast milk. 1978;16:579-580.
230. Mulley BA, Parr GD, Pau WK. Placenta transfer of chlorthalidone and its elimination in maternal milk. *European Journal of Clinical Pharmacology.* 1978;13(2):129-131.
231. Nilsson S, Nygren KG, Johansson ED. d-Norgestrel concentrations in maternal plasma, milk, and child plasma during administration of oral contraceptives to nursing women. *American journal of obstetrics and gynecology.* 1977;129(2):178-184.
232. Nilsson S, Nygren KG, Johansson ED. Megestrol acetate concentrations in plasma and milk during administration of an oral contraceptive containing 4 mg megestrol acetate to nursing women. *Contraception.* 1977;16(6):615-624.
233. Pacifici GM, Placidi GF. Rapid and sensitive electron-capture gas chromatographic method for the determination of pinazepam and its metabolites in human plasma, urine and milk. *Journal of chromatography.* 1977;135(1):133-139.
234. Buchanan RA, Eaton CJ, Koeff ST, Kinkel AW. Breast milk excretion of flufenamic acid. *Current Therapeutic Research, Clinical & Experimental.* 1969;11:533-538.
235. Fríguls B, Joya X, García-Algar O, Pallás CR, Vall O, Pichini S. A comprehensive review of assay methods to determine drugs in breast milk and the safety of breastfeeding when taking drugs. *Anal Bioanal Chem*. 2010;397(3):1157-1179. doi:10.1007/s00216-010-3681-0
236. McGuire MK, Seppo A, Goga A, et al. Best Practices for Human Milk Collection for COVID-19 Research. *Breastfeed Med*. 2021;16(1):29-38. doi:10.1089/bfm.2020.0296
237. Ballard O, Morrow AL. Human milk composition: nutrients and bioactive factors. *Pediatr Clin North Am*. 2013;60(1):49-74. doi:10.1016/j.pcl.2012.10.002
238. P˘aduraru L, Zonda GI, Avasiloaiei A-L, Moscalu M, Dimitriu DC, Stamatin M. Influence of refrigeration or freezing on human milk macronutrients and energy content in early lactation: results from a tertiary centre survey. Paediatr Child Health 2018;24: 250–7.
239. Peters MD, McArthur A, Munn Z. Safe management of expressed breast milk: a systematic review. Women Birth 2016;29:473–81.
240. Garc a-Lara NR, Escuder-Vieco D, Garc a-Algar O, De la Cruz J, Lora D, Pall s-Alonso C. Effect of freezing time on macronutrients and energy content of breastmilk. Breastfeed Med 2012;7: 295–301.
241. Leghi GE, Middleton PF, Netting MJ, Wlodek ME, Geddes DT, Muhlhausler BS. A Systematic Review of Collection and Analysis of Human Milk for Macronutrient Composition. *J Nutr*. 2020;150(6):1652-1670. doi:10.1093/jn/nxaa059

Appendix 2.1 Systematic review protocol and search terms

Objectives: We aim to better understand the collection methods of breastmilk. As well as the analytical techniques used to study drugs in breastmilk.

Methods: Literature Review
The specific purpose of this systematic review will be to examine the literature on:

1. collection methods and analytical techniques used to study drugs in breastmilk
2. historical changes in breastmilk collection and drug analysis procedures over time
3. gaps in the existing literature to aid in determining where further research is needed

Search Strategy

An experienced health sciences librarian will create a peer-reviewed comprehensive search strategy using a combination of subject terms and keywords. The search will be conducted in Medline (OVID, Embase (OVID), PsycINFO (OVID), International Pharmaceutical Abstracts (Ovid), and the Cochrane Library Databases (Wiley), Global Health (Ovid), and Scopus and focus on studies of any design that examined drugs which includes prescription, non-prescription and non-medicinal used in lactating mothers. There will be no date restrictions or article type restrictions. Articles will be restricted to English and human only.

Study Selection and Data Extraction

To meet the aims of this systematic review, article selection for inclusion in this study will be comprehensive and involve an iterative process. All articles that evaluate medication use in lactating mothers will be included, irrespective of study design, type or year of publication. Non-human articles will be excluded. There will be no restriction on the country and geographic location.

There will be a two-step process for study selection. First, two research assistants, under the guidance of an expert methodologist, will independently screen the titles and abstracts of search results to determine if they meet the broad eligibility criteria. The screening process will be completed on Rayyan. Full-text reports of all eligible citations will be retrieved for formal review. Second, two reviewers will independently assess each full-text report using a standardized form outlining the pre-determined inclusion and exclusion criteria. One researcher (principal investigator) will review any disagreements that could not be resolved by discussion by the two independent researchers.

To ensure the appropriateness of the inclusion and exclusion criteria, the initial stage will involve two research assistants to independently review a random selection of 25 eligible full-text articles. Once all relevant literature has been identified, two researchers will independently apply the inclusion and exclusion criteria for each article identified as described above. Authors of applicable articles and conference proceedings will be contacted if more information is required.

We will use Endnote X9™ to manage citations. The reference ID number, first author, year of publication, location of study, article type/study design, objectives, outcomes measured, population, sample size, interventions, results, other general information or comments about the article, and grading of scientific strength of evidence (if presented in systematic reviews) will be extracted using standardized and piloted forms. The research team will do a final review and chart of all included articles. Collected data will be quantified and reported in graphs and tables using Microsoft® Excel.

Sample Search Terms

"Population" Terms of Interest:
- Lactating mothers
- Breastfeeding mothers
- Nursing human mothers
- Postpartum/Perinatal
- Types of Drugs: prescription, over the counter, non-medicinal (cannabis, alcohol, tobacco)

"Intervention" Terms:
- Collection methods: method of expression, type of pump, the timing of collection relative to drug intake, setting (home/clinic/other), duration of pumping, the volume of breastmilk collected, number/frequency of samples collected, storage procedures
- Drug Analysis Techniques: equipment used (HPLC, LC-MS etc), the timing of analysis relative to the collection of samples, number of samples analyzed, validation methods used

Main Outcome(s):
- Historical changes in collection and drug analysis methods throughout time
- Summary of development and validation strategies for collecting and analyzing drugs in breastmilk
- Rationale (advantages/disadvantages) of different collection and drug analysis methods that are used.

Inclusion/Exclusion Criteria:

Include if:
1. Evaluation of the most common drugs (prescription, non-prescription and non-medicinal) used during breastfeeding
2. The collection methods used for breastmilk
3. The analytical methods to analyze drugs in breastmilk
4. Collection for the purpose of drug analysis

Exclude if:
1. Non-Human: anything done on animals or in vitro
2. Vitamins/minerals or supplements or natural health products or food products
3. Experimental or illicit drugs
4. Languages other than English

Appendix 2.2 Data collection form

Study Information	**Description as stated in report/paper**
Title: Title of paper/abstract / report that data are extracted from	
Study ID	
Journal	
Lead author contact details	
Country in which the study conducted	☐ United States ☐ UK ☐ Canada ☐ Australia ☐ Other
Year of Publication	
Study funding sources	
Possible conflicts of interest for study authors	

Characteristics of included studies	**Description as stated in report/paper**
Aim of study	
Study design	☐ Randomised controlled trial ☐ Systematic review ☐ Observational study o Longitudinal o Cross-sectional
Study duration	

Participants Data	**Description as stated in report/paper**
Samples size	
Post-partum ages/ lactation stage	
Age of mother	
Recruitment details	
Inclusion/Exclusion	
Illness/medical condition of participant	

Outcomes

Medication information	**Description as stated in report/paper**
Number of medications studies in article	
Name of medication	
Therapeutic category	
Medication type	☐ Prescription ☐ Over the counter ☐ Non-medicinal
Method of administration	
Dosage range	
Dosage frequency	
Length of time taking medication	
Setting of drug administration	
Collection procedures	
Number of participants milk samples collected	
Mode of collection	☐ Manual ☐ Pump ☐ Both
Volume collected per sample	
Collection time points	
Number of samples collected per participant	
Total samples collected (if stated)	
Sample storage procedures	☐ Temperature samples stored ☐ Analyzed immediately
Other material collected	☐ Blood (serum, plasma) ☐ Urine ☐ Other
Infant blood collected	☐ Yes ☐ No
Analytical procedures	
Techniques	
Equipment	
Number of samples analyzed	
Volume of milk used for analysis per sample	
Validation method used	

Appendix 2.3 Medical conditions/illness of participants of included studies (N=224)

Medical condition/illness	No. Articles	%
Depression	36	16.1%
No specific medical conditions (healthy participants)	32	14.3%
HIV	16	7.1%
Postpartum pain relief (Delivery, Caesarean section, Episiotomy)	16	7.1%
Hypertension	13	5.8%
Contraceptive	12	5.4%
Epilepsy	11	4.9%
Opioid use disorder	9	4.0%
Operations (Dental treatment, Caesarean section, General)	7	3.1%
Malaria	6	2.7%
Psychiatric conditions (Bipolar depression, Manic disorder, Schizo-affective disorder, Schizophrenia, Mood disorders)	6	2.7%
Asthma	4	1.8%
Diabetes	4	1.8%
Inflammatory Bowel Disease	4	1.8%
Multiple Sclerosis	4	1.8%
Various conditions	4	1.8%
Chagas disease	3	1.3%
Anaerobic infection prophylaxis	2	0.9%
Chronic Inflammatory Diseases: Rheumatoid arthritis, Crohn's, Psoriatic arthritis, Axial spondylarthritis/ ankylosing spondylitis)	2	0.9%
Incomplete postpartum uterine involution	2	0.9%
Organ transplant	2	0.9%
Perioperative prophylaxis	2	0.9%
Postpartum infections	2	0.9%
Tubal ligation	2	0.9%

Allergies (pollen allergy/allergic rhinitis)	1	0.4%
Anxiety	1	0.4%
Cardiovascular disease	1	0.4%
Caesarean section sepsis prevention	1	0.4%
Connective tissue diseases	1	0.4%
Gynecologic and obstetric infections	1	0.4%
Leprosy	1	0.4%
Lymphatic filariasis	1	0.4%
Mastitis	1	0.4%
Medical abortion	1	0.4%
Migraine	1	0.4%
Narcolepsy/Cataplexy	1	0.4%
Postpartum endometritis	1	0.4%
Postpartum haemorrhage (Uterotonic agent)	1	0.4%
Premature rupture / prolonged delivery	1	0.4%
Respiratory tract infection	1	0.4%
Retinal vascular disease	1	0.4%
Sedative for labour	1	0.4%
Sickle cell anemia	1	0.4%
Thromboprophylaxis	1	0.4%
Toxaemia	1	0.4%
Trichomoniasis	1	0.4%
Tuberculosis	1	0.4%

Appendix 2.4 Medications and therapeutic categories of included studies (N=224)

Number of medications included in an article

No. of medications	No. of articles	%
1 Medication	197	87.9%
2 Medications	9	4.0%
3 Medications	5	2.2%
5 Medications	3	1.3%
9 Medications	1	0.4%
Combination medication	8	3.6%
Review article (13 medications)	1	0.4%

Therapeutic categories (N=46) of included studies

Therapeutic categories	No. of articles	%
Antidepressant	58	25.9%
Anti-retroviral agent (HIV)	43	19.2%
Antibiotic	16	7.1%
NSAID	14	6.3%
Opioid	14	6.3%
Anticonvulsant	12	5.4%
Contraceptive	11	4.9%
Antimalarial	9	4.0%
Antipsychotic	9	4.0%
Beta Adrenergic Blocker	8	3.6%
Analgesic	7	3.1%
Antiparasitic (Anthelmintic)	7	3.1%
Biologics/monoclonal antibody	6	2.7%
Sedative-Hypnotic	6	2.7%
Anesthetic (Local)	6	2.7%
Antidiabetic	5	2.2%
Corticosteroid	5	2.2%
Calcium-channel blockers	5	2.2%
Anti-Inflammatory	5	2.2%
Antihistamine	4	1.8%
Anticoagulant	4	1.8%
Immune Suppressant	3	1.3%
Antiasthma	3	1.3%
Antihypertensive	3	1.3%

Benzodiazepine (Antianxiety)	3	1.3%
Anesthetic (General)	3	1.3%
Laxative	2	0.9%
Vasoconstrictor	2	0.9%
ACE inhibitor	2	0.9%
Antimigraine	1	0.4%
Antiarrhythmic	1	0.4%
Immune Modulator	1	0.4%
Prostaglandin	1	0.4%
Beta Blocker (Non-selective)	1	0.4%
Decongestant	1	0.4%
Antihemorrhagic	1	0.4%
Leprostatic	1	0.4%
Hemorheologic	1	0.4%
Antiprogesterone	1	0.4%
Diuretic	1	0.4%
Antineoplastic (Antimetabolite)	1	0.4%
Antitussive	1	0.4%
Progestin	1	0.4%
Diagnostic Agent	1	0.4%
Antitubercular	1	0.4%
Antithyroid Agent	1	0.4%

Over the counter medication (N= 8) of included studies

Over the counter medications (OCT)	**Therapeutic category**	**No. of articles**
Acetaminophen (Tylenol)	Analgesic	1
Acetylsalicylic Acid (Aspirin)	Anti-Inflammatory	3
Cimetidine	Antihistamine	1
Loratadine	Antihistamine	1
Pseudoephedrine	Decongestant	1
Bisacodyl (Dulcolax)	Laxative	1
Sodium picosulfate (Dulcolax Pico Liquid)	Laxative	1
Ibuprofen (Advil)	NSAID	2

Medications (N=186) of included studies

Medication name	No. of articles (N)	%
Fluoxetine	11	4.9%
Sertraline	8	3.6%
Nevirapine	8	3.6%
Paroxetine	7	3.1%
Lamivudine	7	3.1%
Methadone	6	2.7%
Citalopram	5	2.2%
Venlafaxine	5	2.2%
Chloroquine	5	2.2%
Tenofovir Disoproxil	5	2.2%
Norfluoxetine	4	1.8%
Zidovudine	4	1.8%
Stavudine	4	1.8%
Acetylsalicylic Acid (Aspirin)	3	1.3%
Dothiepin	3	1.3%
Buprenorphine	3	1.3%
Benznidazole	3	1.3%
Efavirenz	3	1.3%
Levonorgestrel	3	1.3%
Methylprednisolone	2	0.9%
Amlodipine	2	0.9%
Flurbiprofen	2	0.9%
Emtricitabine	2	0.9%
Fluvoxamine	2	0.9%
Moclobemide	2	0.9%
Haloperidol	2	0.9%
Ibuprofen	2	0.9%
Ritonavir	2	0.9%
Tramadol	2	0.9%
Escitalopram	2	0.9%
Carbamazepin	2	0.9%
Metronidazole	2	0.9%
Levetiracetam	2	0.9%

Cefoxitin	2	0.9%
Nifedipine	2	0.9%
Lidocaine	2	0.9%
Olanzapine	2	0.9%
Dexmedetomidine	2	0.9%
Propofol	2	0.9%
Mesalamine	2	0.9%
Azithromycin	2	0.9%
Metformin	2	0.9%
Tacrolimus	2	0.9%
Centchroman	2	0.9%
Methylergometrine	2	0.9%
Lamotrigine	2	0.9%
Lopinavir	2	0.9%
Certolizumab Pegol	1	0.4%
Morphine	1	0.4%
Acetaminophen (Tylenol)	1	0.4%
Bevacizumab	1	0.4%
Noscapine	1	0.4%
Albendazole	1	0.4%
Sotalol	1	0.4%
Ethamsylate	1	0.4%
Dabigatran Etexilate	1	0.4%
Ethinyl Estradiol	1	0.4%
Phenoxymethylpenicillin	1	0.4%
Ethosuximide	1	0.4%
Reboxetine	1	0.4%
Etravirine	1	0.4%
Terbutaline	1	0.4%
Fentanyl	1	0.4%
Natalizumab	1	0.4%
Flecainide	1	0.4%
Norethindrone Acetate (Net-A)	1	0.4%
Fleroxacin	1	0.4%
Pentoxifylline	1	0.4%
Flufenamic Acid	1	0.4%

Piperaquine	1	0.4%
Bupropion	1	0.4%
Pseudoephedrine	1	0.4%
Atazanavir	1	0.4%
Cefmenoxime	1	0.4%
Suprofen	1	0.4%
Gabapentin	1	0.4%
Tiapamil	1	0.4%
Gadopentetate Dimeglumine	1	0.4%
Vedolizumab	1	0.4%
Garenoxacin	1	0.4%
Nelfinavir	1	0.4%
Gentamicin	1	0.4%
Nifurtimox	1	0.4%
Glipizide	1	0.4%
Dapsone	1	0.4%
Glyburide	1	0.4%
Parecoxib	1	0.4%
Cefonicid	1	0.4%
Perindopril Erbumine	1	0.4%
Hydralazine	1	0.4%
Pinazepam	1	0.4%
Hydromorphone	1	0.4%
Prednisolone	1	0.4%
Hydroxychloroquine	1	0.4%
Propranolol	1	0.4%
Hydroxyurea	1	0.4%
Quazepam	1	0.4%
Atenolol	1	0.4%
Rituximab	1	0.4%
Imipramine	1	0.4%
Sodium Oxybate	1	0.4%
Indinavir	1	0.4%
Sulbactam	1	0.4%
Indomethacin	1	0.4%
Duloxetine	1	0.4%

Infliximab	1	0.4%
Theophylline	1	0.4%
Insulin	1	0.4%
Tocilizumab	1	0.4%
Isoniazid	1	0.4%
Valacyclovir	1	0.4%
Ivermectin	1	0.4%
Ximelagatran	1	0.4%
Ketoprofen	1	0.4%
Nefopam	1	0.4%
Ketorolac	1	0.4%
Nestoron (Progestin ST-1435)	1	0.4%
Cefprozil	1	0.4%
Dalteparin	1	0.4%
Celecoxib	1	0.4%
Nitrofurantoin	1	0.4%
Azapropazone	1	0.4%
Norethisterone	1	0.4%
Levobupivacaine	1	0.4%
Norgestrel	1	0.4%
Azathioprine	1	0.4%
Desmethylsertraline	1	0.4%
Alpha Methyldopa	1	0.4%
Desvenlafaxine	1	0.4%
Lithium	1	0.4%
Perindopril Arginine	1	0.4%
Chlorpromazine	1	0.4%
Phenacetin	1	0.4%
Zolpidem	1	0.4%
Phenytoin	1	0.4%
Zuclopenthixol	1	0.4%
Pindolol	1	0.4%
Meperidine	1	0.4%
Pre-Gabalin	1	0.4%
Mepindolol	1	0.4%
Prednisone	1	0.4%

Chlorthalidone	1	0.4%
Propoxyphene	1	0.4%
Cimetidine	1	0.4%
Propranolol Glucuronide	1	0.4%
Amitriptyline	1	0.4%
Pyrimethamine	1	0.4%
Methimazole	1	0.4%
Quetiapine	1	0.4%
Methohexital	1	0.4%
Diazepam	1	0.4%
Methyldopa	1	0.4%
Ropivacaine	1	0.4%
Clindamycin	1	0.4%
Dipyrone	1	0.4%
Clofazimine	1	0.4%
Sodium picosulfate (Dulcolax Pico Liquid)	1	0.4%
Metoprolol	1	0.4%
Bisacodyl (Dulcolax)	1	0.4%
Clomipramine	1	0.4%
Sumatriptan	1	0.4%
Midazolam	1	0.4%
Doxepin	1	0.4%
Mifepristone	1	0.4%
Tenoxicam	1	0.4%
Misoprostol	1	0.4%
Terfenadine	1	0.4%
Clorazepate	1	0.4%
Thiopentone	1	0.4%
Montelukast	1	0.4%
Tinidazole	1	0.4%
Codeine	1	0.4%
Budesonide	1	0.4%
Moxidectin	1	0.4%
Trifluoperazine	1	0.4%
Nadolol	1	0.4%
Valproic Acid	1	0.4%

Nalbuphine	1	0.4%
Bupivacaine	1	0.4%
Nandrolone	1	0.4%
Epinastine	1	0.4%
Naphthoxylactic Acid	1	0.4%
Zonisamide	1	0.4%
Loratidine	1	0.4%
Abacavir	1	0.4%
Megestrol Acetate	1	0.4%

Appendix 2.5 Human milk collection method categories and subcategories of included studies (N=224)

Collection method categories	No. of studies (N)	%
Time interval	**124**	**55.36%**
24-hour interval	55	24.55%
12-hour interval	17	7.59%
8-hour interval	13	5.80%
48-hour interval	10	4.46%
6-hour interval	5	2.23%
72-hour interval	4	1.79%
4-hour interval	3	1.34%
10-hour interval	3	1.34%
120-hour interval	3	1.34%
5-hour interval	2	0.89%
16-hour interval	2	0.89%
36-hour interval	2	0.89%
3-hour interval	1	0.45%
7-hour interval	1	0.45%
9-hour interval	1	0.45%
14-hour interval	1	0.45%
18-hour interval	1	0.45%
20-hour interval	1	0.45%
23-hour interval	1	0.45%
25-hour interval	1	0.45%
30-hour interval	1	0.45%
34-hour interval	1	0.45%
40-hour interval	1	0.45%
46-hour interval	1	0.45%
126-hour interval	1	0.45%
160-hour interval	1	0.45%
217-hour interval	1	0.45%
219-hour interval	1	0.45%
227-hour interval	1	0.45%
Multiple collection days	**40**	**17.86%**
Specified interval	*27*	12.05%
4 days	1	0.45%
5 days	3	1.34%
7 days	1	0.45%
14 days	1	0.45%

17 days	1	0.45%
20 days	1	0.45%
21 days	2	0.89%
22 days	1	0.45%
28 days	6	2.68%
30 days	1	0.45%
6 weeks	2	0.89%
12 weeks	1	0.45%
14 weeks	1	0.45%
6 months	3	1.34%
12 months	1	0.45%
24 months	2	0.89%
Consecutive days	*10*	4.46%
2 days	*1*	0.45%
3 days	2	0.89%
4 days	3	1.34%
5 days	1	0.45%
7 days	2	0.89%
9 days	1	0.45%
Specified range	*3*	1.34%
Collection at specific time range	**29**	**12.95%**
Hours	19	8.48%
Days	7	3.13%
Months	3	1.34%
Collection at specific time point	**23**	**10.27%**
1 time point	15	6.70%
2 time points	6	2.68%
3 time points	2	0.89%
Multiple collection time points in a day	**6**	**2.68%**
2 time points	1	0.45%
3 to 5 time points	1	0.45%
6 time points	1	0.45%
9 time points	1	0.45%
Per and post samples at every feed	2	0.89%
Not specified	**5**	**2.23%**
Various	**1**	**0.45%**

Appendix 2.6 Analytical techniques used to measure medications in human milk (N=224)

Analytical Techniques	No. articles	%
HPLC	74	33.04%
HPLC-UV	18	8.04%
LC-MS/MS	18	8.04%
LC-MS	13	5.80%
RIA	12	5.36%
GC	9	4.02%
GLC	8	3.57%
HPLC-MS/MS	7	3.13%
GC-MS	7	3.13%
ELISA	7	3.13%
HPLC-FLD	6	2.68%
RP-HPLC	4	1.79%
RP-HPLC-UV	4	1.79%
EIA	4	1.79%
UHPLC-MS/MS	3	1.34%
UPLC-MS/MS	3	1.34%
Disk diffusion method	3	1.34%
Fluorometric method	3	1.34%
LC	2	0.89%
LC-APCI-MS/MS	2	0.89%
HPTLC	2	0.89%
HPLC-ECD	1	0.45%
HPLC-MS	1	0.45%
HPLC-UV-DAD	1	0.45%
RP-HPLC-FLD	1	0.45%
RP-HPLC-MS/MS	1	0.45%
IP-HPLC-UV	1	0.45%
IP-RP-HPLC	1	0.45%
IEX-HPLC-EC	1	0.45%
LC/ESI-MS/MS	1	0.45%
GC-ECD	1	0.45%
GC-EI-MS	1	0.45%
GC-MS/MS	1	0.45%
GC/NICI-MS	1	0.45%
GLC-ECD	1	0.45%
TLC-MS	1	0.45%
Agar dilution method	1	0.45%
ECLIA	1	0.45%
FACS	1	0.45%
FPIA	1	0.45%
Clotting time assay	1	0.45%
Trichloroacetic acid method	1	0.45%
ICP-AES	1	0.45%
ISE	1	0.45%
CMIA	1	0.45%

STUDY 2 INTRODUCTION

This study includes the following chapters:

*Chapter 3: Parent and healthcare providers preference factors, decision making and knowledge on medication use during lactation: scoping review

Chapter 4: Parent engagement interviews

*Chapter 5: Parent and healthcare providers preference factors, decision making and knowledge on medication use during lactation: a Canada-wide survey study

* Chapters 3 and 5 are intended for publication in a peer-reviewed scientific journal

Scoping review (chapter 3) was conducted to understand the current literature on parent and health care providers' preferences factors and decision making around medication use during lactation. Parent engagement interview (chapter 4) was conducted to further understand preferences and views of parent with lived experiences around medication use during human milk feeding. A preliminary survey was pilot tested by the parents for feedback. Both the scoping review and parent interviews helped inform the design and direction of the parent and healthcare provider surveys (chapter 5).

CHAPTER 3 MANUSCRIPT

Parent and healthcare providers preference factors, decision making and knowledge on medication use during lactation: scoping review

Uma Yakandawala[1], Evan Frost[2], Christine Leong[1], Lauren E Kelly[3]

1. College of Pharmacy, Rady Faculty of Health Science, University of Manitoba, Winnipeg, Manitoba, Canada
2. Department of Community Health Sciences, University of Manitoba, Winnipeg, MB, Canada.
3. Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba, Canada

To be submitted to journal (undecided)

Corresponding author:
Christine Leong, BSc (Gen), BSc (Pharm), PharmD
750 McDermot Avenue, Winnipeg, MB, Canada R3E 0T5
Tel: 204-318-5276
Email: christine.leong@umanitoba.ca

Running title: Decision making around medication use during lactation

Funding sources: Rady Innovation Fund, Centre for Health Innovation

Key words: breastmilk, human milk, medication, preferences, decision making, parents, breastfeeding, lactation, healthcare provider

CHAPTER 3. PARENT AND HEALTHCARE PROVIDERS PREFERENCE FACTORS, DECISION-MAKING AND KNOWLEDGE ON MEDICATION USE DURING LACTATION: SCOPING REVIEW

3.1 ABSTRACT

Background: Decisions around medication use during infant feeding is often a challenge for parents due to limited evidence-based information.

Aim: The scoping review aims to determine the extent, nature, and range of methods for measuring values and preferences towards medication use and to identify factors that may be important to consider in the decision to take medication during infant feeding.

Methods: A scoping review was conducted to examine parents' and healthcare providers' preferences and values around medication use during lactation. The study included only English-language studies and searched the following databases: Medline (OVID, Embase (OVID), PsycINFO (OVID), International Pharmaceutical Abstracts (Ovid), and the Cochrane Library Databases (Wiley), Global Health (Ovid), Scopus and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

Results: Forty-six articles were included. Quantitative studies which include questionnaires/surveys (n=19) were the most used methods followed by quantitative studies which include interviews (n=9). Three primary themes (preference factors, decision making, and knowledge) were categorized from an initial twelve sub-themes that were identified. The most frequently presented theme included statements on factors influencing decisions making (35 statements) on medication use during lactation.

Conclusion: Future studies should examine the decision-making processes of parents and healthcare providers regarding medication use during infant feeding. The focus should also include evaluating the shared decision-making process between parents and healthcare providers and what factors would help facilitate a better parent-provider relationship.

3.2 Introduction

Many people require the use of medications during lactation to treat acute or chronic health conditions. Sixty-four percent of women who are pregnant received at least one prescription medication based on administrative data from Manitoba and British Columbia.[1,2] Roughly the same proportion at 63% receive a prescription medication in the first three months postpartum.[2] Medication use has been identified as an important barrier to continued breastfeeding, due to concerns of drug exposure risks to the infant through milk.[3] Most drugs transfer into milk in small amounts.[4] As pregnant and breastfeeding people have historically been excluded from research and drug development, there is a paucity of information about the overall safety and appropriateness of medication use in these populations. Therefore, parents requiring medications and their healthcare providers may be ill-informed about the risks of nursing while taking medications

Mothers may take an absolute risk avoidance approach due to understudied medications and stop breastfeeding or discontinue taking necessary medications to avoid possible (unknown) adverse effects on their child. It is important to know the risks (including the risks of not breastfeeding) and benefits for both mother and child when advising on medication decisions during breastfeeding, while also considering the preferences and experiences of the mother before, during and after pregnancy.

Shared decision-making involves patients and their clinicians sharing the best available evidence when faced with the task of making health decisions.[5] Patients are encouraged and supported to consider different options and to weigh the benefit and risks of the choices. Shared decision-making allows patients to be involved and better informed about their healthcare decisions and to relay their preferences to the clinicians. Shared decision-making is essential for good patient-centred care and has benefits for patients such as increased confidence in their decisions, active involvement, and improved knowledge.[6]

For individuals making decisions around medication use while breastfeeding is often a challenge due to limited evidence-based information. To facilitate shared decision-making, it is important to understand both the parent and healthcare providers' experiences, preferences, values, concerns, and knowledge around medication use during breastfeeding.

This scoping review was conducted to understand mothers’ as well as health care professionals' preference factors that contribute to the decision to take or not to take medication

during breastfeeding. The existing literature on parent values and preferences is limited but important to ensure future research will study parent important outcomes and shed light on factors that contribute to the decision to take medication during breastfeeding.

3.3 Objectives

This scoping review aimed to determine the extent, nature, and range of methods for measuring values and preferences towards medication use and to identify factors that may be important to consider in the decision to take medication during breastfeeding.

Specific objectives include:

1. To understand parents' experiences, preferences, opinions, and concerns around medication use during breastfeeding
2. To understand healthcare professionals' views on mothers' decisional needs and preference factors regarding medication use during breastfeeding.
3. To identify gaps in the existing literature to aid in determining where further research is needed and what future resources are needed to help guide decision making for both parents and healthcare providers

3.4 Methods

This scoping review was guided by the methodological framework proposed by Arskey and O'Malley.[7]

Search strategy

A comprehensive search strategy was developed by UY and CL (Appendix 3.1). The following databases were searched using a combination of subject terms and keywords: Medline (OVID, Embase (OVID), PsycINFO (OVID), International Pharmaceutical Abstracts (Ovid), and the Cochrane Library Databases (Wiley), Global Health (Ovid), Scopus and Cumulative Index to Nursing and Allied Health Literature (CINAHL). Articles from inception to January 2021 that evaluate views of parents and/or health care providers about medication use while breastfeeding were included. Only articles there were in the English language were included. There was no restriction to study design, study type, country, and geographic location. Studies assessing views

on alcohol, illicit drugs, recreational drugs, tobacco, vitamins, minerals, experimental drugs were excluded. Non-human articles were excluded.

The searching process was conducted over the dates of 12/10/2020 to 12/21/2020. All final search results were imported into Endnote and deduplicated by UY. The deduplicated results were exported into Rayyan (a web tool used to conduct article screening), blinded by a librarian. Study selection involved a two-step process. First, title and abstract screening were independently screened by two investigators (UY and EF) to determine if they met the broad eligibility criteria. The investigators (UY and EF) discussed any discrepancies after initial screening and articles where an agreement that could not be made was resolved by a third investigator (CL).

Full-text reports of all eligible citations were retrieved and imported into a blinded Rayyan for formal review. Second, each full-text article was independently assessed by one investigator (UY) using a standardized form outlining pre-determined inclusion and exclusion criteria

Data extraction was completed by one investigator (UY). The data charting form was developed using Covidence which captured study information, such as article title, author, year of publication, study setting, study design, the aim of the study, data collection methods, population characteristics and results.

The textual data that was extracted from the articles were then coded and evaluated using thematic analysis. Coding of the extracted data was performed using Dedoose software. Initial review of the coded data presented 12 themes which were later assigned to three broader themes (preference factors, decision making and knowledge). Descriptive statistics were used to describe the characteristics of publications included in the scoping review.

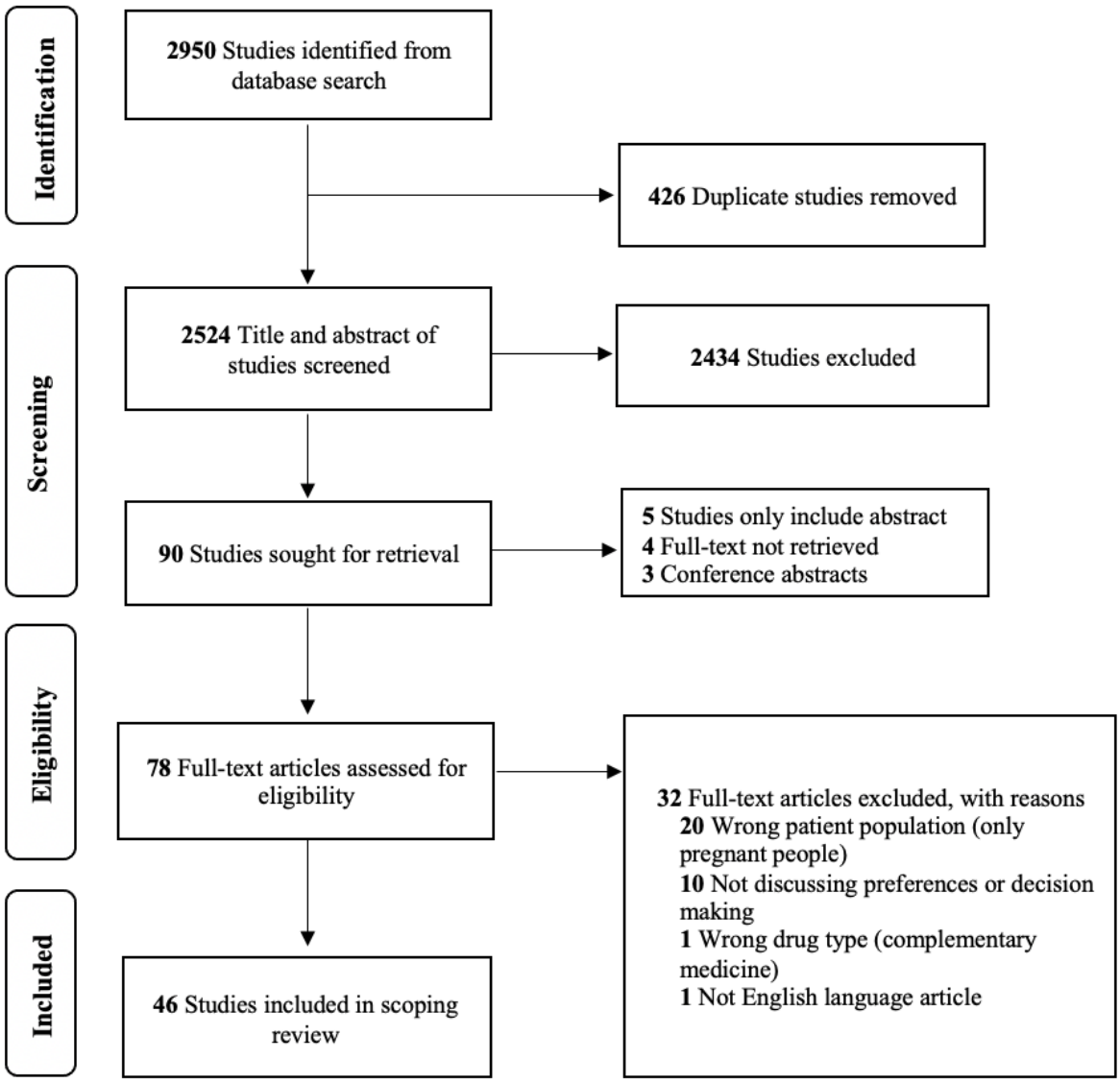


Figure 3.1 PRISMA flow diagram depicting articles included and excluded for thematic analysis in the scoping review

3.5 RESULTS

After de-duplication was performed and articles were removed, 2524 records were retrieved and screened for eligibility. Full-text reviews for eligibility were completed for 78 articles. A total of 46 publications met the inclusion criteria for data extraction (Fig 3.1). Thirty-two articles were excluded for the wrong patient population (only pregnant people) N= 20; not discussing preferences or decision-making N=10; wrong drug type (complementary medicine) N =1; not English language article N=1.

Among the articles that were included, 20 were Quantitative studies (questionnaires/survey and social media mining) [8-27], 19 were qualitative studies (interviews, focus group, Delphi process, patient-reported treatment review) [28-46] three were mixed mixed-methods studies) [47-49], two observational studies [50-51], and two review articles [52-53], please refer to Table 1. Most articles (n = 35) were published between 2015-2020 [8, 9, 10, 11, 12, 13, 14, 15, 16,17, 19, 22, 24, 26, 27, 29, 30, 31, 32, 33, 34, 37, 38, 39, 40, 41, 42, 43, 44, 46, 47, 49, 50, 52, 53].

Population characteristics

Among the 46 articles included, the parent population consisted of 25 (54.3%) articles, healthcare providers were included in 16 (34.8%) articles and both parents and healthcare providers were included in 5 (10.9%) articles. Among the articles (21/46) that included healthcare providers, 8 articles (38.1%) included more than one provider type. Pharmacists were represented the highest in one single category with 7 (33.3%) articles followed by physicians with 4 (19.0%) and pharmacology experts and health workers with both one (4.8%) article each.

Medical conditions

Of the 46 included articles 18 studies did not focus on a particular medical condition [8,9,12,16,18,20,21,22,30,31,35,38,39,40,41,47,49,50]. Four articles discussed medications used for lactation insufficiency [13,14,42,51]. Studies about HIV [33,44,46] and rheumatoid arthritis [28,29,32] were included in three studies each. Birth control [23,46], inflammatory bowel disease [17,26], influenza (Influenza, H1N1) [25,45], migraines [10,11], and rheumatic diseases [24,43], were included in two studies each. One article each was included for that discussed chronic diseases generally, drug-related problems (DRPs), fibromyalgia, gender dysphoria,

hyperthyroidism, opioid-related disorders, postpartum depression, and recreational marijuana use.

Medications

Many included studies (18 of 46, 39.1%) did not focus on a specific medication [8,9,12,16,18,20,21,22,30,31,35,38,39,40,41,47,49,50]. Three studies focused on participants who made decisions around the use of rheumatoid arthritis medication [28,29,32]. Three studies focused on parents using anti-retroviral treatment [33,44,46]. Two studies were included for each of the following medication groups anti-rheumatic drugs [24,43] antidepressants [19,36] contraceptives [23,46], domperidone [42,51], galactagogue [13,14], inflammatory bowel disease medications [17,26], influenza vaccines [25,45], migraine medications [10,11]. One study focused on prescription medication generally [49] and another focused on non-prescription medications [37]. The following medications were included in one study each marijuana [15] methadone therapy [34], propylthiouracil therapy [48], and testosterone [27].

Themes

From the coded data, three primary themes (preference factors, decision making, and knowledge) were categorized from an initial twelve sub-themes that were first identified, presented in Figure 3.2.

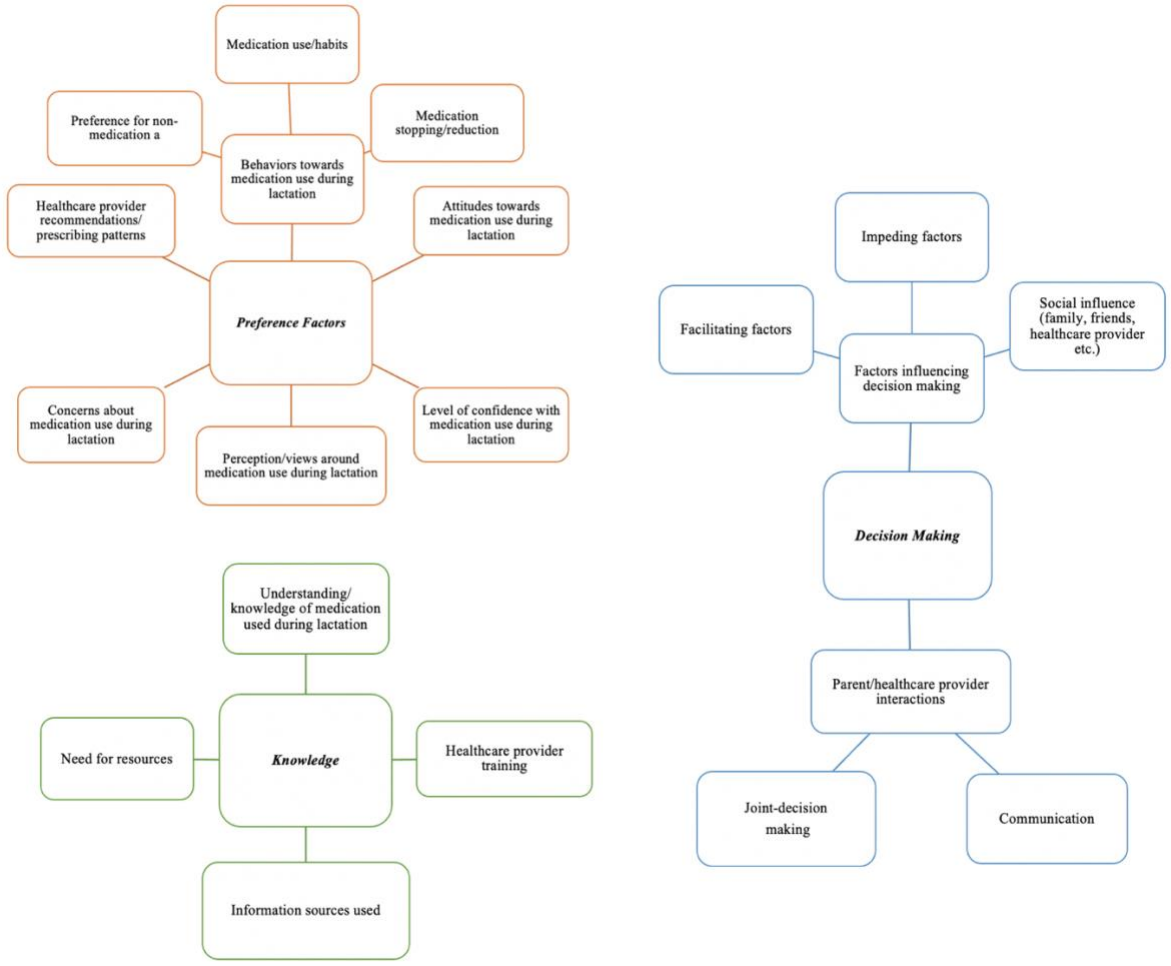


Figure 3.2. Themes and sub-themes identified in the included studies

Preference factors

Preference factors consisted of six sub-themes which are presented in Table 3.3. Sub-themes included *attitudes towards medication use during lactation, level of confidence with medication use during lactation, perception/views around medication use during lactation, concerns about medication use during lactation, healthcare provider recommendations/prescribing patterns and behaviours towards medication use during lactation.*

The most frequently presented sub-theme included statements about *behaviours towards medication use during lactation*. Number of studies (n=13,16 statements) reported on medication use and habits [10,11,13,19,21,35,39,40,41,42,49,51,52]. One study stated that "(91.0 %) of the women planned to or were using at least one prescription drug, over the counter (OTC) drug, or vitamin, mineral, or herbal remedy during breastfeeding" [39]. Participants' desire to reduce medication load or discontinue taking medication entirely was reported in 11 statements. Another common behaviour was the preference for using non-medication alternatives (5 statements), participants "believed that natural products are safer than medication" [47].

The second most encountered sub-theme consisted of *healthcare providers' recommendations and prescribing patterns* (11 statements). One study about opinions of pharmacists described risk vs. benefit and infant age as the most frequently mentioned factors that were important to consider when supplying medication to breastfeeding women [16]. Another study stated, "qualitative feedback from participants suggests that prescribing for breastfeeding women is a nuanced process that requires careful consideration and that one size, fits all classification system might lead to uninformed and incorrect decision-making by clinicians" [31].

The most common *concern about medication use during lactation* includes statements about adverse effects on the child (4 statements). Other concerns include the safety of medication (3 statements) and a statement about the effect on breastmilk quality and parents having negative feelings such as anxiety and guilt around the use of medication.

Parents had varied *perceptions/views around medication use during lactation*. One study using both quantitative and qualitative methods reported that "pregnant women and new mothers believe that the combination of breastfeeding and pharmacotherapy is not preferable" [47]. Another study stated that the "trade-off effective disease management with providing best possible nutrition for the child" [43].

Regarding the *level of confidence with medication use during lactation*. An article assessing pharmacists stated they were confident in advising breastfeeding women [16]. There were also statements about healthcare providers feeling more confident advising on conventional medicines over complementary medicine [37] and "some medicines were regarded as "safe" include drugs with a long history of use" [18].

Decision-making

Decision-making consists of two sub-themes which include: *factors influencing decision making and parent/healthcare provider interactions.*

The sub-theme *factors influencing decision-making* included 35 statements. Twelve of those statements consisted of facilitating factors for medication use during lactation, these include previous experience, empowering and education for parents, having medication information, hearing other parents' experiences, healthcare provider recommendations and infant wellbeing. Factors impeding the decision to use medication during lactation include fear of adverse or harmful effects on the infant from the medication passage through the milk, age of the infant, receiving conflicting advice, feeling negative emotions, healthcare provider recommendations, lack of data about medication used during lactation, lack of support from others, misinformation, concerns over the safety of drug transmission, risk vs. benefit and self-efficacy.

The impact of social influence on decision-making was also discussed in several articles. Friends, families and spouses can both support or have a negative influence such as causing anxiety around the decision to use medication or breastfeed. One study stated that "most women reported that they felt pressure to breastfeed, whilst some also reported that they felt pressure to discontinue breastfeeding to re-instate certain medications. Several other mothers talked about how they felt pressured to stop breastfeeding, either by their health care professionals or by family members" [43].

Parent and healthcare provider interactions included statements about communication and joint decision-making. Parents expressed for "closer follow-up and more understanding from healthcare professionals" [10]. Regarding routine inquiry from parents, if they were breastfeeding, one study states that "seventy-one percent of the participants mentioned that their physician asked them if they were breastfeeding before writing the prescription, while around 60% of the pharmacist asked whether they were breastfeeding before dispensing any medication" [30]. Conversely another study states that "very few pharmacists asked all women if they were breastfeeding (15%). More than half of the pharmacists reported never asking women if they were breastfeeding (58%)" [20]. It is important to evaluate how frequently healthcare providers are asking their patients if they are breastfeeding when offering advice.

Patient preference was rated as the most important factor by clinicians [23]. A study stated that advice given by clinicians would also be influenced if parents expressed a desire to breastfeed. Suggesting that the decision-making process of physicians seemed to be influenced by parents' attitudes [48]. There was a favour for shared decision-making between parents and healthcare providers "GPs felt that certain situations warranted the involvement of several parties in the decision-making process rather than a quick decision on their part. Although this would involve more time and work for GPs, they thought this would help to make a more appropriate and safe decision and increase mothers' compliance with the recommended/prescribed medicine"[18].

Knowledge

The third theme "knowledge" that emerged consists of four sub-themes which include: *understanding/knowledge of medications used during lactation, healthcare provider training, information sources used and need for resources*.

Knowledge of parents and healthcare providers, as well as information needs about medications and use during lactation, was a recurrent theme that was encountered during qualitative synthesis. One study stated, "regarding the use of medications, majority of women think that many drugs cannot be used during breastfeeding (19.7% agreement; 67.8% disagreement), and if a breastfeeding mother has a minor problem (eg, headache, toothache, back pain), it is better to endure the pain rather than take a pain reliever (61.2% agreement; 31.9% disagreement) *understanding/knowledge of medication used during lactation*" [47].

There was some variability in *healthcare provider training* for instance for the use of IBD medication among breastfeeding parents. "Gastroenterologists demonstrated a high level of knowledge in accordance with best practice regarding" compared to non-specialty physicians who also actively care for parents with IBD in their practice [17]. One study stated that regarding pharmacists' belief in providing active drug information services there was no significant difference in the periods of work experience between 1-year work experience compared to 10 or more years [12]. Another statement suggests most pharmacist knowledge around medication use during breastfeeding was acquired from "day-to-day work experience, self-directed training, personal or close-contact breastfeeding experience, and university training as part of their pharmacy degree" [38].

Information sources used to learn about medication use during lactation included healthcare providers, the internet and websites, breastfeeding counselling services, product information, books and articles, family and friends, past personal experiences and other parents' experiences, policies/guidelines/reference books, specialized groups and organizations, breastfeeding support groups, and training/conferences.

Resources that parents and healthcare providers expressed that would be beneficial include education programs for healthcare providers, breastfeeding counselling, and education resources for parents. A need for consistent and evidence-based information was requested as well as for more safety data about medication use during lactation.

3.6 Discussion

The current scoping review summarized a total of 46 articles on parents' and healthcare providers' preference factors, decision-making and knowledge around medication use during lactation. It was noted that most studies employed quantitative study designs, particularly using questionnaire/survey methodology. Many of the studies included did not focus on decision-making on a specific medication (18 of 46, 39.1%). Medications used to treat lactation insufficiency, rheumatoid arthritis, and antiretrovirals were the most frequent studies with three articles each.

To our knowledge, three articles have previously evaluated similar topics to this current review. A scoping review conducted by Spiesser-Robelet L, et al: Knowledge, Representations, Attitudes, and Behaviors of Women Faced with Taking Medications While Breastfeeding was included in our study [53]. Two articles were not captured during our database search and were later found through Google search. A review by Hussainy SY, et al: Knowledge, attitudes and practices of health professionals and women towards medication use in breastfeeding: A review [54]. As well as a systematic review conducted by Saha MR, et al: Postpartum women's use of medicines and breastfeeding practices: a systematic review [55].

The systematic reviews by Saha MR, et al suggest a need for qualitative studies to understand how postpartum parents make their decisions around medication use and what factors influence decision-making [55]. In this review, we were able to gather new information on facilitating and impeding factors that influence parents' decision-making on medication use during lactation. Facilitating factors include previous experience of their own or other parents,

empowering and education for parents, having medication information and healthcare provider recommendations and infant wellbeing. Factors impeding decision-making include fear of adverse or harmful effects on the infant, age of the infant, conflicting advice, negative emotions, healthcare provider recommendations, lack of data, lack of support, misinformation, concerns over the safety of drug transmission and self-efficacy. Knowing these factors will help design qualitative studies to measure the level of importance and priority of these factors in the decision-making process. Future studies should also identify factors that impact healthcare providers' decision-making around providing advice and recommendations on medication use during lactation.

Healthcare providers are a primary source of information for parents and their advice is greatly valued by parents during their decision-making process. One study stated that "most women consulted their physician or pharmacist before initiating any medication (74%) and few women changed or stopped taking any of their medications without consultation (16.5%)" [30]. Therefore, it is important to nurture a positive relationship between parents and healthcare providers. Several studies note that patient preferences and values were important factors for healthcare providers when offering advice and would increase compliance with recommendations [18,23,42,48]. Healthcare providers should use a tailored approach considering the values and preferences of the parents when offering advice. This will enhance shared decisions making and a positive experience for parents during their decisions making.

We evaluated the knowledge of parents and healthcare providers which included the resources used to gather information, training healthcare providers received, and most importantly what type of resources are requested by parents and healthcare providers to better educate and help make decisions around medication use during lactation. Eighteen articles commented on the need for various types of resources. There were statements by parents about the lack of information on the safety of medication which was also a key impeding factor contributing to their decision making for using medication or breastfeeding. Healthcare providers felt frustration and uncertainty around making clinical recommendations when there was a lack of safety data and clear guidelines [18]. There were also statements from both parents and healthcare providers for resources that are evidence-based, reliable, consistent, and easily accessible. Parents relied on healthcare providers as a reliable and trusted resource for breastfeeding information, however “some women felt that they were provided with

contradictory information about the safety of drugs during breastfeeding from different health professionals" [43] this can lead to frustration and distrust with healthcare providers. Therefore, healthcare providers need to offer consistent and evidence-based recommendations and advice. Resources mentioned that would be beneficial include the need for more public and tailored education programs for parents. One article state that "less than half of pharmacists agreed that they have satisfactory knowledge to resolve the medication and health-care problems in pregnant (47.82%) and breastfeeding women (39.13%) while 43.78% of pharmacists were neutral" [22]. Healthcare providers would benefit from continued education on medication use during lactation which will enhance confidence and the ability to provide services in their practice.

Although a comprehensive search protocol was developed and reviewed some articles were not captured during our search. This may be due to the databases chosen to be included, search terms used and only including articles in the English language. We also did not search grey literature therefore unpublished studies were not identified.

3.7 Conclusion

The current scoping review evaluated 46 articles on parents' and healthcare providers' preference factors, decision-making and knowledge around medication use during lactation. We gathered information on key factors that influence decision-making. Communication and shared decision-making between parents and healthcare provider was found to be of importance. These findings highlight the need for future studies to examine the decision-making processes of parents and healthcare providers regarding medication use during infant feeding. Because the decision-making process involves many considerations and different options it would be important to examine the type of decisions parents have made and what factors were prioritized that led to those decisions. Future research should also focus on evaluating the shared decision-making process between parents and healthcare providers and what factors would help facilitate a better parent-provider relationship. It would be informative to understand healthcare providers' comfort and confidence in offering advice on specific medications or medication classes. Efforts should also be made to develop consistent and easily accessible resources about medication safety during lactation. This will better enable parents and physicians to make evidence-based decisions about the risks of drug exposure and the benefits of human milk for their children.

3.8 REFERENCES

1. Leong C, Chateau D, Dahl M, et al. Prescription medication use during pregnancies that resulted in births and abortions (2001-2013): A retrospective population-based study in a Canadian population. *PLoS One*. 2019;14(3):e0211319.
2. Smolina K, Hanley GE, Mintzes B, Oberlander TF, Morgan S. Trends and Determinants of Prescription Drug Use during Pregnancy and Postpartum in British Columbia, 2002-2011: A Population-Based Cohort Study. *PLoS One.* 2015;10(5):e0128312.
3. Wang J, Johnson T, Sahin L, et al. Evaluation of the Safety of Drugs and Biological Products Used During Lactation: Workshop Summary. *Clin Pharmacol Ther*. 2017;101(6):736-744.
4. Hale TW. Maternal medications during breastfeeding. *Clin Obstet Gynecol*. 2004;47(3):696-711. doi:10.1097/01.grf.0000135653.56778.3f
5. Elwyn G, Laitner S, Coulter A, Walker E, Watson P, Thomson R. Implementing shared decision making in the NHS. *BMJ*. 2010;341:c5146. Published 2010 Oct 14. doi:10.1136/bmj.c5146
6. Stacey D, Bennett C, Barry M, Col N, Eden K, Holmes-Rovner, M Llewellyn-Thomas, H Lyddiatt A, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database of Systematic Reviews. 2011;as well as(10):CD001431.
7. Arksey H, O'Malley L. Scoping studies: Towards a Methodological Framework. *Int J Soc Res Methodol.* 2005;**8**:19–32. doi: 10.1080/1364557032000119616.
8. Al-Sawalha NA, Sawalha A, Tahaineh L, Almomani B, Al-Keilani M. Healthcare providers' attitude and knowledge regarding medication use in breastfeeding women: a Jordanian national questionnaire study. *Journal of Obstetrics and Gynaecology.* 2018;38(2):217-221.
9. Albassam A, Awad A. Community pharmacists' services for women during pregnancy and breast feeding in Kuwait: A cross-sectional study. *BMJ Open.* 2018;8(1).
10. Amundsen S, Ovrebo TG, Amble NM, Poole AC, Nordeng H. Use of antimigraine medications and information needs during pregnancy and breastfeeding: a cross-sectional study among 401 Norwegian women. *European Journal of Clinical Pharmacology.* 2016;72(12):1525-1535.
11. Amundsen S, Øvrebø TG, Amble NMS, Poole AC, Nordeng H. Risk perception, beliefs about medicines and medical adherence among pregnant and breastfeeding women with migraine: Findings from a cross-sectional study in Norway. *BMJ Open.* 2019;9(2).
12. Anggraini S, Utami W, Zairina E. Factors affecting community pharmacist's service for women with chronic diseases during pregnancy and breastfeeding: application of the Health Belief Model. *Journal of Basic & Clinical Physiology & Pharmacology.* 2019;30(6):19.
13. Bazzano AN, Cenac L, Brandt AJ, Barnett J, Thibeau S, Theall KP. Maternal experiences with and sources of information on galactagogues to support lactation: A Cross-Sectional study. *International Journal of Women's Health.* 2017;9:105-113.
14. Bazzano AN, Littrell L, Brandt A, Thibeau S, Thriemer K, Theall KP. Health provider experiences with galactagogues to support breastfeeding: A cross-sectional survey. *Journal of Multidisciplinary Healthcare.* 2016;9:623-630.
15. Bergeria CL, Heil SH. Surveying Lactation Professionals Regarding Marijuana Use and Breastfeeding. *Breastfeeding Medicine: The Official Journal of the Academy of Breastfeeding Medicine.* 2015;10(7):377-380.
16. De Ponti M, Stewart K, Amir LH, Hussainy SY. Medicine use and safety while breastfeeding: Investigating the perspectives of community pharmacists in Australia. *Australian Journal of Primary Health.* 2015;21(1):46-57.

17. Huang VW, Chang HJ, Kroeker KI, et al. Management of Inflammatory Bowel Disease during Pregnancy and Breastfeeding Varies Widely: A Need for Further Education. *Canadian Journal of Gastroenterology & Hepatology.* 2016;2016:6193275.
18. Jayawickrama HS, Amir LH, Pirotta MV. GPs' decision-making when prescribing medicines for breastfeeding women: Content analysis of a survey. *BMC Research Notes.* 2010;3.
19. Lewis BA, Schuver K, Gjerdingen D, Avery M, Sirard J, Marcus BH. The Relationship between Prenatal Antidepressant Use and the Decision to Breastfeed among Women Enrolled in a Randomized Exercise Intervention Trial. *Journal of Human Lactation.* 2016;32(3):NP67-NP72.
20. Ronai C, Taylor JS, Dugan E, Feller E. The identifying and counseling of breastfeeding women by pharmacists. *Breastfeeding Medicine: The Official Journal of the Academy of Breastfeeding Medicine.* 2009;4(2):91-95.
21. Schirm E, Schwagermann MP, Tobi H, de Jong-van den Berg LT. Drug use during breastfeeding. A survey from the Netherlands. *European Journal of Clinical Nutrition.* 2004;58(2):386-390.
22. Shiromwar SS. Perceived services and reported opinions about self-care during pregnancy and lactation by community pharmacists: A cross-sectional study. *Asian Journal of Pharmaceutical and Clinical Research.* 2019;12(7):325-331.
23. Strauss LT, Speckhard M, Rochat RW, Senanayake P. Oral contraceptive during lactation: a global survey of physician practice. *International Journal of Gynaecology & Obstetrics.* 1981;19(3):169-175.
24. Talabi MB, Clowse MEB, Blalock SJ, et al. Development of ReproKnow, a reproductive knowledge assessment for women with rheumatic diseases. *BMC Rheumatology.* 2019;3(1).
25. Yudin MH, Salaripour M, Sgro MD. Pregnant women's knowledge of influenza and the use and safety of the influenza vaccine during pregnancy. *Journal of Obstetrics & Gynaecology Canada: JOGC.* 2009;31(2):120-125.
26. Keller MS, Mosadeghi S, Cohen ER, Kwan J, Spiegel BMR. Reproductive Health and Medication Concerns for Patients With Inflammatory Bowel Disease: Thematic and Quantitative Analysis Using Social Listening. *Journal of Medical Internet Research.* 2018;20(6):e206.
27. MacDonald T, Noel-Weiss J, West D, et al. Transmasculine individuals' experiences with lactation, chestfeeding, and gender identity: a qualitative study. *BMC Pregnancy & Childbirth.* 2016;16:106.
28. Ackerman I, Ricardo M, Briggs A. Understanding the specific information needs of women with rheumatoid arthritis regarding pregnancy and post-natal challenges. *Internal Medicine Journal.* 2014;44:8.
29. M, Briggs AM. Understanding the information needs of women with rheumatoid arthritis concerning pregnancy, post-natal care and early parenting: A mixed-methods study. *BMC Musculoskeletal Disorders.* 2015;16:194.
30. Al-Sawalha NA, Tahaineh L, Sawalha A, Almomani BA. Medication use in breastfeeding women: A national study. *Breastfeeding Medicine.* 2016;11(7):386-391.
31. Amir LH, Ryan K, Barnett C. Delphi survey of international pharmacology experts: an attempt to derive international recommendations for use of medicine in breastfeeding women. *Breastfeeding Medicine: The Official Journal of the Academy of Breastfeeding Medicine.* 2015;10(3):168-174.
32. Briggs AM, Jordan JE, Ackerman IN, Van Doornum S. Establishing cross-discipline consensus on contraception, pregnancy and breast feeding-related educational messages and clinical practices to support women with rheumatoid arthritis: An Australian Delphi study. *BMJ Open.* 2016;6(9).

33. Cataldo F, Chiwaula L, Nkhata M, et al. Exploring the Experiences of Women and Health Care Workers in the Context of PMTCT Option B Plus in Malawi. *Journal of Acquired Immune Deficiency Syndromes: JAIDS.* 2017;74(5):517-522.
34. Demirci JR, Bogen DL, Klionsky Y. Breastfeeding and Methadone Therapy: The Maternal Experience. *Substance Abuse.* 2015;36(2):203-208.
35. Ito S, Lieu M, Chan W, Koren G. Continuing drug therapy while breastfeeding. Part 1. Common misconceptions of patients. *Canadian Family Physician.* 1999;45:897-899.
36. Schaefer KM. Breastfeeding in chronic illness: the voices of women with fibromyalgia. *MCN, American Journal of Maternal Child Nursing.* 2004;29(4):248-253.
37. Sim TF, Hattingh H, Sherriff J, Tee LB. The use of non-prescription medicines during lactation: A qualitative study of community pharmacists' attitudes and perspectives. *Research in Social & Administrative Pharmacy.* 2018;14(5):464-470.
38. Sim TF, Hattingh HL, Sherriff J, Tee LBG. Towards the implementation of breastfeeding-related health services in community pharmacies: Pharmacists' perspectives. *Research In Social & Administrative Pharmacy.* 2017;13(5):980-988.
39. Smedberg J, Brathen M, Waka MS, Jacobsen AF, Gjerdalen G, Nordeng H. Medication use and drug-related problems among women at maternity wards-a cross-sectional study from two Norwegian hospitals. *European Journal of Clinical Pharmacology.* 2016;72(7):849-857.
40. Spiesser-Robelet L, Maurice A, Gagnayre R. Understanding Breastfeeding Women's Behaviors Toward Medication: Healthcare Professionals' Viewpoint. *Journal of Human Lactation.* 2019;35(1):137-153.
41. Suksamarnwong M, Hemachatra A, Laosooksatit W, Baiya N, Puapornpong P. The lactating mothers' drug use and associated factors during the first month postpartum. *Journal of the Medical Association of Thailand.* 2017;100(10):S48-S53.
42. Tauritz Bakker LA, van Dijk L, van den Bemt P. Exploring the Prescribing Process of Domperidone for Low Milk Supply: A Qualitative Study Among Mothers, IBCLCs, and Family Doctors. *Journal of Human Lactation.* 2020:890334420964070.
43. Williams D, Webber J, Pell B, et al. "Nobody knows, or seems to know how rheumatology and breastfeeding works": Women's experiences of breastfeeding whilst managing a long-term limiting condition – A qualitative visual methods study. *Midwifery.* 2019;78:91-96.
44. Chadambuka A, Katirayi L, Muchedzi A, et al. Acceptability of lifelong treatment among HIV-positive pregnant and breastfeeding women (Option B+) in selected health facilities in Zimbabwe: a qualitative study. *BMC Public Health.* 2017;18(1):57.
45. Lynch MM, Mitchell EW, Williams JL, et al. Pregnant and recently pregnant women's perceptions about influenza a pandemic (H1N1) 2009: implications for public health and provider communication. *Maternal & Child Health Journal.* 2012;16(8):1657-1664.
46. Straten Avd, Ryan JH, Reddy K, et al. Influences on willingness to use vaginal or oral HIV prep during pregnancy and breastfeeding in Africa: the multisite MAMMA study. *Journal of the International AIDS Society.* 2020;23(6).
47. Colaceci S, Giusti A, De Angelis A, et al. Medications, "Natural" Products, and Pharmacovigilance during Breastfeeding: A Mixed-Methods Study on Women's Opinions. *Journal of Human Lactation.* 2016;32(2):324-332.
48. Lee A, Moretti ME, Collantes A, et al. Choice of breastfeeding and physicians' advice: A cohort study of women receiving propylthiouracil. *Pediatrics.* 2000;106(1):27-30.

49. Lurie Y, Bar M, Levdov IA, Tkachenko D, Bentur Y, Kurnik D. Adherence with prescription drugs in pregnant and breastfeeding women consulting with the Israel Poison Information Center Teratology Service. *Clinical Toxicology*. 2020.
50. Hegedus E, Oakes DJ, Hill M, Ritchie HE, Kennedy DS. Calls to a Major Teratogen Information Service Regarding Exposures During Breastfeeding. *Breastfeeding Medicine: The Official Journal of the Academy of Breastfeeding Medicine.* 2019;14(9):674-679.
51. Mannion C, Mansell D. Breastfeeding self-efficacy and the use of prescription medication: a pilot study. *Obstetrics & Gynecology International.* 2012;2012:562704.
52. Stanton TA, Blumenthal PD. Postpartum hormonal contraception in breastfeeding women. *Current Opinion in Obstetrics & Gynecology*. 2019;31(6):441-446.
53. Spiesser-Robelet L, Brunie V, de Andrade V, Gagnayre R. Knowledge, Representations, Attitudes, and Behaviors of Women Faced With Taking Medications While Breastfeeding. *Journal of Human Lactation.* 2017;33(1):98-114.
54. Hussainy SY, Dermele N. Knowledge, attitudes and practices of health professionals and women towards medication use in breastfeeding: A review. *Int Breastfeed J*. 2011;6:11. Published 2011 Aug 26. doi:10.1186/1746-4358-6-11
55. Saha MR, Ryan K, Amir LH. Postpartum women's use of medicines and breastfeeding practices: a systematic review. *Int Breastfeed J*. 2015;10:28. Published 2015 Oct 28. doi:10.1186/s13006-015-0053-6

Table 3.1 Characteristics of publications sampled for scoping review (N=46 publications)

Characteristic	No.	%
Study methodology		
Quantitative	20	
Questionnaire/Survey	19	43.5%
Social media min	1	
Qualitative	19	
Interviews	9	
Focus Group	2	41.3%
Interview + Focus Group	5	
Delphi Process	2	
Patient-reported treatment review	1	
Mixed Methods	3	
Interview + Questionnaire	2	6.5%
Interview + Focus Group + Questionnaire	1	
Observational	2	4.3%
Reviews	2	4.3%
Study Location		
Australia	9	19.6%
Canada	6	13.0%
France	2	4.3%
Indonesia	1	2.2%
Italy	1	2.2%
Jordan	2	4.3%
Kuwait	1	2.2%
Malawi	1	2.2%
Netherlands	2	4.3%
Norway	3	6.5%
Saudi Arabia	1	2.2%
Sub-Saharan Africa	1	2.2%
Thailand	1	2.2%
United Kingdom	1	2.2%
United States	11	23.9%

Zimbabwe	1	2.2%
Multi-Site*	2	4.3%

*Multi-site includes: 65 Countries (Africa, Asia, Latin America, Europe, Oceania, and North America) and North America, Europe, and Australia

Year of publication		
2020	3	6.5%
2019	8	17.4%
2018	5	10.9%
2017	6	13.0%
2016	7	15.2%
2015	6	13.0%
2014	1	2.2%
2012	2	4.3%
2010	1	2.2%
2009	2	4.3%
2004	2	4.3%
2000	1	2.2%
1999	1	2.2%
1981	1	2.2%
Participant population		
Parent	25	54.3%
Healthcare Provider	16	34.8%
Both	5	10.9%
Healthcare Provider Types	21	
Pharmacist*	7	33.3%
Physicians**	4	19.0%
Pharmacology Experts	1	4.8%
Health worker	1	4.8%
Included more than one provider type***	8	38.1%

**Subspecialties include for physicians: General Practitioner, Rheumatologists, Pediatricians, Obstetricians/Gynecologists, Psychiatrists, Endocrinologists

*Subspecialties include for pharmacists: Community pharmacist, Clinical Geneticists Pharmacists,
** Included more than one provider type consisted of a mixture of the following providers: Nurse, Pharmacist, Physician, Medical Assistants, Community Health Workers, Lactation consultant, public health/WIC personnel, Nutritionist, Doula/Midwife, La Leche League Affiliate, Breastfeeding Counsellors, Genetic counsellors, Mental health teams, Child Care Assistant

Medical conditions		
Nonspecific	18	39.1%
Lactation insufficiency	4	8.7%
HIV	3	6.5%
Rheumatoid Arthritis	3	6.5%
Birth Control	2	4.3%
Inflammatory Bowel Disease	2	4.3%
Influenza (Influenza, H1N1)	2	4.3%
Migraine	2	4.3%
Rheumatic diseases	2	4.3%
Chronic Disease	1	2.2%
Drug-related problems (DRPs)	1	2.2%
Fibromyalgia (FM)	1	2.2%
Gender dysphoria	1	2.2%
Hyperthyroidism	1	2.2%
Opioid-related disorders	1	2.2%
Postpartum depression	1	2.2%
Recreational marijuana use	1	2.2%
Medications studied		
Nonspecific	18	39.1%
Rheumatoid Arthritis medications	3	6.5%
Anti-retroviral treatment (ART, PrEP, Option A/B+)	3	6.5%

Anti-rheumatic drugs	2	4.3%
Antidepressants	2	4.3%
Contraceptives	2	4.3%
Domperidone	2	4.3%
Galactagogue	2	4.3%
Inflammatory Bowel Disease Medications	2	4.3%
Influenza Vaccine	2	4.3%
Migraine medication (analgesics, NSAIDS, migraine-specific medications)	2	4.3%
Prescription medications	1	2.2%
Non-prescription medications	1	2.2%
Marijuana	1	2.2%
Methadone therapy	1	2.2%
Propylthiouracil (PTU) therapy	1	2.2%
Testosterone	1	2.2%

Table 3.2 Characteristics of settings and recruitment sources of studies sampled for scoping review (N=46 publications)

Setting / Recruitment Source	No.	%
Clinical Practice	19	41.3%
Advertisement*	7	15.2%
Mail	4	8.7%
Email	3	6.5%
Phone	3	6.5%
Database	3	6.5%
Included more than one recruitment source**	3	6.5%
Conference	2	4.3%
Snowball	1	2.2%
Social media mining	1	2.2%

* "Advertisement" recruitment included posted advertisements, flyers or brochures, convenience sampling or online advertisements

** "Included more than one recruitment source" consisted of a combination of the following: support group, GP office, snowball, professional recruitment firm, community partners, phone, email

Table 3.3 Thematic Analysis

Theme	Example	Number of statements
Preference Factors		
Attitudes towards medication use during lactation	"The women's attitudes toward medicine use during pregnancy and breastfeeding were categorized as follows: 160(75.5 %) only used medicines in accordance with healthcare personnel, 38 (17.9 %) had a zero-tolerance, 11 (5.2 %) believed self-medication with safe drugs were okay, and 3(1.4 %) endorsed a relaxed attitude toward drugs" (Smedberg 2016)	4
Level of confidence with medication use during lactation	"Women reporting lower breastfeeding confidence used both formula and domperidone, two interventions undertaken to ensure their babies were fed but which may be reflective of the lack of confidence in the ability to exclusively breastfeed." (Mannion 2012)	9
Perception/views around medication use during lactation	"Both qualitative and quantitative results confirm that pregnant women and new mothers believe that the combi-nation of breastfeeding and pharmacotherapy is not preferable." (Colaceci 2016)	8
Concerns about medication use during lactation	"Of greatest concern to participants was the need for more information regarding the toxicity of RA medications and the possible effects on their unborn or breast-fed baby." (Ackerman 2015)	10
Healthcare provider recommendations/ prescribing patterns	"40.3% of surveyed physicians would continue sulfasalazine treatment among women with IBD who are breastfeeding, while 64.8% would continue oral mesalamine and 70.8% would continue topical mesalamine. Among gastroenterologists, a higher proportion would continue sulfasalazine during pregnancy than during breastfeeding" (Huang 2015)	11

Behaviors towards medication use during lactation		32
Medication use/habits	"In all, 193 (91.0 %) of the women planned to or were using at least one prescription drug, OTC drug, or vitamin, mineral, or herbal remedy during breastfeeding. Current or planned use of prescription, or OTC drugs was reported by 140 (66.0 %) of the women, compared to 127 (40.1 %) currently using or planning to use vitamin/mineral/herbal remedies, and 157(74.1 %) currently using or planning to use a substance whose product name they could not remember (no ATC code)." (Smedberg 2016)	16
Medication stopping/reduction	"In case of a treatment that is potentially risky for the baby, 43.5% of the women think that breastfeeding should be temporarily discontinued and 21.8% believe that breastfeeding should be definitively stopped." (Colaceci 2016)	11
Preference for non-medication alternative options	"Women believe that natural products are safer than medications (75.0% agreement; 12.5% disagreement), although there is not a predominant opinion on their effectiveness" (Colaceci 2016)	5
Decision Making		
Factors influencing decision making		35
Facilitating factors	"Learning from other woman's experiences was an important source of emotional support, particularly when managing post-partum flares and making difficult decisions such as ceasing breastfeeding in order tore-commence RA medications." (Ackerman 2015)	12
Impeding factors	"The main reasons given for not wanting to take medications was fear of harming the unborn child and/or breastfed infant, recommendations from their doctor or other	17

	healthcare professionals and information from other sources (eg, internet and family/friends) about potential harmful effects." (Amundsen 2019)	
Social influence (family, friends, healthcare provider etc.)	"Several other mothers talked about how they felt pressured to stop breastfeeding, either by their health care professionals or by family members" (Williams 2019)	6
Parent/healthcare provider interactions		30
Communication	"Seventy-one percent of the participants mentioned that their physician asked them if they were breastfeeding before writing the prescription, while around 60% of the pharmacist asked whether they were breastfeeding before dispensing any medication. Less than half of the participants stated that their physicians or pharmacists took time to talk with them about their prescribed medications" (Al-Sawalha 2016)	26
Joint- Decision making	"GPs felt that certain situations warranted involvement of several parties in the decision-making process rather than a quick decision on their part. Although this would involve more time and work for GPs, they thought this would help to make a more appropriate and safe decision and increase mothers' compliance with the recommended/ prescribed medicine" (Jayawickrama 2010)	4
Knowledge		
Understanding/knowledge of medication used during lactation	"Regarding the use of medications, the majority of women think that many drugs cannot be used during breast-feeding (19.7% agreement; 67.8% disagreement), and if a breastfeeding mother has a minor problem (eg, headache, toothache, back pain), it is better to endure the pain rather than take a	16

	pain reliever (61.2% agreement; 31.9% disagreement)" (Colaceci 2016)	
Healthcare provider training	"Participants reported they had acquired most of their knowledge regarding the use of medicines whilst breastfeeding and breastfeeding in general from their day-to-day work experience, self-directed training, personal or close-contact breastfeeding experience, and university training as part of their pharmacy degree" (Sim 2017)	7
Information sources used	"Respondents reported a variety of different informational sources including Internet sources, trainings or conferences, literature and other related readings, specialty groups such as the La Leche League or the International Board of Lactation consultant Examiners." (Bazzano 2016)	24
Need for resources	"This illustrates the need for more available and consistent information to pregnant and breastfeeding women about the safety of their medicines. Our study clearly illustrates the need for adequate and individually tailored counselling of women in how to manage their disease during pregnancy and breastfeeding period" (Amundsen 2019)	18

Appendix 3.1 Sample Search Terms

"Population" Terms of Interest:

- **Parents** (lactating mothers, breastfeeding mothers/parent, nursing mother/parent, pregnant woman/individual, chestfeeding,)
- **Health care providers** (primary care physician, nurses, lactation consultants, pharmacists, midwifery, rheumatologist, OB, physician, rehabilitation providers, OT, physiotherapist, chiropractors, massage therapists, dentist, osteopath, naturopath, alternative medicine, allied health provider
- **Types of Drugs**: prescription, over the counter, cannabis

"Intervention and Outcome" Terms:

- Parents and healthcare providers *values, preferences, input, views, experiences, perspectives, choices, opinions, beliefs, attitudes, motivation, intention, dialogue, conversation and satisfaction, confidence, decision-making needs, perception, risk and benefits, concerns, shared decision making, patient-centred informed decision making* on the topic of medication use during breastfeeding

Inclusion/Exclusion Criteria:

Include if:

- The article mentions the evaluation of parents' views in any way towards medication use while breastfeeding
- Include if the article also includes the views of health care providers or other professionals
- Studies if they just look at healthcare provider views in addition to the studies that look at parents only and both

Exclude if:

- The article does not have any mention of assessing parents' or healthcare providers views
- Exclude if the article is assessing views on alcohol, illicit drugs, tobacco
- The article only assesses views during pregnancy
- Language not in English

Appendix 3.2 Data collection form

Study Information

	Description as stated in report/paper
Title: Title of paper/abstract / report that data are extracted from	
Study ID	
Journal	
Lead author contact details	
Country in which the study conducted	☐ United States ☐ UK ☐ Canada ☐ Australia ☐ Other
Year of Publication	
Study funding sources	
Possible conflicts of interest for study authors	

Characteristics of included studies

	Description as stated in report/paper
Aim of study	
Study design	☐ Randomised controlled trial ☐ Non-randomized experimental study ☐ Cohort study ☐ Cross-sectional study ☐ Case-control study ☐ Systematic review ☐ Qualitative research ☐ Prevalence study ☐ Case series ☐ Case report ☐ Diagnostic test accuracy study

	☐ Clinical prediction rule ☐ Economic evaluation ☐ Text and opinion ☐ Other
Start date	
End date	

Participants Data Collection

	Description as stated in report/paper
Data collection method	☐ Questionnaire ☐ Focus group ☐ Interview ☐ Other
Content of collection method	
Data Analysis	

Results

	Description as stated in report/paper
Themes	
Key Findings	
Limitations of Study	
Recommendations/ Future work	

CHAPTER 4. PARENT ENGAGEMENT INTERVIEWS

4.1 INTRODUCTION

Parent engagement interviews were integrated into this study to support engagement activities to co-design a survey on values and preferences related to the decision-making of using medications during breastfeeding for clinical practice. The parent interviews helped to identify how to design research studies with mothers/birthing parents and provided their perspectives on challenges faced when making decisions about medication use during breastfeeding. The knowledge shared from the parent engagement activities is extremely valuable to guide the development of methods, identify items to be included in the parent questionnaire and improve recruitment efforts for this study.

Funding for the parent engagement interviews was provided by the Center for Health Innovation (CHI) Preparing for Research by Engaging Public & Patient Partners (PREPPP) Award.

4.2 OBJECTIVES

The objectives of the parent interviews are: (1) to learn about parents' experiences and decision-making concerning medication use during infant feeding (2) to identify priority areas for study design and pilot test the parent survey which will further inform and guide the study.

4.3 METHODS

We engaged with mothers/ birthing parents in structured individual interviews to better understand their lived experiences, preferences, values, concerns, and decision-making process around medication use during breastfeeding. These interviews helped inform the study direction, priority setting and outcome selection for the design of a parent survey that can help guide decision-making around medication use during lactation.

Participants

Six parents over the age of 18 between April 16, 2021, to May 14, 2021, were recruited. CHI assisted in providing avenues for the recruitment of participants. We used convenience sampling by advertising on social media platforms on parent groups (connections made through

CHI) and the research team's Facebook accounts. Interested participants were asked to fill out an initial screening survey on Survey Monkey to assess eligibility and to ensure there was some diversity in sociodemographic characteristics in the sample size. Participants were chosen on a first come first serve basis. Participants were compensated $25.00 CDN per hour of their time for a total of $75.00 CAD for completion of both parts, pilot testing the survey and participating in the interview. The honorarium was distributed by either cheque which was mailed to the participant or an Amazon gift card that was emailed based on the participants' preference. We experienced barriers to recruitment due to the COVID-19 pandemic, as it was not possible to facilitate in-person meetings for those participants that do not have access to a computer or phone. It was also a challenge to reach under-represented groups such as those living in remote communities during this time as well.

Data collection

Participation in the study consisted of two parts. The first part involved pilot testing the parent preference survey. This was conducted to help gain feedback and input on the design and content of the survey. The second part included one scheduled interview session through Zoom or over the phone, depending on the participants' preference. The discussion session ranged from 45 minutes to 1.5 hours in length. The principal investigator (UY) conducted all the interview sessions through Zoom, and they were recorded and stored on SharePoint.

Interview format and procedure

The interview began with introductions and a brief overview of the proposed study and the goals of the parent interviews and how they will contribute to the overall study. Next, the participants received a verbal consent script, for future publication purposes, and were informed they can end the discussion at any time. Once verbal consent was received recording started for the interview. The first part of the session consisted of 11 interview questions about views, decision making, experiences and available resources on medication use while infant feeding. We also asked about things we should consider in designing the study, and the best ways to communicate the results to the public. The second part of the session involved going over the survey the participants had pilot-tested before the interview. Nine questions were asked in total about the survey content, format, readability and if it captured their experiences/challenges. We

also asked participants for any suggestions or advice for us to consider when recruiting parents to do this survey

Data analysis

Recorded interviews were transcribed verbatim by the principal investigator (UY) to ensure accurate reporting of the information that was provided. The recorded sessions were stored on SharePoint before and after being transcribed. Direct identifiers (name, phone number, e-mail) were coded and the responses were de-identified to maintain anonymity before analysis and kept confidential. The summary of results will be emailed to each parent if requested at the time of consent/enrollment and was also shared with the steering committee.

The content was analyzed for patterns and key ideas using Dedoose software, this allowed for a deeper understanding of the input from parents and to identify priority areas and important research outcomes. During the review of the transcripts of the interviews key ideas and common themes were listed for each interview question and general notes were made about reoccurring statements and feedback provided from the interviews. The responses for each of the objectives were then consulted and discussed with the steering committee. The key ideas/themes and feedback identified from the parent interviews were used to inform further development and refinement of the parent survey design to better meet the study objectives.

4.4 RESULTS

Structured interviews were completed with six parents. A summary of key ideas emerging from qualitative analysis of the interview transcripts is shown in Table 4.1.

Table 4.1 Key ideas on medication use during infant feeding from parent engagement interview

Questions	Key ideas
Current views about medication use during infant feeding with human milk	Evidence based- gathering information Benefit outweighs the risk Situation dependent Medication dependent Personal decision
Feelings when decision making about medication use during infant feeding with human milk	Stressed Apprehensive Anxious Unsure Feel more comfortable (reliable resources, recommendations from healthcare providers) Confidence in decision making (research/going over information)
Factors making decision difficult	Lack of evidence Unknows Situation dependent Conflicting advice from different providers Not having right or clear set answers
Involvement in decision making process (excluding self and prescriber)	No one else Discuss with spouse Discuss with healthcare provider (midwife, doctor, pharmacist, healthcare colleagues that have experience)

Decision making process	Evidence based approaches used 1. Assess the situation → weigh pros and cons→ try non pharmaceutical alternatives as first line treatment 2. Assess the situation → try non pharmaceutical alternatives as first line treatment → try previously used/ familiar medications first→ own research on the medication 3. Risk vs. benefit assessment → talk to healthcare providers about medications/other parents experiences→ own research on the medication
Factors that help decision making	Community of other moms Easily accessible app or program Open communication with doctors
Factors that hinder decision making	Lack of evidence-based information Lack of trust in difference studies Mistrust in the healthcare system A provider being pushy Lack of communication with health care providers Mass amount of information available Misinformation Judgments
Resources used for information gathering	Doctor Public health nurses Up to date Lexicomp Lactmed Facebook groups: ex. Dr.milk Websites: ex. kellymom Breastfeeding center in Winnipeg Infant risk app Le leach League

4.5 Discussion

Parents' preferences, views, decision making, experiences and available resources on medication use while infant feeding

Current views about medication use during infant feeding with human milk

Participants' responses include that it was a personal decision. One participant stated that "it depends on what the medication is supposed to do, and it depends on what the effects will be on my child". Another parent stated, "important to take medication prescribed by the doctor if the risk to child through breastmilk exposure is explained and information is made clear". Participants commonly stated that they would assess if the benefit outweighed the risk and used evidence-based information to make their decision. It also depended on the situation "for infections comfortable taking antibiotics because there are no other options, but for post-partum anxiety chose CBT as the first option prior to medication use". Another participant stated, "in emergency and critical situations when medication use is necessary it shouldn't be avoided in order to breastfeed".

Feelings when decision making about medication use during infant feeding with human milk

Parents described feeling stressed or apprehensive when making decisions about medication use. They also felt anxious particularly going through the literature and making an informed decision. "Hard to find reliable sources, most drugs don't have the evidence behind it, information not out there for a lot of medications". Parents also felt unsure "questioned whether it's the right decision or not". Parents stated they would feel more comfortable making decisions by finding reliable resources with recommendations from healthcare providers. Confidence in their decision-making would increase by "doing research and going over information".

Factors making the decision difficult

Common responses included lack of evidence and the unknown, situation dependent and not having the right or clear set answers. One parent stated, "Unknown are definitely things when there's now data available or bad studies like reviewing some of the literature from medication studies".

Receiving conflicting advice from different providers also made it difficult for decision-making. One parent stated “find that most doctors they don't bother to look up like what class the medication is. I've had experiences like that before where I'll be like is this safe and they're like “yeah it's okay” and then I go to the pharmacy, and I say can you look this up and they're like oh that one is not safe. I find that some doctors don't maybe they don't have access, or they don't want to look it up or take the time to look it up”.

Involvement in the decision-making process

Most of the participants stated that no one else would be involved in the decision-making process. Some participants mentioned they would discuss with their spouse or healthcare provider (midwife, doctor, pharmacist) or colleagues with experience but would ultimately make the decision on their own.

Decision-making process

All the participants followed a similar decision-making process which involved an evidence-based approach. Common methods include assessing the situation, weighing the pros and cons, risk vs. benefit assessment, doing their research, discussing with a healthcare provider, learning about other parents’ experiences, and trying non-pharmaceutical alternatives as first-line treatment. One parent shared “I assess the situation you know for example if I'm having back pain I determine if this is something that could be cured with like a bath or warm bath or massage or something nonpharmaceutical. If it really bothers them and I think I need to step it up, then usually I'll try something like Tylenol, and you know if it's a medication that I have no familiarity with or I haven't used it or I'm not aware of whether there is safety data then we usually look it up in more reliable resources then just Google”.

Factors that help decision making

An important factor that came up was having a community of other parents. One participant mentioned that “having a community will be helpful to bounce off ideas. People like to talk about things that are medicine related with others that are not in the medical field”. Another parent stated, “some parents would be helped by being able to see that other parents are doing it so there is that the ease of making a decision knowing that other people have made that

same decision". Other factors include having open communication with their doctors and an "easily accessible app or program that would have the information available readily in an evidence-based fashion".

Factors that hinder decision making

There were many factors mentioned that would hinder parents' decision making these include lack of evidence-based information, lack of trust in studies and deciphering through the mass amount of information. Parents also mentioned distrust in the healthcare system, getting misinformation and conflicting advice from different healthcare providers and providers being pushy as factors hindering decision making. Feelings judged by others for their preferences also was a factor hindering decision making. One parent stated, "lack of like discussion whether with the pharmacist or physician and lack of like knowing whether other pregnant or breastfeeding women ever taken it and what the risk is".

Resources used for information gathering.

Participants generally preferred to use sources that provided evidence-based information such as journal articles, Up to Date, Lexicomp, Lactmed, le leach league and infant risk app. Participants also consulted with their healthcare providers such as their family doctors, pharmacists, and public health nurse. Participants mentioned being part of mom groups on social media platforms such as Facebook, Instagram, and Reddit where information was available.

Parent suggestions and feedback for survey design

Parents were asked what kind of resources would be useful to help make decisions about medication use during infant feeding.

Overwhelmingly parents suggested an app or website would be the most helpful. Important features mentioned that would be important include "really easy interfaces", "easy to use easy to navigate" and "something user-friendly, simple to use with less medical jargon". One participant suggested "having someone that is accessible to talk to about the medications – specialized pharmacists or something like that" would be a good resource. Parents also

mentioned that handouts or pamphlets not being very useful and journal articles require too much time to access information.

Participants were asked if they had any suggestions for the research team to consider when designing this survey.

Suggestions include considering cultural perspectives/barriers: “Consider like culturally sensitive stuff so like medications that are common and over-the-counter stuff that are common in different cultures I think is super important because there are some cultural barriers that make it difficult for us to find out what our patients are taking they think it's normal 'because everybody takes it but it's like for example mint peppermint it reduces your or can reduce your milk supply but some people have it in their daily teas and such and we don't even think about asking right so culturally sensitive approaches and identifying what are the major cultures in Winnipeg…. target people in each culture that would have an idea of what kind of supplements are common in this culture or practices and incorporating those I think are very important”.

Accessibility of the survey to various populations: “Accessibility of that survey for different income brackets some people might not have access to do things like that [survey]… um so like I don't know if you're planning on reaching out to like a lower income”

Social determinants of health: “Social determinants of health and how that would play into the way people answer these sorts of questions and we parents would approach making decisions about medication, their health and the newborn.”

Parents were asked about the best way to communicate results to the public once the study is completed.

Most common suggestions include using social media platforms to communicate information. Parents suggest using infographics to provide information “everybody loves a picture forward presentation something that catches eyes… something fun and interactive”. They suggested reaching out to specific mom groups or breastfeeding groups on Facebook and Instagram to post information. Other suggestions include making it publicly available on a website, posters and handouts in clinics and using public health outreach campaigns. One parent stated “I think that the best way for communication once the study is finished would be through health care providers. I think it's difficult to get information out in other ways reliably these days

just because there's so much misinformation available on social media and so you don't always know if you're reading something whether it's real or not".

Suggestions for survey development

The second half of the interview was dedicated to going over the survey that was pilot tests and hearing the parents' feedback. Feedback included that the questions were well-rounded and looked at multiple perspectives. Parents said the language used in the survey was easy to understand, appropriate and inclusive. There were suggestions to reduce the length of the survey and to reduce the number of questions to 30 (maximum). There were suggestions to remove/reword two questions that were lengthy and hard to understand. Overall, the feedback was positive on the initial draft of the survey. Participants thought the survey was comprehensive and met the objectives of the study.

4.6 Conclusion

The parent engagement interviews allowed us to collaborate with mothers/birthing parents with lived experience to co-design a parent survey assessing preferences, decision making and knowledge around medication use during lactation. We were able to gain a better understanding of parents' opinions, experiences, and decision-making processes. Additionally, we were able to identify important areas and key concepts to focus on when designing the study.

Feedback received from pilot testing of the initial survey draft was vital for further development and refinement to better meet the study objectives. Collaboration with all the parents during these interviews was very important because the same stakeholders that are involved in the decision aid development will be the same individuals that will be ultimately using the decision aid. The knowledge gained from this study and our future work will better enable mothers and healthcare providers to make evidence-based decisions about the risks of drug exposure and the benefits of human milk for their children.

Appendix 4.1 Parent Engagement Interview Questions and Survey Evaluation

Parent Engagement Interview Questions

1. What are your current views about medication use during breastfeeding (infant feeding with human milk)?
2. How do you feel when making decisions about taking medications during breastfeeding (infant feeding with human milk)?
3. What makes the decision difficult for you?
4. Who else besides the prescriber and you are usually involved in making this decision?
5. How do you usually go about making such a decision?
6. What would help parents to make this decision? What will hinder parents from making this decision?
7. What type of educational resources are currently available to you about medication use while breastfeeding (infant feeding with human milk)?
8. What types of resources would you find useful to help make decisions about medication use during breastfeeding (infant feeding with human milk)?
9. What are the best ways for communicating results to the public once the study is finished?
10. Is there anything you would like us to consider in designing this study?
11. Would you like to share any experiences you have had?

Survey Evaluation

1. Do you think this survey reflects your experiences?
2. Is this survey capturing your perspectives on the experiences/challenges you faced in decision-making around medication use while breastfeeding?
3. Is there anything we should focus more/less on?
4. What are your thoughts on the content of the survey?
5. Were you able to understand the survey? Were there any questions that were hard to understand? Any questions that you found to be repetitive
6. What are your thoughts about the length of the survey? Format?
7. What are your thoughts on the language used in this survey?
8. Do you have any suggestions or advice for us to consider when recruiting parents to do this survey?
9. Do you have any other feedback or suggestions?

Appendix 4.2 Parent interview verbal consent script

Title of Study: Questionnaire for assessing parent and clinician views on decision needs and preferences on medication use around breastfeeding

Principal Investigator: Uma Yakandawala, College of Pharmacy, University of Manitoba

Co-Investigator: Dr. Christine Leong, Dr. Lauren Kelly, Zina Zaslawski

Sponsor: Rady Innovation Fund

Funder: Center for Health Care Innovation (CHI): Preparing for Research by Engaging Public and Patient Partners (PREPPP) Award

Verbal Consent Script

Study Information

Many people require the use of medications during lactation to treat acute or chronic health conditions. For individuals making decisions around medication use while pregnant or breastfeeding is often a challenge due to limited evidence-based information. The purpose of this study is to better understand pregnant people and mothers' lived experiences, preferences, values, and concerns around medication use during breastfeeding and pregnancy.

Research Activities

You are being asked to participate in this study because we would like to collaborate with mothers and pregnant people over the age of 18 about the decision-making process, priority setting and outcome selection for the design of a parent-informed survey. A total of 5-10 participants will be asked to participate.

Participation in the study will consist of two parts:

- Part 1: Pilot testing survey. Help to gain feedback and input on the design and content of the preference questionnaire.

- Part 2; One scheduled interview session through Zoom or over the phone depending on your preference. The discussion session will be approximately 1.5 hours in length.

- The principal investigator will be conducting the interview.
- The interview will ask questions to understand parents decision-making process, priority setting and outcome selection for the design of a questionnaire and parent-informed decision aid that can help guide decision-making around medication use while breastfeeding. As well as to help us to better understand what key concerns mothers/pregnant people have regarding decision-making around medication use during breastfeeding.

Interviews will be recorded so that the researchers don't miss anything important. The recording will begin only after you agree to participate in this study. Only selected members of the research team will have access to the tapes. The data from the recorded interviews will be transcribed and stored on SharePoint. During the interview, you can ask the researcher to stop the interview and/or the recording any time you feel uncomfortable.

Do you have questions about the activities this study involves? (Yes/No)

If yes: Have all your questions been answered? (Yes/No)

Confidentiality and Privacy

We will respect your privacy. We will not give your personal information to anyone without your permission unless the law requires us to do this. We will publish or discuss only summary results of the research at conferences; no information will be included that would reveal your identity.

We understand that information about your health is personal, and we are committed to protecting the privacy of that information. Your personal information collected for this study may include information that might directly identify you, such as your name and address, telephone number, email address, or mobile phone number. All information collected about you will be "de-identified" by replacing your identifiable information (i.e., name) with a "study number." Only the "study code key" can connect the information collected about you to your identity. The study code key will be safeguarded by the research team at the University of Manitoba and will not be available to the other participating centres. Even though the risk of identifying you from the study data is minimal, it can never be completely eliminated.

The research team will keep any personal health information about you, recordings of the interview, transcribed interviews, study code key, and any data related to this study in a secure and confidential location at the University of Manitoba for 5 years. After 5 years the data will be permanently destroyed. All study data will then be destroyed, according to the University of Manitoba's policy.

Some people or groups may need to check the study records to make sure all the information is correct. All these people have a professional responsibility to protect your privacy.

These people or groups are:

- The Health Research Ethics Board of the University of Manitoba which is responsible for the protection of people in research and has reviewed this study for ethical acceptability

Do you have questions about how your privacy will be protected? (Yes/No)

If yes: Have all your questions been answered? (Yes/No)

Participation Information

This study is voluntary. You can choose if you want to participate, you can change your mind at any time during the interview and you can choose not to answer specific questions. If you don't want to participate in the study anymore, you can contact the research team either by phone or email to have your data withdrawn from the study.

Do you have questions about the voluntary nature of participation in this study? (Yes/No)

If yes: Have all your questions been answered? (Yes/No)

Potential benefits and harms

Participating in this study will not have any direct benefit to you. However, information gained will help to better understand decision-making around medication use while breastfeeding and the future development of a parent decision aid.

The interviews may cause some emotional distress to you as you discuss your experiences around medication use during pregnancy/breastfeeding. You do not have to answer any question that makes you feel uncomfortable or that you find too upsetting. If you were found to be distressed at the end of the call, the interview will be stopped and we would arrange a follow-up call to check your wellness.

Do you have questions about the benefits/potential risks of this study? (Yes/No)

If yes: Have all your questions been answered? (Yes/No)

Reimbursement

As a token of our appreciation for your time and for sharing your experience, you will be given $25.00 CDN per hour of your time for taking part in this study. For a total of $75.00 CDN for completion of both parts, pilot testing the survey and participating in the interview. The compensation will be sent to you by mail.

Do you have questions about reimbursement? (Yes/No)

If yes: Have all your questions been answered? (Yes/No)

Contact Information

In case you would like to know more about your rights as a research participant or have any other research ethics questions, here are some contact numbers that are good to have. Do you have a pen and paper ready?

For questions about your rights as a research participant, you may contact The University of Manitoba, Bannatyne Campus Research Ethics Board Office at (204) 789-3389.

If any questions come up during or after the study, contact the principal investigator and the study [redacted]

Questions

Do you have questions about anything that we've talked about so far? (Yes/No)

If yes: Have all your questions been answered? (Yes/No)

Consent

Do you want to participate in this study?

- If no: Thank you for your time. Goodbye.
- If yes: Please confirm that you have been informed regarding the information about this study and are giving your consent to be a part of it.

Verbal Consent

Name of the person providing consent:

Name of the person obtaining consent:

Time: Date: DD/MM/YYY

Signature of Person Obtaining Consent

Next Steps

- Determine the date and time for the interview.
- We will need your mailing address or email to send you the participant compensation payment. What is your mailing address or email? (This will be separately documented in the telephone or mailing/email log list of the study and not here)

CHAPTER 5 MANUSCRIPT

Parent and healthcare providers preference factors, decision making and knowledge on medication use during lactation: a Canada-wide survey study

Uma Yakandawala[1], Christine Leong[1], Lauren E Kelly[2], Christina Raimondi[3], Katherine Kearns[3], Angela Blouin,[4] Karine Toupin April[5], Laurie Proulx[6]

1. College of Pharmacy, Rady Faculty of Health Science, University of Manitoba, Winnipeg, Manitoba, Canada
2. Department of Pediatrics and Child Health, University of Manitoba, Winnipeg, Manitoba, Canada
3. Family Physician, Winnipeg Breastfeeding Centre, Department of Family Medicine, College of Medicine, University of Manitoba
4. Community Health Nurse, Youville Centre Winnipeg
5. School of Rehabilitation Sciences, Affiliated to the Department of Pediatrics, University of Ottawa
6. Community Representative Advisory Member and Indigenous Health Advisor

To be submitted to journal (undecided)

Corresponding author:
Christine Leong, BSc (Gen), BSc (Pharm), PharmD
750 McDermot Avenue, Winnipeg, MB, Canada R3E 0T5
Tel: 204-318-5276
Email: christine.leong@umanitoba.ca

Running title: Survey on decision making on medication use during lactation

Funding sources: Rady Innovation Fund, Centre for Health Innovation

Key words: breastmilk, human milk, medication, preferences, decision making, parents, breastfeeding, lactation, healthcare provider

CHAPTER 5. PARENT AND HEALTHCARE PROVIDERS PREFERENCE FACTORS, DECISION-MAKING, AND KNOWLEDGE ON MEDICATION USE DURING LACTATION: A CANADA-WIDE SURVEY STUDY

5.1 ABSTRACT

Background: Decision-making around medication use during lactation is often a challenge for both birthing parents and healthcare providers due to limited evidence-based information.
Objectives: To understand preference factors, knowledge and decision-making of Canadian parents and healthcare providers regarding medication use during infant feeding with human milk.
Methods: Two separate online surveys were disseminated to (1) birthing parents (2) healthcare providers over three months. Participants were recruited through advertisements and social media. The surveys collected demographic information, participants' attitudes and preference factors, decision-making factors and knowledge regarding medication use during infant feeding.
Results: There were 149 parents and 47 healthcare providers that completed the surveys at the one-month time point. * Within three months post-partum almost all the participants (N=141/149,94.6%) had fed directly from the breast/chest. The majority of the parent participants in this study used medication during pregnancy (N=139/149,93.3%) and postpartum (N=138/146,94.5%). Almost half (N=72/146, 49.3%) of the participants had changes in their medications within six months of giving birth. Over half (N=68/124, 54.8%) of the parents found decision-making on medication use while nursing to be difficult and very few parents felt certain about what to do when making decisions (N=11/124,8.8%). Parents ranked the leading factor impeding decision-making to be lacking information about options, benefits, and risks of medications followed by knowing what resources are reliable. healthcare providers' role in parents' decision-making included sharing the decision with parents (N=19/29,65.5%) and providing support/advice for parents to make the decision on their own (N=17/29,58.6%) and no provider made the decision for the parents. Healthcare providers listed their training on medication use during lactation as being below average (N=9/29,31.0%) and extremely poor (N=9/29,31.0%). Healthcare providers stated reliable resources, improved patient

resources/pamphlets and more education on medication safety would help them better support parents' decision making.

Conclusion: Parents' decision-making process on medication use during lactation and healthcare providers' role in parents' decision-making was evaluated. Parents and healthcare providers would benefit from improved educational material and reliable sources for information on medication use during lactation. Finding from this study suggests a shared decision-making tool could be beneficial for clinical practice.

*Only preliminary data for one month of collection from November 9 to December 9, 2021, will be presented in this thesis paper.

5.2 Introduction

Parents may require the use of medications during lactation to treat acute or chronic health conditions which may be crucial for their clinical care and maternal well-being. Based on administrative data from Manitoba and British Columbia (63%) of women received a prescription medication 0-3 months postpartum.[1] The use of medications during lactation is an identified barrier to continued human milk feeding, due to concerns of exposure risks to the infant.[2] Mothers requiring medications may be left ill-informed about the risks of nursing while taking medications given there is historical exclusion from research and drug development. In the study by Colacec et al., only 19.5% of the woman agreed that many drugs can be used during breastfeeding, while the majority (67.8%) disagreed and 12.5% did not know.[3]

Parents depend on healthcare providers as a reliable and trusted source for breastfeeding information, however "some women felt that they were provided with contradictory information about the safety of drugs during breastfeeding from different health professionals".[4] It is critical for healthcare professionals to offer advice based on scientific evidence there are often knowledge gaps and variability in healthcare providers' training on medication use during lactation.[5] In a previous study, healthcare providers stated they felt frustration and uncertainty around making clinical recommendations when there was a lack of safety data and clear guidelines.[6] It is important to understand the advantage and disadvantages for both parent and child when advising on medication decisions during lactation, while also considering the preferences and experiences of the parent.

A scoping review was conducted to examine the literature on parents' experiences, preferences, opinions, and concerns around medication use during breastfeeding along with healthcare providers' views on mothers' decisional needs and preference factors. It was determined that the existing literature is limited on the decision-making process of parents and the role healthcare providers play in their decisional needs. The scoping review informed the study design and items for the current survey study. The findings highlight the need to examine the shared decision-making process between parents and healthcare providers and the factors that would help facilitate a better parent-provider relationship. The decisions parents have to make may be more complex than deciding to take or not to take a medication. The process may involve considerations of different options and various factors such as the infant's health, their own health needs, changing, starting, or discontinuing a drug, methods of infant feeding etc.

Therefore, it is important to evaluate the type of decisions parents have made and what factors were prioritized that led to those decisions. This will better enable parents and physicians to make evidence-based decisions about the risks of drug exposure and the benefits of human milk for their children.

5.3 Objectives

The specific objectives of this study are to understand:

1. Preference factors of mothers and birthing parents contribute to the decision to take medication during breastfeeding.
2. Parents and clinicians' views on parents' decisional needs and preference factors regarding medication use during breastfeeding

5.4 Methods

This study included two surveys for the following populations (1) Mothers/birthing parents (2) Healthcare providers (physicians, nurses, pharmacists, others). Parent and healthcare provider survey consent statements are included in Appendix 5.1 and 5.2. The survey data collection was carried out between November 2021 to February 2022. The study has been reviewed and approved by the Health Research Ethics Board (HREB) of the University of Manitoba, approval number HS24663 (H2021:069).

Survey Development

Ottawa Decision Support Framework (ODSF)[7] was used as the framework to guide this study. ODFP "conceptualizes the support needed by patients, families, and their practitioners for 'difficult' decisions with multiple options whose features are valued differently. It guides practitioners and researchers to assess participants' decisional needs, provide decision support interventions (clinical counselling, patient decision tools, decision coaching) and evaluate their effects on decisional outcomes". The workbook by Jacobsen et al: Decisional needs assessment in populations[8] for assessing patients' and practitioners' decision-making needs, was referenced to develop the questions for the surveys in this study.

The three main themes (preference factors, decision making and knowledge) found from the scoping review informed the items included in the surveys. Specifically, to explore the

decision-making process of parents and healthcare providers, including the impeding and facilitating factors for making decisions. Items were included to learn about the comfort level of parents' using a medication and health care providers' recommendations on medications. Communication between healthcare providers and parents was also explored. Finally, questions were included on sources used for information gathering and types of resources that would be beneficial for decision making.

In addition to the scoping review, an advisory steering committee of parents with lived experience, physicians, pharmacists, researchers, and nurses who have an interest in research related to medications in human milk was assembled to help guide this study and provided input during the survey development. Furthermore, interviews were conducted with six parent participants where the survey was pilot tested and provided feedback which further developed and refined the survey items.

Participant and Setting

The survey distribution was restricted to participants residing in Canada who were 18 years of age and older. Parents were eligible to participate if they were pregnant, mothers/birthing parents and planning to have children regardless of medication-taking history. Healthcare providers such as family physicians, nurse practitioners, clinical pharmacists and other practitioners that provide services to parents with young children around medication use while infant feeding was eligible to participate.

Recruitment

Participants were recruited through online recruitment methods using social media platforms such as Facebook and Instagram and other online parent pages. Several infant and parent groups were contacted to help advertise the surveys on their social media/web pages. Recruitment sources include Winnipeg Breastfeeding Support Group, Southeast Breastfeeding Support Group, La Leche League Canada, Breastfeeding centre (MBMilkDocs), Healthy start, The Birth Centre, Women's health clinic, MBLB Support network FB page, BC Lactation Consultant association FB page, Douglas College breastfeeding course DC Blackboard communication system, Youville and Canadian Arthritis Patient Alliance. We also employed snowballing method for recruitment to expand our sample and teach a broader demographic group. The survey link was shared with the steering committee and Manitoba Interdisciplinary

Lactation group at the University of Manitoba to help distribute and asked to share with colleagues and parents. The survey advertisement also asked participants to share the link with others to participate in the study.

Sample Size

No restrictions were made on the number of participants who can participate in this survey. The sample size is determined based on recruitment and the voluntary response of individuals.

Data Collection

The surveys were anonymous, self-reported and web based. The survey was administered using the secure online application Research Electronic Data Capture (REDCap). Data was collected over 3 months between November 9, 2021, to February 9, 2022*. The survey consists of a section on the background information on medications used and the condition they treat, demographic information, participant's attitudes and preference factors, treatment selection and knowledge regarding medication use during infant feeding. Before the final administration of the survey, the survey was pilot tested during the parent engagement interviews with six participants and reviewed with the project steering committee to ensure the survey questions will be understood by respondents and to ensure the survey will capture information as it pertains to the study objectives.

*Only preliminary data for 1 month of collection from November 9 to December 9, 2021, will be presented in this thesis paper.

Data Analysis

The data from the surveys were exported from REDCap and analyzed using password-protected statistical software (Microsoft Excel). Descriptive statistics were shown as frequency, percentage and means as applicable. Qualitative data (free response questions) were coded, the content was analyzed for patterns and themes to allow a deeper understanding of the input from participants.

5.5 Results

Parent survey

There were 149 parent participants that completed the survey at the one-month time point where data was collected for analysis. The demographic characteristics of the parent participants are shown in Table 5.1.

Demographic characteristics

The majority of respondents were in the age category between 30-39 (69.8%) and of white/European descent (90.6%). A large number of participants had formal education with completed college/university (48.3%), completed graduate education (19.5%) and a professional degree (16.1%). The majority of the respondents had a high household income of >$80,000 (67.8%), resided in Manitoba (66.2%) and live with a partner (94.5%). Almost all the participants that completed the survey were postpartum and/or have children (96.6%) most of the parents have one (60.8%) or two (30.4%) biological children.

Medications and medical conditions

Over half (52.3%) of the participants did not have a chronic health condition during pregnancy or postpartum. While almost one-third (28.9%) had a chronic health condition during both pregnancy and post-partum and only during pregnancy or post-postpartum consisted of 6% and 11.4% respectively, see Table 5.1.

Medications and products (vitamins/minerals, natural health products, alcohol, caffeine, and recreational cannabis) used during pregnancy and post-partum are listed in Tables 5.2 and 5.3. The majority of the participants used medications or products during pregnancy (93.3%) and postpartum (94.5%).

The 10 most used medications/products during pregnancy (N=149) include vitamins/minerals (73.8%), caffeine (59.1%), pain medication such as ibuprofen, opioid and muscle relaxant (49.7%), medications to treat gastrointestinal conditions such as nausea, constipation, diarrhea, heartburn and irritable bowel syndrome (32.9%), allergies (22.1%), creams or ointments for skin conditions (14.10%), psychiatric condition (13.40%), infections (12.80%), thyroid hormone therapy (10.70%) and blood clot prevention (9.40%)

The 10 most used medications within six months post-partum (N=146) include vitamins/minerals (62.3%), pain medications (58.9%), caffeine (54.1%), alcohol (25.3%), medications to treat gastrointestinal conditions (21.9%), allergies (19.2%), psychiatric conditions (17.1%), infections (14.4%), creams or ointments for skin conditions (13.7%) and natural health products (9.6%)

Almost half (48.0%) of the participants had changes in their medications/products within six months of giving birth. The changes in the medication use of the participants (N=72) during pregnancy and within six months postpartum are listed in Table 5.3. There was a decrease in vitamin/minerals used from pregnancy (82%) to postpartum (56%). There was also a decrease in the number of people that took medications used to treat gastrointestinal conditions during pregnancy (40%) compared to postpartum (17%). Additionally, fewer people used caffeine during postpartum (61%) compared to pregnancy (74%). There was an increase in the use of pain medications post-partum (61%) compared to pregnancy (44%). No participants consumed alcohol during pregnancy compared to 39% who reported consuming it during postpartum.

Infant feeding duration

Within three months post-partum 95% of the participants had fed directly from the breast/chest, 57% fed using pumped milk in bottles and 34% used formula (refer to Table 5.1). Parents were asked to list their infant feeding goals and duration for each child displayed in Table 5.4. The mean infant feeding duration for the first child was 17.3 months and the mean feeding intention was 13.6 months. For the second, third and fourth children the mean feeding duration was 18.6, 23.7 and 12 months respectively. Mean feeding intention was 13.5,12.8, and 1.5 months for the second, third and fourth children.

Table 5.5 displays infant feeding duration and intentions set by parents and if they reached their infant feeding goals. For the first child, 51.7% of the participants achieved their goal, 17.2% did not achieve their goal and 31.0% were currently infant feeding and had not reached their intention. For the second child, 35.7% of the participants achieved their goal, 16.1% did not achieve their goal and 48.2.% were currently infant feeding. For the third child, one-third of the participants reached their goal, a third did not reach their goal and a third were currently infant feeding. There was only one participant with a fourth child, and they achieved their feeding goal.

Infant feeding experience

The majority of the parents experienced challenges during lactation/infant feeding with human milk (66.4%). Parents were asked about factors that influenced their decision to stop infant feeding with human milk, shown in Figure 5.1. The most common choice was something else (47%), followed by infant age (35%), and breastfeeding challenges (22%).

Parents' preference factors towards medication use during human milk feeding

Parents were asked to rank eight statements from most (1) to least (8) important concerning taking medication while nursing, shown in Table 5.6. The most important statement was that the medication has been taken by many breastfeeding people without evidence of adverse effects in nursing infants. The least important factor was that their social network thinks this medication is a good choice.

Parents rated their comfort level using a prescription medication based on certain statements, displayed in Figure 5.2. Parents were very uncomfortable (54%) or uncomfortable (25%) when there were no studies on the risk of infant exposure through human milk feeding. Parents were also very uncomfortable (17%) or uncomfortable (42%) if it was their first time using the medication. Whereas if they had used the medication during pregnancy small percentage was very uncomfortable (2%) or uncomfortable (8%). When the medication has been taken by many people without evidence of adverse effects on nursing infants' parents were comfortable (49%) and very comfortable (18%). Parents were mostly comfortable/very comfortable (44%/7%) and neutral (33%) if their health care provider thinks the medication is a good choice for them. The majority of parents were neutral/comfortable using prescription medication if it is used to treat a chronic (55%/26%) or acute (45%/42%) illness.

Parent's decision making on medication use during human milk feeding

More than half (N=68, 54.8%) of the parents responded that they found the decision to take a medication while feeding their child human milk difficult. Parents were asked how they feel when making decisions about taking medications during nursing, shown in Figure 5.3. Almost half (49%) of the parents worried about what could go wrong, followed by wavering between choices or changing your mind (37%) and unsure about what to do (34%). Very few parents selected they felt certain about what to do (9%).

Parents ranked statements that would make their decisions about medication use while human milk feeding difficult and easier, shown in Figures 5.4 and 5.5 respectively. Overall rank (refer to Table 5.7) of these statements shows the leading factor being lacking information about options, benefits, and risks of medications followed by knowing what resources are reliable. The last ranked factor for causing difficulty in decision making is feeling pressure from others such as family and friends. Overall rank (refer to Table 5.8) for factors making it easier for decision making showed having information on the pros and cons of taking the medication while nursing as being the most helpful followed by receiving advice from their healthcare provider. Receiving advice from their social support had the lowest overall rank.

Parent's knowledge and information sources on medication use during human milk feeding

Parents (N=100) responded if they received information from their healthcare provider about medication use while infant feeding with human milk. The majority (64%) of the parents received information from their providers and listed the specialty of the providers, which is summarized in Table 5.9. Almost three-quarters (71.4%) of the parents received advice from their family doctor and one-third of the participants received information from their pharmacists. Almost one-fifth of parents received information from both Midwives and OBGYNs (19%).

Parents selected pharmacists (75%), family physicians (73%) and obstetrician/gynecologists (63%) as trusted sources for information gathering about medication use during infant feeding. While blogs (5%), social media (6%), family (5%) and friends (6%) were not selected by many participants as trusted sources, refer to Figure 5.7.

Parents were asked an open-ended question about the advice they have been given about medication use while infant feeding human milk. Eighty-two participants responded and their responses were categorized into common themes and presented in Table 5.10. Most stated responses include, no advice given (17.1%), followed by advice on drug safety or what medications are okay to use (14.6%) and parents were given advice that their medication and most medications are fine to use while infant feeding (14.6%).

Healthcare provider survey

Forty-seven healthcare providers completed the survey at the one-month time point where data was collected for analysis. The demographic characteristics of the parent participants are shown in Table 5.11.

Demographic characteristics

The majority of respondents were in the age category between 30-39 (70.2%), identified as a woman (89.4%), and were primarily of white/European descent (68.9%). The majority of the participants practiced in an urban setting (76.6%) at outpatient clinics (68.9%) followed by hospital settings (46.7%). Almost all the participants were physicians (93.6%) and over half (57.8%) of the participant's area of practice was in primary care/family medicine. Over half (53.2%) of the respondent had less than 5 years in practice and a little over one-third (36.2%) had between 5-10 years of experience. Around 40 percent of the providers interacted with patients' that have young children <25% and almost a quarter of the providers interacted with these patients between 25-49% in their practice.

Health care providers' preference factors towards medication use during human milk feeding

Healthcare providers rated their comfort level in recommending a prescription medication based on certain statements, displayed in Figure 5.8. Most of the providers were uncomfortable (66%) or very uncomfortable (21%) when there were no studies on the risk of infant exposure through human milk feeding. When the medication has been taken by many people without evidence of adverse effects on nursing infants, providers were mostly comfortable (59%) recommending a medication. Practitioners were very comfortable (52%) and comfortable (38%) making a recommendation if controlled studies have not shown evidence of risk. If parents had used the medication in the past while nursing with no evidence of adverse effects on the nursing infant practitioners was mostly neutral (45%) or comfortable (38%). Practitioners felt generally comfortable (36%) and neutral (29%) making recommendations if parents are able to space the timing of the medication during infant feeding.

Providers rated their level of confidence in advising on medication use during lactation as somewhat confident (41.4%), quite confident (31.0%) and slightly confident (20.7%), displayed in Figure 5.9.

Healthcare providers' communication with parents on medication use during lactation was explored with a series of questions, displayed in Figure 5.10. Providers would routinely always (24.1%), often (27.6%) and sometimes (37.9%) ask parents if they were human milk feeding when discussing a medication. Almost half of providers would often (34.5%) or always (13.8%) ask parents if they were infant feeding human milk beyond 12 months. Almost all the providers often (51.7%) or always (44.8%) consider parents' values when giving recommendations. Largely, providers' advice on medication uses while nursing rarely (34.5%) or sometimes (44.8%) varies based on the infant's age. Providers described their shift in views based on the infants' age at 0-3 months vs. 3-6 months vs. 6-12 months and 1 year and order (refer to Appendix 5.3).

Over three-fourths of the providers (22 out of 29) answered that they provide direct counselling to lactating parents about medication use. Providers described the type of counselling they provide, when counselling is given, what it entails, how long the sessions are and if it is covered by health insurance. Eighteen participants provided a response which is listed in Appendix 5.4. Providers counselled on potential risks vs. benefits, recommendations, and safety in lactation. Discussions are given during appointments, anytime someone is chestfeeding and before prescribing a new medication. Sessions generally range between 5-15 minutes and sometimes up to 45 minutes.

Healthcare provider's decision making on medication use during human milk feeding

Healthcare provider's role in parents' decision making on medication use while nursing included sharing the decision with parents (65.5%) and providing support/advice for parents to make the decision on their own (58.6%) and no provider made the decision for the parents, refer to Figure 5.11.

Providers were asked based on their opinion what makes a decision about medication use during lactation difficult for parents, shown in Figure 5.12. Most frequently selected statements to include, lacking information about options, benefits, and risks of medication (75.0%) followed by maternal fear/anxiety/expectations/ideas/feelings on medication use while lactation (71.4%). Unsupported in decision making was selected the least (3.6%).

Providers were asked open-ended questions about factors that make it difficult and easier for them to support parents' decision-making. Responses are shown in Appendix 5.5. Common

factors that make it difficult for providers include lack of time available to spend with patients, parents coming with misinformation (internet, family and friends, healthcare providers), patients' expectations, conflicting advice from different providers, and lack of definitive information and education. Common factors that would make it easier for providers include reliable resources, improved patient resources/pamphlets and more education on medication safety.

Healthcare providers' knowledge and information sources on medication use during human milk feeding

Providers rated the training they received on medication use during lactation during professional education as average (34.5%), below average (31.0%) and extremely poor (31.0%), displayed in Figure 5.13.

Out of the twenty-nine participants that responded, around half (51.7%) answered that there are specific medications or medication classes that they are not confident in providing counselling to parents. Specific medications mentioned include pain medications, biologics, immunosuppressants, chemotherapy, sedatives, hypnotics, antiretrovirals, antibiotics, psychiatric medications, and newer medications. Responses are provided in Appendix 5.6.

Providers were asked an open-ended question about where they find information on medication use during lactation. Twenty-six participants responded and their responses were categorized into common groups and presented in Table 5.12. The most common resource mentioned was UpToDate (46%), followed by Lactmed (35%) and Infant Risk (31%).

5.6 Discussion

From our study, we were able to better understand Canadian mothers/birthing parents' and healthcare practitioners' preferences, decision-making and knowledge around medication use during lactation. The scoping review performed (Yakandawala U, unpublished data, 2022) suggested future studies to investigate the shared decision-making process between parents and healthcare providers and what factors would help facilitate a better parent-provider relationship. As well as to understand healthcare providers' comfort and confidence in offering advice on specific medications or medication classes. Our study was able to explore these gaps, specifically evaluating factors that facilitate and hinder parents' decision-making process. We were also able to evaluate healthcare providers' role in parents' decision-making and factors that impact their role.

Within three months post-partum 95% of the participants had fed directly from the breast/chest, which is slightly higher compared to the breastfeeding initiation rate of 90% (2015/16) of Canadian mothers.[9] In Canada 40–50% of parents stopped breastfeeding by 6 months.[10] Compared to in our study only 22.2% of parents stopped feeding human milk by 6 months for their first child, 28.6% and 50% for their second and third child respectively. The participants of this survey had a high mean infant feeding duration of 17.3 months and feeding intention was 13.6 months for parents' first child. Of the participants that completed infant feeding and including those that are currently feeding and passed their intended goal 51.7% achieved their feeding goal, 17.2% did not achieve their goal and 31% were still nursing (Table 5.5).

Most of the parent participants in this study used medication or product during pregnancy (93.3%) and postpartum (94.5%). Similar results are reported in another study "91.0 % of the women planned to or were using at least one prescription drug, OTC drug, or vitamin, mineral, or herbal remedy during breastfeeding".[11] Excluding products, the top five medication categories most used within six months post-partum (N=146) include pain medications (58.9%), medications to treat gastrointestinal conditions (21.9%), allergies (19.2%), psychiatric conditions (17.1%) and infections (14.4%). In this study, almost half (N=72/146, 49.3%) of the participants had changes in their medications/products within six months of giving birth. Looking at these participants' changes in their prescription and non-prescription medications there were a few medication classes that are interesting to note. There was a decrease in medications used to treat

gastrointestinal conditions, allergies and blood clot prevention during post-partum. There was an increase in the use of medication used to treat pain, cough/cold, eye/ear infection and psychiatric medications, and hormonal contraceptives post-partum. A systematic review done by Saha et al. on postpartum women's use of medicines and breastfeeding practices reports "The most commonly used medicines in register-based studies were systemic antibacterial if sex hormones (e.g., oral contraceptive) were not considered. In the rest of the studies, analgesics/antipyretics, nonsteroidal anti-inflammatory drugs (NSAIDs) and antibacterial/antibiotics were the most commonly used medicines if vitamins, minerals, or iron preparations were not considered".[12] Additionally, a study conducted by Schirm et al., reports that the most commonly used drugs in the postpartum period include analgesics, laxatives, vitamins, anti-infectives, antiemetics, sedatives and hypnotics.[13]

The majority of the parents experienced challenges during lactation/infant feeding with human milk (66.4%). Reasons include low milk supply, oversupply, latching issues, oral ties, infant not gaining weight, sore/cracked/painful nipples, clogged ducts, mastitis, engorgement and allergies. Over half (N=68, 54.8%) of the parents found decision-making on medication use while nursing to be difficult and very few parents felt certain about what to do when making decisions (9%). Almost half (49%) of the parents worried about what could go wrong, followed by wavering between choices or changing your mind (37%) and unsure about what to do (34%). Interestingly only 12% (N=14) of parents listed maternal medications as a reason for their decision to stop nursing (Figure 5.1). Something else (N=53) was selected by almost half of the participants for influencing the decision to stop nursing. Most listed reasons in this category include child-led weaning (N=17), return to work (N=12) and parents becoming pregnant or planning for pregnancy (N=12). Accurate representation of the reasons parents discontinue nursing is limited because the answer choice options did not include some of the common responses in the "something else" category.

Prescription medications that have no studies on the risk of infant exposure through human milk created the most discomfort for both parents and healthcare providers. With 79% of parents being very uncomfortable/uncomfortable using such a medication. Similarly, 87% of healthcare providers were very uncomfortable/uncomfortable providing recommendations on these medications to parents. Therefore, it is of priority for both parents and healthcare providers to have access to information from evidence-based studies on medications exposure through

milk. Additionally, parents ranked the statement ‘lacking information about options, benefits, and risks of medications’ first for factors causing barriers to their decision making, followed by ‘knowing what resources are reliable’. Healthcare providers rated the same statements based on their perception of factors making it difficult for parents in their decision making. Seventy-five percent of the providers selected ‘lacking information about options, benefits and risks of medication’. Followed by ‘maternal fear/anxiety/expectations/ideas/feelings on medication use while lactation’ selected by 71.4% of the providers. Interestingly this was only ranked fifth out of 12 by parents for a factor making a decision difficult. A study conducted by Spiesser-Robelet et al. on healthcare providers’ perceptions of breastfeeding women states “almost all the feelings that participants perceived from mothers were negative and most involved fear. According to the participants, this maternal fear was related to harming their child either by transmitting their disease via milk or by causing drug adverse effects. Maternal fear was described by participants regardless of the decision made during a maternal illness: that is, taking medication to treat the condition and continuing breastfeeding, or refraining from taking medication”.[14] Our findings suggest that there may be some discrepancies between which factors healthcare providers view as barriers for parents compared to factors that cause difficulty for parents during decision making.

Our study also evaluated parents’ perceptions of healthcare providers. Healthcare providers’ advice and recommendation were important and were considered by parents when making decisions. Parents selected healthcare providers as trusted sources for information. A large portion of the parents (64%) received information from their healthcare providers. Family doctors were selected the most (71.4%) followed by pharmacists (30%), they were also listed as the most trusted sources for information. Around half of the parents selected they were comfortable/very comfortable (44%/7%) while 33% felt neutral using a prescription medication while feeding their child human milk if their healthcare provider thinks the ‘medication is a good choice for them’. Additionally, parents ranked ‘receiving advice from their healthcare provider’ as the second most helpful factor in their decision making, the first being ‘having information on the pros and cons of taking the medication while nursing’.

Conversely, many of the healthcare providers listed their training on medication use during lactation as being below average (31.0%) and extremely poor (31.0%). Around a third of healthcare providers felt quite confident (31.0%) while 41.4% felt somewhat confident about

advising on medication use during lactation to parents. This is consistent with a study on pharmacists stating that "less than half of the pharmacists agreed that they have satisfactory knowledge to resolve the medication and health-care problems in pregnant (47.82%) and breastfeeding women (39.13%) while 43.78% of pharmacists were neutral".[15] Additionally around half of the healthcare providers (51.7%) answered that there are specific medications or medication classes that they are not confident in providing counselling to parents. Specific medications mentioned include pain medications, biologics, immunosuppressants, chemotherapy, sedatives/hypnotics, antiretrovirals, antibiotics, psychiatric medications, and newer medications. These findings further support the need for improved education and professional development for healthcare providers. Findings from this study can help prioritize future research efforts on medications that are most used by parents along with medications healthcare providers feel less confident in providing advice.

The healthcare providers' role in parents' decision-making in this study includes 'sharing the decision with parents' (65.5%) and 'providing support/advice for parents to make the decision on their own (58.6%). None of the providers made the decision for the parents. Parents described the type of advice they had received about medication use during infant feeding. Most of the advice was given by healthcare providers and included advice on drug safety, contraindications, the importance of parent health etc. Parents also mentioned that they have received conflicting advice from different providers. Some parents were told that most medications are safe to use while infant feeding while others were told to avoid medication use.

Examples of advice parents received from their healthcare providers included:

"That my well-being is a priority, and it is important that I take care of myself through medication so that I can take care of my baby."

"I have been told by my doctor to take my medication despite low risks and to continue breastfeeding. I was also told to time feedings before medication by the pharmacist, but this was not possible because I was told not to feed 12 hours after the medication, but I was still needing to feed every 2 hours. I called health links breastfeeding hotline and was not given any advice other than to consult a doctor."

A study by De Point et al. on opinions of pharmacists, described risk vs. benefit and infant age as the most frequently mentioned factors that were important to consider when

supplying medication to lactating women[16]. In our study providers commonly described their counselling on medication use to include discussion of risk vs. benefit and safety in lactation.

Example of a providers counselling:

"Depends on the medication and my familiarity with its safety profile in breastfeeding. Usually, counselling is done whenever I prescribe a new medication. Going over risks and benefits and what adverse events to look out for with regards to the baby. Depends, but usually 5 min. The visit would be covered. I always implore patients to take counsel from the pharmacist as well if I'm uncertain or unable to answer specific medication questions."

In a survey study conducted by Jones et. al: The medication vs breastfeeding dilemma,[17] examined what information parents received and wished to be given on medication safety during breastfeeding. Of the parents that were given a prescription medication 62% recall their doctor asking about how they were infant feeding and 29.1% stated they were not asked. Whereas 94% of GPs that took the survey stated before prescribing they would ask the parent how she was infant feeding. In our study, twenty-four percent of healthcare providers answered that they would always and 27.6% would often routinely ask their patients if they were infant feeding with milk when discussing a medication. The same study reports "only 21.9% (n=129) of GPs who responded to the survey said that they would ask the mother of a 'toddler' (taken to be older than 12 months) if she were breastfeeding before prescribing". In our study healthcare providers' advice for medication used while nursing rarely (34.5%) or sometimes (44.8%) varies based on the infant's age. Overall providers were more likely to ask parents about lactation with younger children compared to older children. They were less concerned, or more comfortable about medication use when the infant was over the age of one, using solids or other nutrition sources.

A study by Al-Sawalha et al., reports "less than half of the participants stated that their physicians or pharmacists took time to talk with them about their prescribed medications".[18] In our study healthcare providers commonly stated that lack of time available to spend with patients was a barrier that made it difficult for them to support parents' decision making. Other common factors include parents coming to them with misinformation, patients' expectations, conflicting advice from different providers, and lack of definitive information and education. Common factors mentioned that would make it easier for providers include reliable and consistent resources for recommendations, improved patient resources/pamphlets and more education on medication safety.

Example of healthcare providers' responses:

"Written information/ handout to help support a patient's self-reflection on their own values and also a centralized, reliable, readable, and trusted by patient's guideline on the safety of medications"
"Safe, reliable, patient-friendly online resource"
"A clear simple database of recommendations including safest period to restart breastfeeding based on the half-life, adverse effects, alternative options"

Therefore, efforts should be made to review and update the resources available for healthcare providers on medication safety in lactation. Inconsistencies should be removed from reference material and reflect the most recent evidence.

A limitation of this study is the population of parents that completed the survey were of similar backgrounds. Although efforts were made to recruit a diverse population by contacting various parent groups and organizations majority of the participants were of white ethnicity, between the age 30-39, highly educated, has a greater household income and lived in Manitoba. Future studies should specifically target under representative groups to include more people from different demographics. Another limitation of the survey was that it was only delivered online, therefore we were not able to reach individuals that did not have access to the internet. The survey was also only offered in English therefore Canadians whose official language is French (22.8%)[19] would not be able to participate. Future versions of this survey can include a version in French as well as translators for underrepresented communities. Additionally, we can include paper copies of the survey that can be sent out to those living in remote areas without internet access. There was also a small sample size for the healthcare provider survey, and almost all the healthcare providers were physicians. For future versions of the survey, we can contact the appropriate associations for the different healthcare providers' specialties to distribute the survey in an attempt to capture a variety of practitioners who work with post-partum parents.

The main strength of this study is that we were able to learn about the facilitating and impeding factors in the decision-making process for parents. Additionally, we were able to understand healthcare providers' role in parents' decision-making and factors that impact how they provide care. The mixed-methods design allowed us to gather richer data from the free-text responses to gain a deeper understanding of parents' and healthcare providers' thoughts and experiences. The study findings support the need for reliable and consistent resources on medication use during lactation and were a recurring theme by both parents and healthcare

providers. Parents valued healthcare providers as reliable sources for information and trusted their advice when decision-making. Therefore, a shared decision-making tool that can facilitate better communication between parents and their healthcare providers could improve parents' decision qualities on medication use during lactation. Future studies could focus on assessing decisional needs of commonly used medications by postpartum parents and medications that were changed postpartum to develop decision aids that can be used in clinical practice.

5.7 Conclusion

Parents' decision-making process on medication use during lactation and healthcare providers' role in parents' decision-making was evaluated in this study. Specifically, this study was able to examine the facilitating and impeding factors for parents during decision-making. Parents and healthcare providers would benefit from improved educational material and reliable sources for information on medication use during lactation. Priority should be made to assess the reliability and consistency of the available resources on commonly used medication by postpartum parents and assess the decisional needs of parents and healthcare providers. Future versions of this survey should focus on reaching underrepresented demographic groups. Findings from this study suggest a shared decision-making tool could be beneficial for clinical practice.

5.8 References

1. Smolina K, Hanley GE, Mintzes B, Oberlander TF, Morgan S. Trends and Determinants of Prescription Drug Use during Pregnancy and Postpartum in British Columbia, 2002-2011: A Population-Based Cohort Study. *PLoS One*. 2015;10(5):e0128312.
2. Wang J, Johnson T, Sahin L, et al. Evaluation of the Safety of Drugs and Biological Products Used During Lactation: Workshop Summary. *Clin Pharmacol Ther*. 2017;101(6):736-744.
3. Colaceci S, Giusti A, De Angelis A, et al. Medications, "Natural" Products, and Pharmacovigilance during Breastfeeding: A Mixed-Methods Study on Women's Opinions. *Journal of Human Lactation.* 2016;32(2):324-332.
4. Williams D, Webber J, Pell B, et al. "Nobody knows, or seems to know how rheumatology and breastfeeding works": Women's experiences of breastfeeding whilst managing a long-term limiting condition – A qualitative visual methods study. *Midwifery*. 2019;78:91-96.
5. Huang VW, Chang HJ, Kroeker KI, et al. Management of Inflammatory Bowel Disease during Pregnancy and Breastfeeding Varies Widely: A Need for Further Education. *Canadian Journal of Gastroenterology & Hepatology.* 2016;2016:6193275.
6. Jayawickrama HS, Amir LH, Pirotta MV. GPs' decision-making when prescribing medicines for breastfeeding women: Content analysis of a survey. *BMC Research Notes.* 2010;3.
7. Stacey D, Légaré F, Boland L, et al. 20th Anniversary Ottawa Decision Support Framework: Part 3 Overview of Systematic Reviews and Updated Framework. *Med Decis Making*. 2020;40(3):379-398. doi:10.1177/0272989X20911870
8. Jacobsen MJ, O'Connor AM, Stacey D. Decisional needs assessment in populations. 1999 [updated 2013].
9. Gionet L. Breastfeeding trends in Canada. Health at a glance. Statistics Canada Catalogue No. 820624-X. Ottawa, ON*: Statistics Canada*; 2015.
10. Francis J, Mildon A, Stewart S, et al. Breastfeeding rates are high in a prenatal community support program targeting vulnerable women and offering enhanced postnatal lactation support: a prospective cohort study. *Int J Equity Health.* 2021;20(1):71.
11. Smedberg J, Brathen M, Waka MS, Jacobsen AF, Gjerdalen G, Nordeng H. Medication use and drug-related problems among women at maternity wards-a cross-sectional study from two Norwegian hospitals. *European Journal of Clinical Pharmacology.* 2016;72(7):849-857.
12. Saha MR, Ryan K, Amir LH. Postpartum women's use of medicines and breastfeeding practices: a systematic review. *Int Breastfeed J*. 2015;10:28. Published 2015 Oct 28. doi:10.1186/s13006-015-0053-6
13. Schirm E, Schwagermann MP, Tobi H, de Jong-van den Berg LT. Drug use during breastfeeding. A survey from the Netherlands. *European Journal of Clinical Nutrition.* 2004;58(2):386-390.
14. Spiesser-Robelet L, Maurice A, Gagnayre R. Understanding Breastfeeding Women's Behaviors Toward Medication: Healthcare Professionals' Viewpoint. *Journal of Human Lactation*. 2019;35(1):137-153. doi:10.1177/0890334418771294
15. Shiromwar SS. Perceived services and reported opinions about self-care during pregnancy and lactation by community pharmacists: A cross-sectional study. *Asian Journal of Pharmaceutical and Clinical Research.* 2019;12(7):325-331.
16. De Ponti M, Stewart K, Amir LH, Hussainy SY. Medicine use and safety while breastfeeding: Investigating the perspectives of community pharmacists in Australia. *Australian Journal of Primary Health.* 2015;21(1):46-57.

17. Jones W, Brown D: The medication vs breastfeeding dilemma. Br J Midwifery. 2003, 11 (9): 550-55.
18. Al-Sawalha NA, Tahaineh L, Sawalha A, Almomani BA. Medication use in breastfeeding women: A national study. *Breastfeeding Medicine.* 2016;11(7):386-391.
19. Statistics Canada, "Total population excluding institutional residents – 100% data", *Census Profile, 2016 Census: Canada [Country] and Canada [Country]*, Statistics Canada Catalogue no. 98-316-X2016001, Ottawa, released November 29, 2017. On-line version accessed January 19, 2018.

Table 5.1 Demographic characteristics of parent participants

Characteristics	No.	%
Age	149	
Under 18	0	0.0%
18-29	30	20.1%
30-39	104	69.8%
40-49	14	9.4%
≥ 50	1	0.7%
Sex	149	
Female	149	100.0%
Male	0	0.0%
Intersex	0	0.0%
Gender	149	
Woman	148	99.3%
Man	0	0.0%
Non-binary	1	0.7%
Province/Territory of Residence	148	
Alberta	8	5.4%
British Columbia	8	5.4%
Manitoba	98	66.2%
New Brunswick	2	1.4%
Newfoundland and Labrador	1	0.7%
Nova Scotia	1	0.7%
Ontario	25	16.9%
Prince Edward Island	3	2.0%
Quebec	1	0.7%
Saskatchewan	0	0.0%
Northwest Territories	1	0.7%
Nunavut	0	0.0%
Yukon	0	0.0%
Household Income	149	
< $20,000	0	0.0%
$20,000-$50,000	11	7.4%
$50,001-$80,000	37	24.8%
>$80,000	101	67.8%

Ethnicity	149	
Black (African, Afro-Caribbean, African Canadian descent)	2	1.3%
East/Southeast Asian (Chinese, Korean, Japanese, Taiwanese descent or Filipino, Vietnamese, Cambodian, Thai, Indonesian, other Southeast Asian descent)	8	5.4%
Indigenous (First Nations, Métis, Inuk/Inuit descent)	12	8.1%
Latino (Latin American, Hispanic descent)	0	0.0%
Middle Eastern (Arab, Persian, West Asian descent (e.g., Afghan, Egyptian, Iranian, Lebanese, Turkish, Kurdish)	0	0.0%
South Asian (East Indian, Pakistani, Bangladeshi, Sri Lankan, Indo-Caribbean)	7	4.7%
White (European descent)	135	90.6%
Do not know	1	0.7%
Education	149	
Some high school	1	0.7%
Completed high school	8	5.4%
Some college/university	15	10.1%
Apprenticeship training and trades	2	1.3%
Completed certificate	5	3.4%
Completed college/university	72	48.3%
Some graduate education	9	6.0%
Completed graduate education	29	19.5%
Professional degree (e.g., MD/JD/OD)	24	16.1%
Marital Status	146	
Living without a partner	8	5.5%
Living with a partner	138	94.5%
Current birthing status	149	
Pregnant	5	3.4%
Postpartum and/or have children	144	96.6%
No children but planning to have children	0	0.0%
Biological Children	149	
None	0	0.0%
1	90	60.8%
2	45	30.4%
3	13	8.1%

≥4	1	0.7%
Challenges during lactation/infant feeding with human milk	146	
Yes	97	66.4%
No	49	33.6%
Chronic health condition(s)	149	
Pregnancy and postpartum	43	28.9%
Pregnancy only	9	6.0%
Postpartum only	17	11.4%
No	78	52.3%
Not applicable	2	1.3%
Infant feeding experience (within 3 months postpartum)	149	
Feeding directly from breast/chest	141	95%
Formula	51	34%
Donor milk	6	4%
Pumped milk in bottles	85	57%
Cup feeding	17	11%
Spoon feeding	17	11%
Supplemental Nursing System (SNS) feeding	12	8%
Something else	5	3%

Table 5.2 Medication used during pregnancy (N=149) and postpartum (N=146)

Medications	**Pregnancy**		**Postpartum (Within 6 months)**	
	No. (N=149)	%	No. (N=146)	%
Allergies (e.g., antihistamine)	33	22.1%	28	19.2%
Arthritis (e.g., hydroxychloroquine)	4	2.7%	3	2.1%
Benzodiazepine or z-drug (e.g., zopiclone)	4	2.7%	4	2.7%
Blood clot prevention (e.g., warfarin, heparin, Aspirin®)	14	9.4%	8	5.5%
Cancer therapy	2	1.3%	2	1.4%
Cannabis (medical purpose)	2	1.3%	1	0.7%
Cough and Cold	8	5.4%	13	8.9%
Creams or ointments for skin conditions (e.g., psoriasis, eczema, fungal)	21	14.1%	20	13.7%
Diabetes (e.g., metformin, insulin)	9	6.0%	6	4.1%
Eye or ear medication	4	2.7%	9	6.2%
Freezing/local anesthesia	6	4.0%	4	2.7%
Gastrointestinal conditions (e.g., nausea, constipation, diarrhea, heartburn, irritable bowel syndrome)	49	32.9%	32	21.9%
Heart conditions (blood pressure, cholesterol, heart rhythm)	9	6.0%	9	6.2%
HIV (e.g., antiretroviral)	0	0.0%	0	0.0%
Hormone contraceptives	5	3.4%	10	6.8%
Infections (e.g., antibiotic, antimalarial, antiviral)	19	12.8%	21	14.4%
Monoclonal antibody/biologic	2	1.3%	2	1.4%
Pain (e.g., ibuprofen, opioid, muscle relaxant)	74	49.7%	86	58.9%
Psychiatric condition (e.g., antidepressant, antipsychotic, mood stabilizer, stimulant)	20	13.4%	25	17.1%
Respiratory conditions (e.g., inhalers for asthma)	9	6.0%	9	6.2%
Seizure disorder (e.g., anticonvulsant)	0	0.0%	0	0.0%
Steroid	3	2.0%	4	2.7%
Stimulant (eg. medications for ADHD, narcolepsy)	2	1.3%	2	1.4%
Thyroid hormone therapy	16	10.7%	12	8.2%
Vitamins/Minerals (e.g., calcium, vitamin D, prenatal vitamins)	110	73.8%	91	62.3%
Natural health products (e.g., ginseng, gingko biloba, St. John's wort)	11	7.4%	14	9.6%

Alcohol	9	6.0%	37	25.3%
Caffeine	88	59.1%	79	54.1%
Recreational Cannabis	2	1.3%	1	0.7%
Something not listed	10	6.7%	9	6.2%
No medication used	10	6.7%	8	5.5%

Table 5.3 Medication used by parents who changed medications postpartum (N=72)

Medications changed within 6 months postpartum	**No.**	**%**
No	74	50.7
Yes	72	49.3

Medications	**Pregnancy**		**Postpartum**		**Percent Difference**
	No.	**%**	**No.**	**%**	**%**
Allergies (e.g., antihistamine)	19	26.4%	14	19.4%	-26%
Arthritis (e.g., hydroxychloroquine)	3	4.2%	2	2.8%	-33%
Benzodiazepine or z-drug (e.g., zopiclone)	3	4.2%	3	4.2%	0%
Blood clot prevention (e.g., warfarin, heparin, Aspirin®)	11	15.3%	6	8.3%	-45%
Cancer therapy	2	2.8%	2	2.8%	0%
Cannabis (medical purpose)	2	2.8%	1	1.4%	-50%
Cough and Cold	3	4.2%	8	11.1%	167%
Creams or ointments for skin conditions (e.g., psoriasis, eczema, fungal)	10	13.9%	9	12.5%	-10%
Diabetes (e.g., metformin, insulin)	5	6.9%	2	2.8%	-60%
Eye or ear medication	1	1.4%	6	8.3%	500%
Freezing/local anesthesia	3	4.2%	1	1.4%	-67%

Gastrointestinal conditions (e.g., nausea, constipation, diarrhea, heartburn, irritable bowel syndrome)	29	40.3%	12	16.7%	-59%
Heart conditions (blood pressure, cholesterol, heart rhythm)	8	11.1%	8	11.1%	0%
HIV (e.g., antiretroviral)	0	0.0%	0	0.0%	
Hormone contraceptives	2	2.8%	7	9.7%	250%
Infections (e.g., antibiotic, antimalarial, antiviral)	9	12.5%	11	15.3%	22%
Monoclonal antibody/biologic	0	0.0%	0	0.0%	
Pain (e.g., ibuprofen, opioid, muscle relaxant)	32	44.4%	44	61.1%	38%
Psychiatric condition (e.g., antidepressant, antipsychotic, mood stabilizer, stimulant)	14	19.4%	19	26.4%	36%
Respiratory conditions (e.g., inhalers for asthma)	5	6.9%	5	6.9%	0%
Seizure disorder (e.g., anticonvulsant)	0	0.0%	0	0.0%	0.0%
Steroid	1	1.4%	2	2.8%	100%
Stimulant (eg. medications for ADHD, narcolepsy)	2	2.8%	2	2.8%	0%
Thyroid hormone therapy	11	15.3%	7	9.7%	-36%
Vitamins/Minerals (e.g., calcium, vitamin D, prenatal vitamins)	59	81.9%	40	55.6%	-32%
Natural health products (e.g., ginseng, gingko biloba, St. John's wort)	3	4.2%	6	8.3%	100%
Alcohol	0	0.0%	28	38.9%	N/A
Caffeine	53	73.6%	44	61.1%	-17%
Recreational Cannabis	2	2.8%	1	1.4%	-50%
Something not listed	7	9.7%	6	8.3%	-14%
No medications used	1	1.4%	0	0.0%	-100%

Table 5.4 Infant feeding with human milk duration, intention, and continued feeding

Child	No. (%)	Mean (months)	Median (months)
First child	145		
Infant feeding duration	90	17.3	14
0 to 6 months	20(22.2%)		
7 to 12 months	21(23.3%)		
13 to 23 months	28(31.1%)		
≥ 24 months	21(23.3%)		
Not completed infant feeding	55		
Infant feeding intention	134 Child weans n=6, Long as possible n=5	13.6	12
Second child	56		
Infant feeding duration	21	18.6	12
0 to 6 months	6 (28.6%)		
7 to 12 months	6 (28.6%)		
13 to 23 months	3 (14.3%)		
≥ 24 months	6 (28.6%)		
Not completed infant feeding	35		
Infant feeding intention	49 Child weans n=4, Long as possible n=3	13.5	12
Third child	12		
Infant feeding duration	8	23.7	20
0 to 6 months	4 (50%)		
≥ 24 months	4 (50%)		
Not completed infant feeding	4		
Infant feeding intention	12	12.8	12
Fourth child	1		
Infant feeding duration	1	12	12
7 to 12 months	1 (100%)		
Infant feeding intention	1	1.5	1.5

Table 5.5 Parents infant feeding with human milk duration compared to intentions

Child (N)	Yes* (n, %)	No (n, %)	Ongoing** (n, %)
First child (145)	75 (51.7)	25 (17.2%)	45 (31.0%)
Second child (56)	20 (35.7%)	9 (16.1%)	27 (48.2%)
Third child (12)	4 (33.3%)	4 (33.3%)	4 (33.3%)
Fourth child (1)	1 (100%)		

*Yes, also includes participants that were currently infant feeding but have passed the time of their infant feeding intention.
**Ongoing, includes participants that are currently infant feeding but have not passed the time of their infant feeding intentions

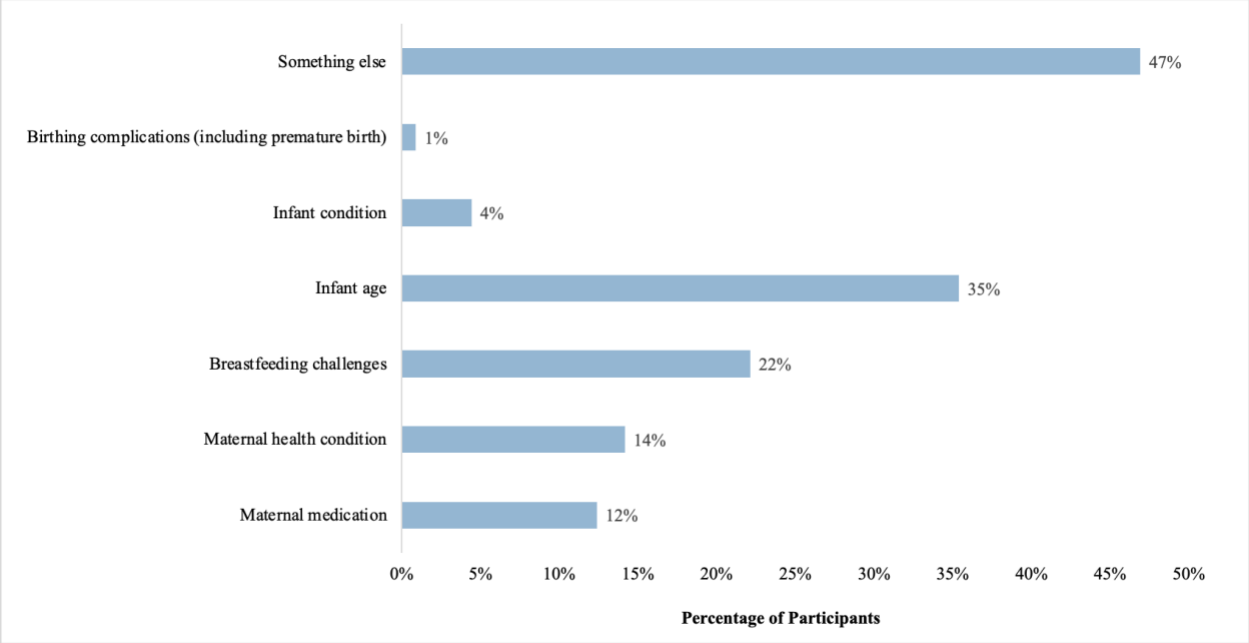


Figure 5.1 Factors that influenced parents' decision to stop infant feeding with human milk (N=113)
Note. Parents answered the question: "What influenced your decision to stop infant feeding with human milk? Please check all that apply".
Something else consists of (n=53): Child-led weaning n=17, parent return to work n=12, pregnancy/planning for pregnancy n=12, milk insufficiency n=7, still nursing n=7, difficulty feeding n=3, discomfort feeding n=3, parents health condition n=3, parent wanted independence n=2, child health condition, n=1, external judgement n=1, external stress, n=1, parent felt ready to stop n=1

Table 5.6 Overall ranking of factors from most to least important when taking a medication while human milk feeding (N=128)

Statements	**Total**	**Overall Rank**
The medication has been taken by many breastfeeding people without evidence of adverse effects in nursing infants	653	1 (Most important)
Studies have found this medication to have a low risk of causing harm to the baby	640	2
Your health care provider thinks this medication is a good choice for you	453	3
It is possible to watch for signs of side effects in the baby (e.g., irritability, change in eating/ sleeping) to show my medication is safe or not safe during breastfeeding	451	4
This medication has the lowest risk of causing side effects for the mother	434	5
This is the most effective medication for treating my depression symptoms/helping me function throughout the day	423	6
It is possible to space the timing of taking the medication and breastfeeding/pumping to reduce the risk of medication exposure to my infant	385	7
Your social network (e.g., family member/friend/ partner) thinks this medication is a good choice for you	271	8 (Least important)

Note. Parents answered the question: "What factors would be important to you with respect to taking the medication while feeding your baby human milk based on the following statements about the medication?".
Eight responses were ranked from 1 (most important) to 8 (least important).

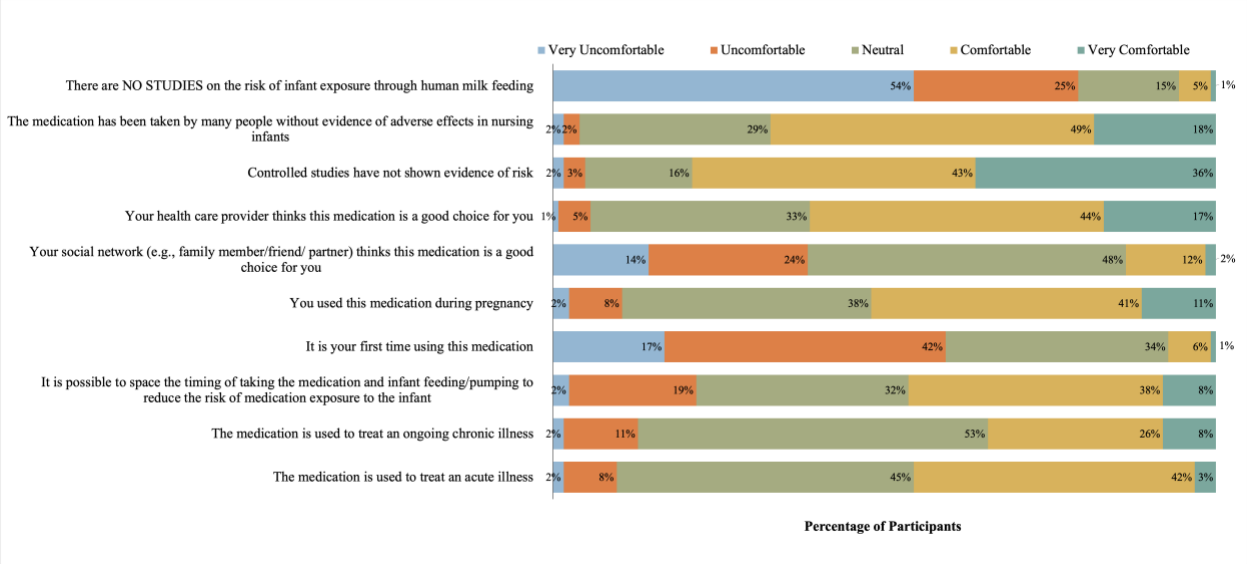


Figure 5.2 Parents' comfort level using a prescription medication (N=125)
Note. Parents answered the question: "Thinking about your own experiences how would you rate your comfort level using a prescription medication during infant feeding with human milk based on the following statements?" Responses were on a 5-point rating scale with the anchors 1 (very uncomfortable), 3(neutral), 5 (very comfortable).

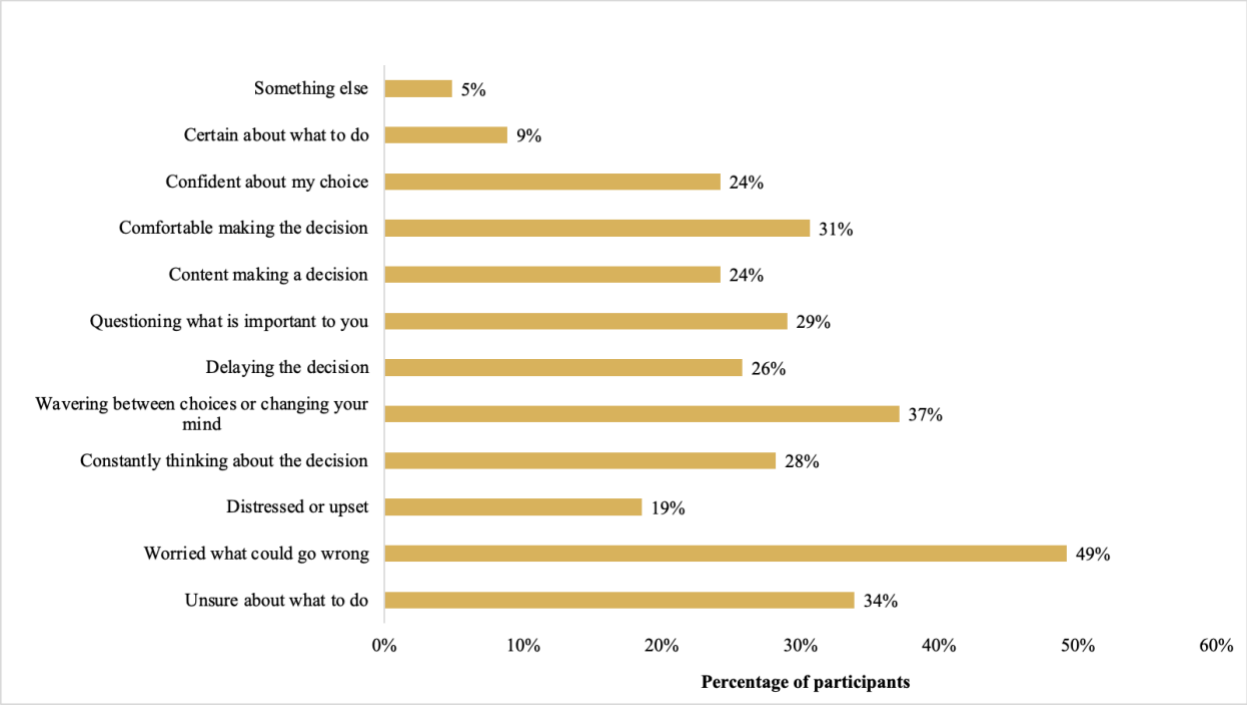


Figure 5.3 Parents feelings when making decisions about medication use during infant feeding with human milk (N=124)
Note. Parents answered the question: "How do you feel when making a decision about taking medications during infant feeding with human milk?"

Table 5.7 Overall ranking of statements from most to least important that make the decision about medication use while human milk feeding difficult for parents (N= 106)

Statements	Total	Overall Rank
Lacking information about options, benefits, risks of medication	813	1 (Most important)
Knowing what resources are reliable	665	2
Lacking information of benefits and harms of continuing/interrupting human milk feeding	654	3
Conflicting information from health care providers	630	4
My fear/anxiety/expectation/ideas/feeling on medication use during lactation	597	5
How to access and filter all the information	591	6
Assessing priorities in regard to my feeding relationship	559	7
Conflicting information from sources (e.g., internet, support groups	551	8
Not feeling ready to make a decision	482	9
Unsupported in decision making	437	10
Feeling social pressure to not take any medications during infant feeding with human milk	435	11
Feeling pressure from others (family, friends, etc.)	410	12 (Least important)

Note. Parents answered the question: "What makes the decision about medication use while infant feeding with human milk difficult for you?" Twelve responses were ranked from 1 (most important) to 12 (least important).

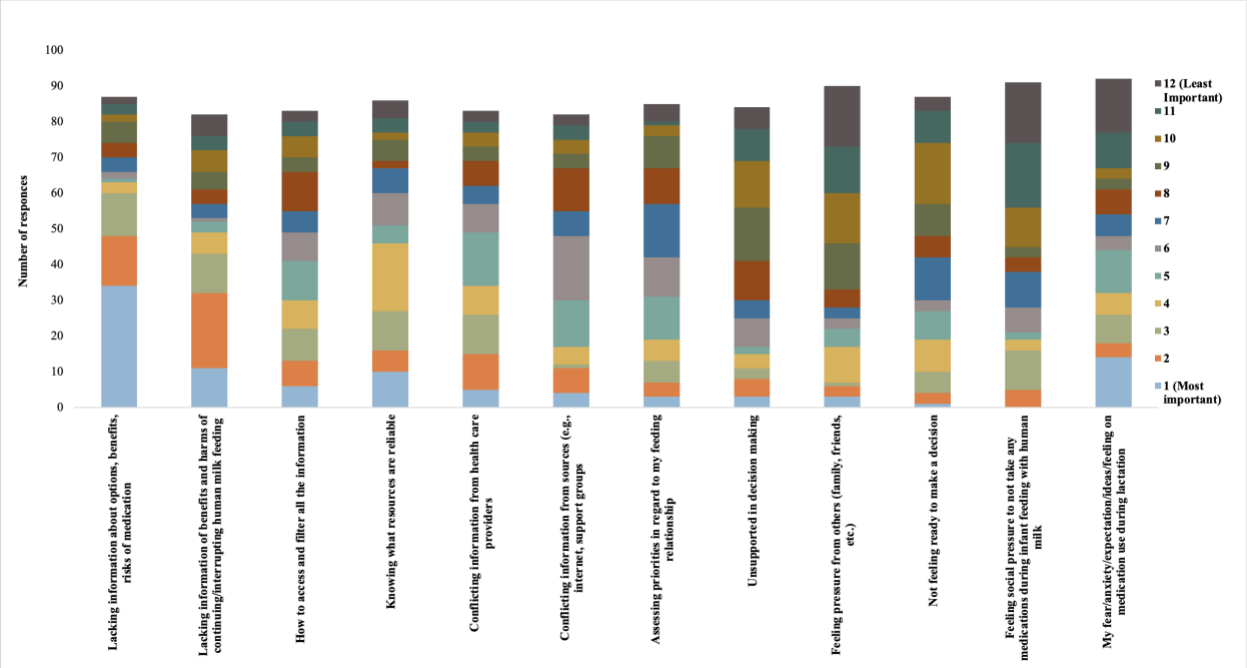


Figure 5.4 Parents raking of statements that make the decision about medication use while human milk feeding difficult for parents (N=106)
Twelve responses were ranked from 1 (most important) to 12 (least important).

Table 5.8 Overall ranking of statements from most to least important that make the decision about medication use while human milk feeding easier for parents (N=107)

Statements	Total	Rank
Having information on the pros and cons of taking the medication while nursing	387	1 (Most important)
Receiving advice from my healthcare provider (e.g., physician, pharmacist)	373	2
Understanding the personal importance of the pros and cons of taking the medication while nursing (i.e., understanding how the pros and cons relate to my own personal values and preferences)	318	3
Having information on how others in a similar situation go about deciding	206	4
Receiving advice from my social support (family, friends, peers, spouse/partner)	179	5 (Least important)

Note. Parents answered the question: "What factors help make the decision about medication use while infant feeding with human milk easier for you?" Five responses were ranked from 1 (most important) to 5 (least important).

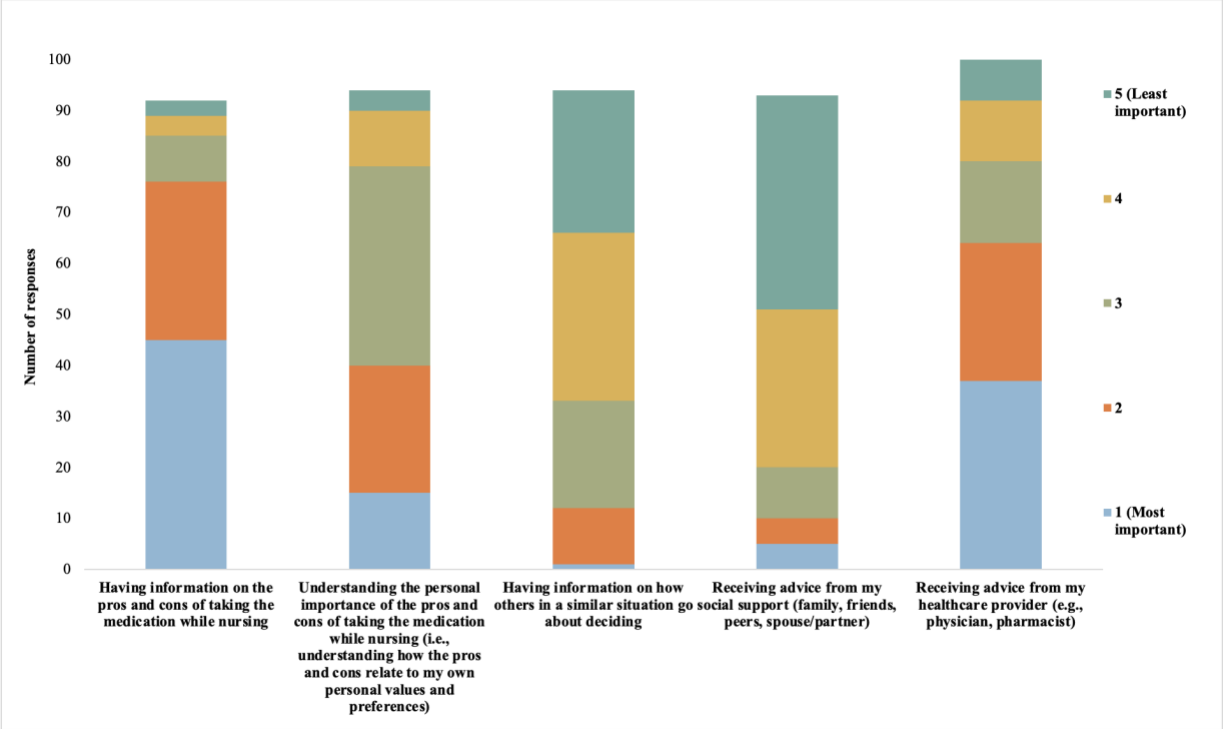


Figure 5.5 Parents raking of statements that make the decision about medication use while human milk feeding easier for parents (N=107)
Five responses were ranked from 1 (most important) to 5 (least important)

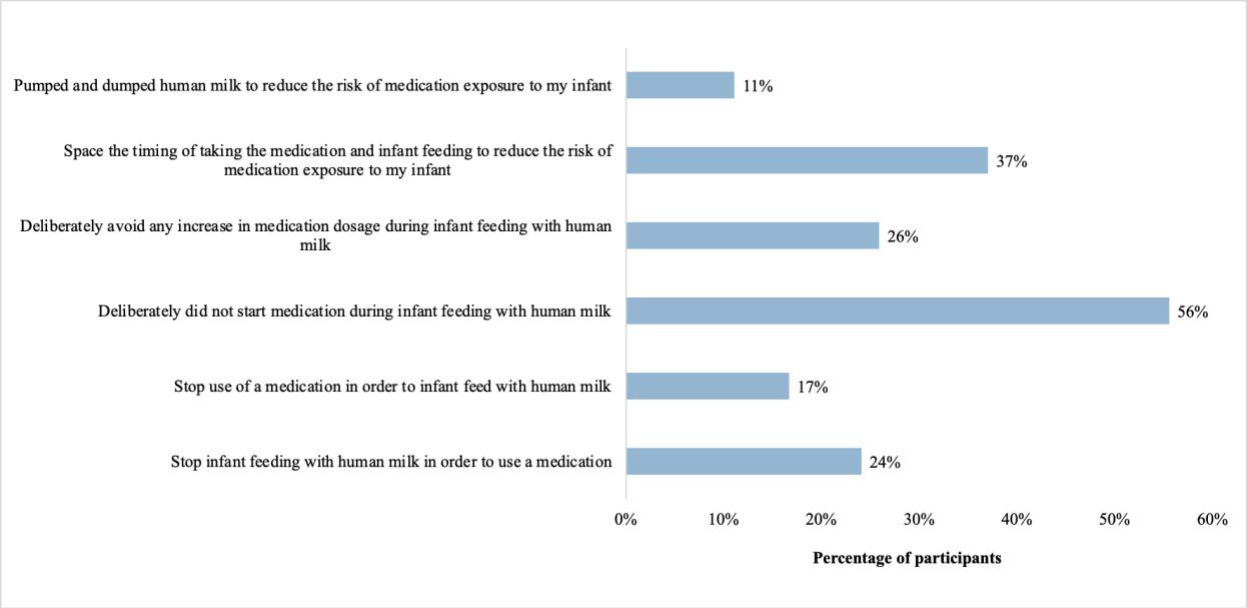


Figure 5.6 Parents decision making on specific scenarios when using medications while infant feeding (N=52)

Note. Parents answered the question: "Did you have to make any of the following decisions? Select all that apply"

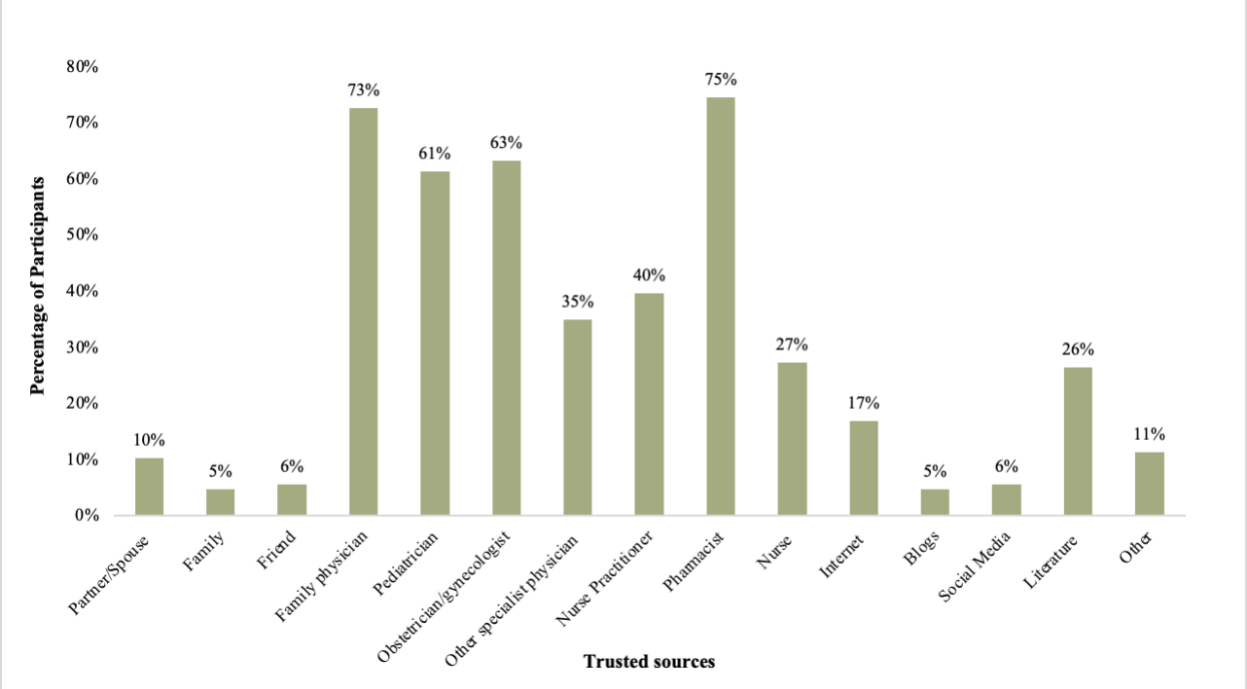


Figure 5.7 Parents' trusted sources for information gathering (N=106)

Note. Parents answered the question: "Who do you trust to get information from about medication use during infant feeding with human milk? Select all that apply"

Other (N=12) includes: Midwife n=5, Infant risk app n=3, Dr.Milk n=1,IBCLC n=1, Lactmed n=2, Lactation consultant n=3, Hales n=2, Breastfeeding network n=1, La Leche League n=1, NIH database n=1.

Table 5.9 Healthcare providers that parents' received information on medication use during infant feeding (N=63)

Provider Specialty	No.	%
Physician		
Doctor (Family)	45	71.4%
Doctor (OBGYN)	12	19.0%
Doctor (Pediatrician)	4	6.3%
Doctor (Psychiatrist)	4	6.3%
Doctor (Breastfeeding specialist)	4	6.3%
Doctor (Rheumatologist)	2	3.2%
Doctor (Allergist)	1	1.6%
Doctor (Emergency)	1	1.6%
Doctor (Endocrinologist)	1	1.6%
Doctor (Infectious Disease)	1	1.6%
Pharmacist	21	33.3%
Midwife	7	11.1%
Nurse	12	19.0%
Nurse practitioner	6	9.5%
Nurse (Public Health)	3	4.8%
Nurse	3	4.8%
Lactation expert/IBCLC	3	4.8%
Naturopath	1	1.6%
Psychologist	1	1.6%

Table 5.10 Advice parents have received about medication use while infant feeding with human milk (N=82)

Responses	**No.**	**%**
None	14	17.1%
Advice on drug safety/what medications okay to use	12	14.6%
Own medication/ most medications are fine to use	12	14.6%
Don't use medications/certain medications	8	9.8%
Most drugs are safe to use	8	9.8%
Conflicting advice from providers	6	7.3%
Space out timing of feeding	6	7.3%
Talk to health care providers first	6	7.3%
Minimal drug transfer to the milk	4	4.9%
Watch child for adverse effects	4	4.9%
Parent health is important	3	3.7%
Do own research	3	3.7%
Most drugs not well studies/ lack of research/ limited data	3	3.7%
Misinformation	2	2.4%
Advice on risk vs. benefit	2	2.4%

Note. Parents answered the question: "What advice have you been given about medication use while infant feeding with human milk?"

Table 5.11 Demographic characteristics of healthcare provider participants

Characteristics	No.	%
Age	47	
< 30	8	17.0%
30-39	33	70.2%
40-49	6	12.8%
50-59	0	0.0%
≥60	0	0.0%
Sex	47	
Female	44	93.6%
Male	3	6.4%
Intersex	0	0.0%
Gender	47	
Woman	42	89.4%
Man	3	6.4%
Non-binary	2	4.3%
Ethnicity	45	
Black (African, Afro-Caribbean, African Canadian descent)	0	0.0%
East/Southeast Asian (Chinese, Korean, Japanese, Taiwanese descent or Filipino, Vietnamese, Cambodian, Thai, Indonesian, other Southeast Asian descent)	3	6.7%
Indigenous (First Nations, Métis, Inuk/Inuit descent)	4	8.9%
Latino (Latin American, Hispanic descent)	1	2.2%
Middle Eastern (Arab, Persian, West Asian descent (e.g., Afghan, Egyptian, Iranian, Lebanese, Turkish, Kurdish))	1	2.2%
South Asian (East Indian, Pakistani, Bangladeshi, Sri Lankan, Indo-Caribbean)	10	22.2%
White (European descent)	31	68.9%
Province/Territory of Residence	47	
Alberta	5	10.6%
British Columbia	6	12.8%
Manitoba	27	57.4%
New Brunswick	1	2.1%
Newfoundland and Labrador	0	0.0%
Nova Scotia	1	2.1%

Ontario	6	12.8%
Prince Edward Island	0	0.0%
Quebec	0	0.0%
Saskatchewan	1	2.1%
Northwest Territories	0	0.0%
Nunavut	0	0.0%
Yukon	0	0.0%
Setting of Practice	47	
Urban Setting	36	76.6%
Rural Setting	11	23.4%
Primary Profession	47	
Physician	44	93.6%
Nurse	2	4.3%
Pharmacist	1	2.1%
Specialty/area of practice	45	
Primary care/Family medicine	26	57.8%
Pediatrics	6	13.3%
Obstetrics/Gynecology	5	11.1%
Surgery	3	6.7%
Psychiatry	2	4.4%
Emergency medicine	2	4.4%
Rheumatology	1	2.2%
Respiratory	1	2.2%
Anesthesiology	1	2.2%
Palliative medicine	1	2.2%
Oncology	1	2.2%
Internal Medicine	1	2.2%
Lactation consultant	1	2.2%
Years in Practice	47	
<5 years	25	53.2%
5-10 years	17	36.2%
10-19 years	5	10.6%
20+ years	0	0.0%
Primary institution of practice	45	
Outpatient clinic	31	68.9%
Outpatient clinic (academic)	9	20.0%
Hospital	21	46.7%
Emergency department	5	11.1%
Community/Outpatient Pharmacy	0	0.0%

Percentage of patient interactions including families with young children	47	
< 25%	19	40.4%
25-49%	11	23.4%
50%	8	17.0%
51-74%	5	10.6%
75-100%	4	8.5%

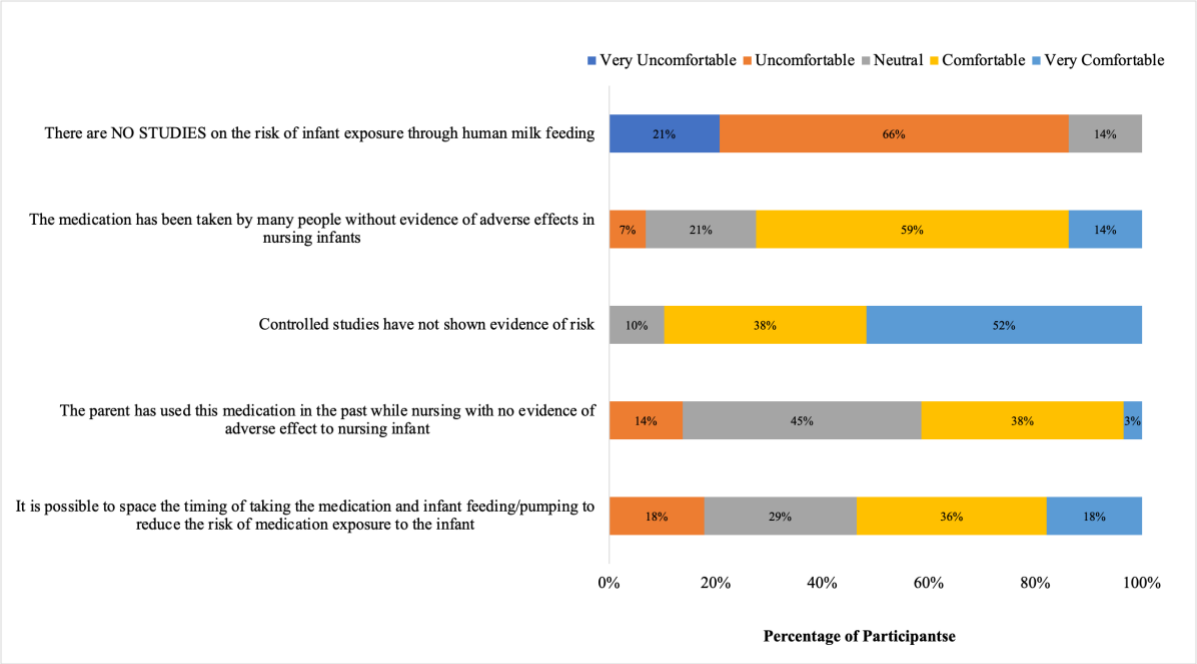


Figure 5.8 Healthcare providers ratings of comfort level recommending a prescription medication to lactating parents (N=29)

Note. Participants answered the question: "How would you rate your comfort level recommending a prescription medication to a lactating parent based on the following statements?".
Responses were on a 5-point rating scale with the anchors 1 (very uncomfortable), 3(neutral), 5 (very comfortable)

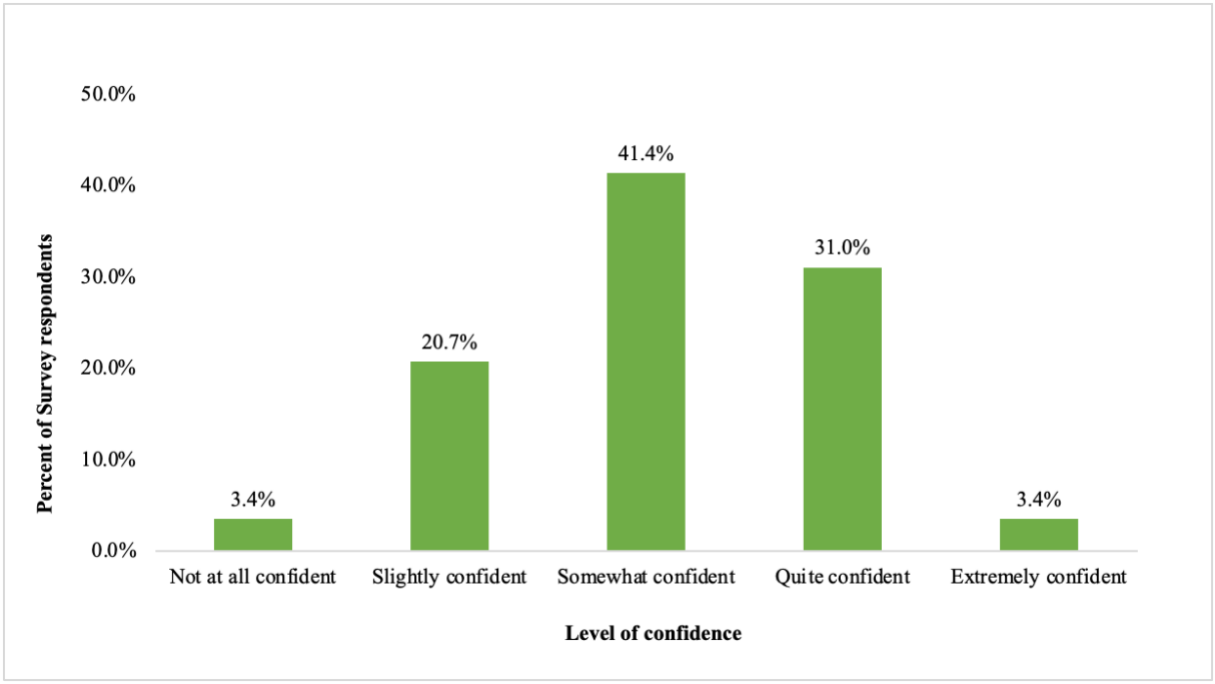


Figure 5.9 Healthcare providers level of confidence about advising on medication use during lactation (N=29)

Note. Participants answered the question: "How confident are you about advising on medication use during lactation?"

Responses were on a 5-point rating scale with the anchors 1 (not at all confident), 3(somewhat confident), 5 (extremely confident)

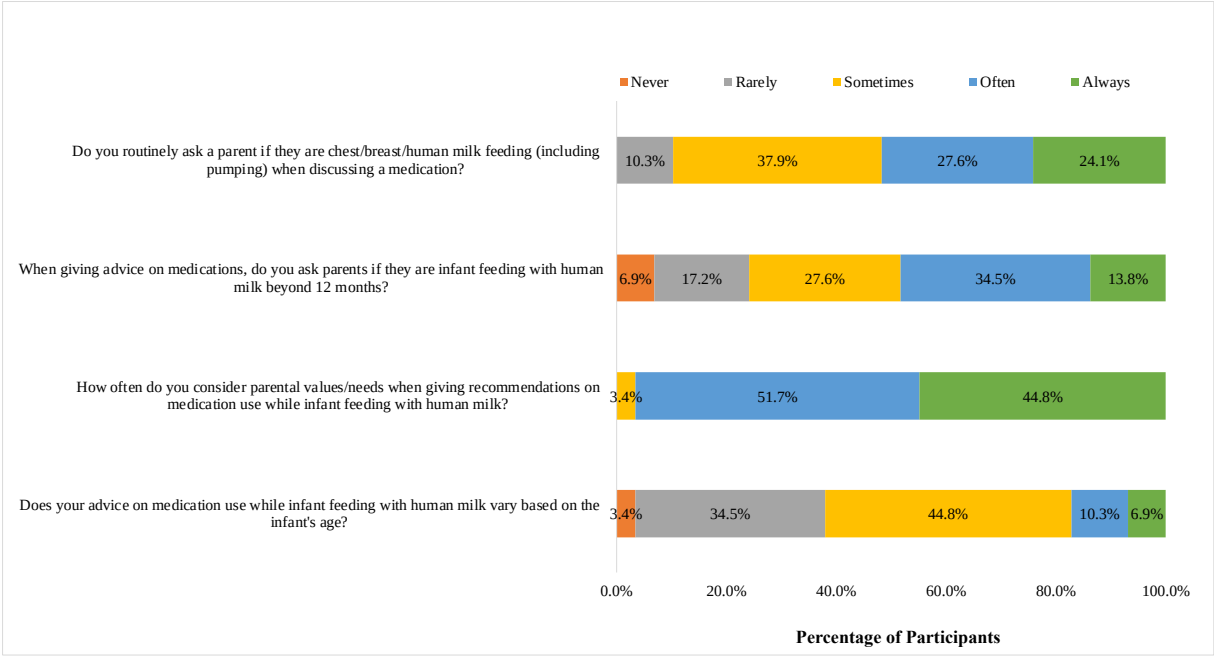


Figure 5.10 Healthcare providers communication about medication use during lactation with parents (N=29)

Note. Participants rated each individual question on a 5-point scale with the anchors 1(never), 3(sometimes), 5(always)

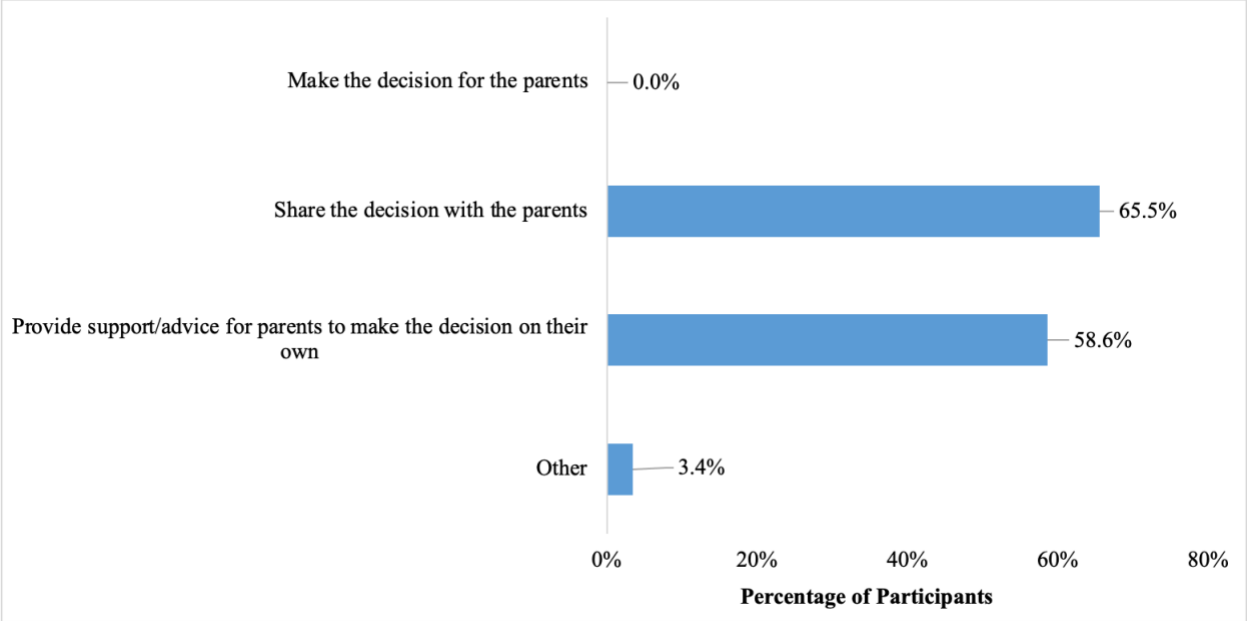


Figure 5.11 Healthcare providers role in parents' decision making on medication use during lactation (N=29)

Note. Participants answered the question: "What is your usual role in making decisions on medication use during lactation? Do you usually:"

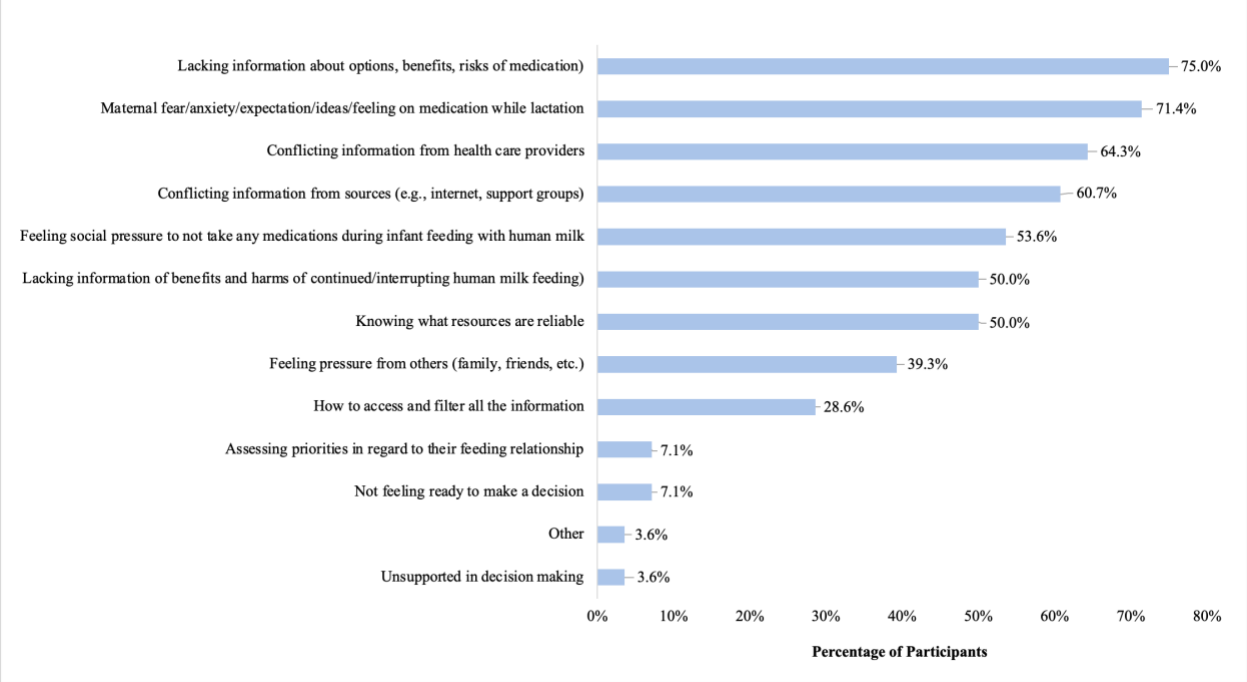


Figure 5.12 Healthcare providers perception of factors that make decisions about medication use during lactation difficult for parents (N=28)

Note. Participants answered the question: "In your opinion and based on what your patients have shared with you, what makes a decision about medication use during lactation difficult for parents?"

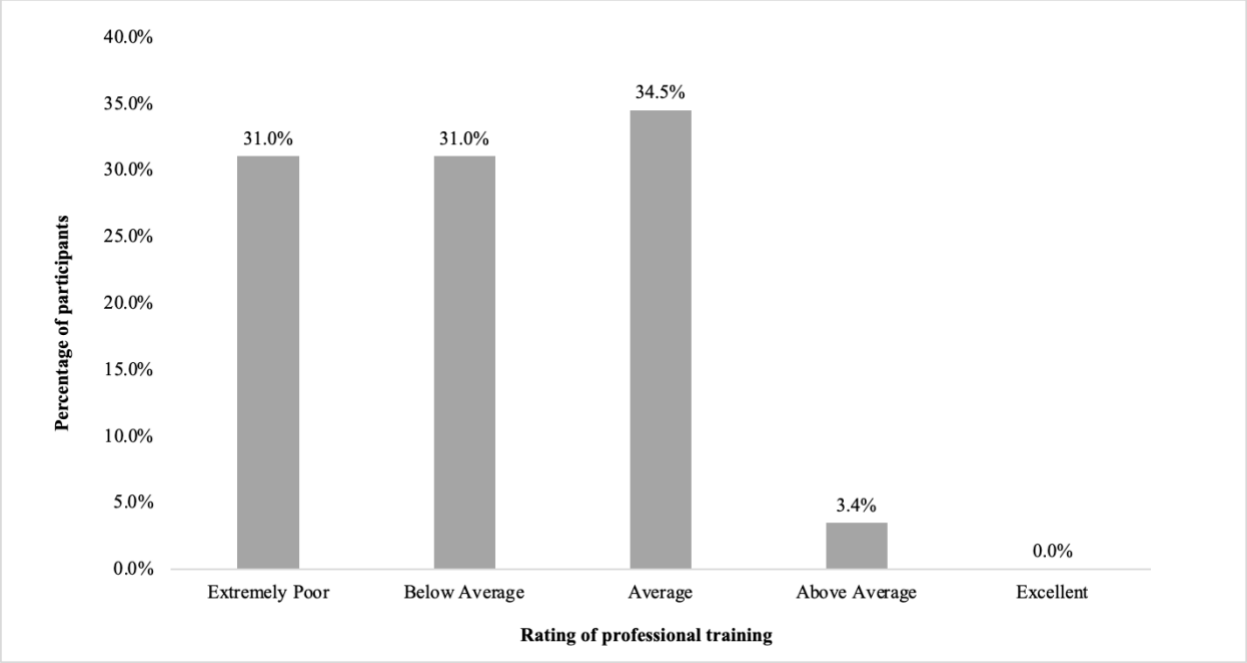


Figure 5.13 Healthcare providers rating of their professional training on medication use during lactation (N=29)
Note. Participants answered the question: "The training you received in your profession about medication use during lactation"

Table 5.12 Resources for information gathering by healthcare providers (N=26)

Resources	**No.**	**%**
Up to date	12	46%
LactMed	9	35%
Infant Risk	8	31%
Textbook	3	12%
Social Media (eg. Dr.milk)	3	12%
Rx files	2	8%
Lexicomp	2	8%
Mother risk	2	8%
Briggs	1	4%
Hospital Resources	2	8%
Internet	1	4%
La Leche	1	4%
Online supports	1	4%
Professional guidelines	1	4%
Pubmed	1	4%
Specialist/Colleague consultation	1	4%

Note. Participants answered the question: "Where do you find information on medication use during lactation. Specify the different sources"

Appendix 5.1 Parent survey consent statement

Confidential

Parents decision needs and preferences around medication use during lactation

Thank-you for your interest in our survey on decision needs and preferences on medication use during lactation.

This study is being conducted by Uma Yakandawala, MSc. student from College of Pharmacy at the University of Manitoba, Dr. Christine Leong, Assistant Professor from the College of Pharmacy at the University of Manitoba and Dr.Lauren Kelly, Assistant Professor from the Department of Pharmacology and Therapeutics and the Clinical Pharmacology Lab.

This survey is being conducted to understand parents lived experiences, preferences, values, and concerns around medication use during lactation.

Your feedback will be collected through an online survey which will ask you a series of questions and should take about 20 to 30 minutes to complete.

Your participation on this online survey is completely voluntary. You are not required to provide any personal information such as your name, address or telephone number, and you don't have to answer any questions you don't want to. The survey system will not record your e-mail address or IP (Internet protocol) address.

In acknowledgement of your time, at the end of the survey you can enter a draw to win a $100 gift card. Once completed the survey, if you want to enter the draw, you will be directed to a new page to enter your name and contact information (email and/or telephone). Your personal information will NOT be linked to your survey responses and will be destroyed once the prize has been awarded.

The risks of participating are low. Risks of participating in this survey may include tiring from answering questions.

If you agree to participate in the survey, please note that you must complete the survey in one sitting (in other words, the system won't let you save your survey responses and return to complete them later.

Also, please note that when you submit your response. You will not be able to withdraw them as we cannot link the survey responses back to you. All responses are anonymous as we cannot link your responses to any identifying information you provide.

Your participation is important to us and will help us inform the future design of a parent-informed decision aid that can help guide decision-making around medication use during lactation.

If you would like to receive a summary of the survey results or have any questions about this survey study, please send your request to Uma Yakandawala (Principal Investigator) by email at umyakand@myumanitoba.ca or Dr. Christine Leong (Supervisor) by e-mail at christine.leong@umanitoba.ca. Your request will be kept separate from your survey response, which will remain confidential.

This study has been approved by the University of Manitoba Health Research Ethics Board.

By continuing on and completing the on-line survey you are consenting to participate in the on-line survey.

1	Current Age	◯ Under 18 ◯ 18-29 ◯ 30-39 ◯ 40-49 ◯ ≥ 50
2	Sex (assigned at birth)	◯ Female ◯ Male ◯ Intersex ◯ Choose not to respond
3	Gender (at time of survey response)	◯ Woman ◯ Man ◯ Choose not to respond ◯ I identify my gender as

Appendix 5.2 Healthcare provider survey consent statement

Confidential

Healthcare providers decision needs and preferences on medication use during lactation

Thank-you for your interest in participating in our survey on decision needs and preferences on medication use around lactation. This study is being conducted by Uma Yakandawala, MSc. student from College of Pharmacy at the University of Manitoba, Dr. Christine Leong, Assistant Professor from the College of Pharmacy at the University of Manitoba and Dr.Lauren Kelly, Assistant Professor from the Department of Pharmacology and Therapeutics.

This survey is being conducted to understand healthcare providers experiences, preferences, values, and concerns around medication use during lactation.

Your feedback will be collected through an online survey which will ask you a series of questions and should take about 20 to 30 minutes to complete.

Your participation on this online survey is completely voluntary. You are not required to provide any personal information such as your name, address or telephone number, and you don't have to answer any questions you don't want to. The survey system will not record your e-mail address or IP (Internet protocol) address.

In acknowledgement of your time to complete this survey, at the end of the survey you can enter a draw to win a $100 gift card. Once completed the survey, if you want to enter the draw, you will be directed to a new page to enter your name and contact information (email and/or telephone). Your personal information will NOT be linked to your survey responses and will be destroyed once the prize has been awarded.

The risks of participating are low. Risks of participating in this survey may include tiring from answering questions.

If you agree to participate in the survey, please note that you must complete the survey in one sitting (in other words, the system won't let you save your survey responses and return to complete them later.

Also, please note that when you submit your response. You will not be able to withdraw them as we cannot link the survey responses back to you. All responses are anonymous as we cannot link your responses to any identifying information you provide.

Your participation is important to us and will help us inform the future design of a parent-informed decision aid that can help guide decision-making around medication use during lactation.

If you would like to receive a summary of the survey results or have any questions about this survey study, please send your request to Uma Yakandawala (Principal Investigator) by email at umyakand@myumanitoba.ca or Dr. Christine Leong (Supervisor) by e-mail at christine.leong@umanitoba.ca. Your request will be kept separate from your survey response, which will remain confidential.

This study has been approved by the University of Manitoba Health Research Ethics Board.

By continuing on and completing the on-line survey you are consenting to participate in the on-line survey.

Current age []	◯ < 30 ◯ 30-39 ◯ 40-49 ◯ 50-59 ◯ ≥60
Sex (assigned to at birth)	◯ Female ◯ Male ◯ Intersex ◯ Prefer not to respond
Gender (at time of survey response)	◯ Woman ◯ Man ◯ I identify my gender as (please specify) ◯ Prefer not to respond
I identify my gender as	_____

Appendix 5.3 Healthcare providers views on medication use during infant feeding (free response)

Healthcare providers views on medication use during infant feeding based on age- 0-3 months vs. 3-6 months vs. 6-12 months vs. 1 year and older (N=20)

1. "No difference"
2. "N/a"
3. "If the infant is younger, I am more likely to ask about breastfeeding"
4. "As children are exclusively breast fed earlier in life- if a medication has a high excretion into milk and has potential adverse effects then I would worry more."
5. "More exposure when younger because sole source of nutrition."
6. "Less likely to remember asking about lactation with older children"
7. "I am less concerned about medication use for toddler nursing (>1 years) as most of my patients feeding human milk to their older babies are able to skip doses/give formula or cow milk/or have pumped milk stored up. Less than 6 months exclusively breastfeeding I am more cautious about protecting breastfeeding"
8. "Some medications may be safer if infant older, less frequent breast feeding"
9. "I use the InfantRisk app which stratifies their recommendations based on age. Also feel more comfortable with prescribing when the infant is older ie has started solids so proportion of breast milk in diet is lower"
10. "If I am on the fence about a medication, infant age (and resulting frequency of breastfeeding and volume of human milk) sometimes plays a role in my comfort in using said medication"
11. "I'm a bit more conservative recommending medications with sedation potential with very new babies. Also, depending on patient preference I would be less concerned about affecting supply with an older child."
12. "If the child is nursing less after establishing solids, typically 1 year and older."
13. "To me it makes a difference whether they are taking in nutrition other than breast milk, also I consider newborns quite vulnerable and give more instruction to the parent about what possible side effects need medical assessment."
14. "Use of certain sedatives overnight for parents of older children changes if child is no longer feeding overnight or before half-life has passes"
15. "Perhaps I would have a higher tolerance for an unknown risk medication in very young infants, however mostly my views would not significantly change."
16. "Most restrictive with meds 0-3 Least restrictive with >1"
17. "Once eating solids (other available nutrition sources) I may be less concerned if the medication is very important for patient care - ie easier to wean if needed, easier to skip/delay feeds"
18. "Unless studies have shown a significant difference in risk between infants and children >1 year of age I treat them all the same. Anybody less than 1 year falls under the same category"
19. "It's difficult because I generally do not recommend medications, I would refer them to speak with their physician or midwife, whomever is most responsible, I wouldn't coach someone to take medications, only do education if the doctor has prescribed medications."
20. "0-3 more cautious of maternal medications 3-6 cautious of maternal meds 6-12 intro to solids, less cautious. 1 or older not concerned."

Appendix 5.4 Healthcare providers counselling to parents (free response)

Do you provide direct counselling to lactating parents who may need to take a medication? (N=29)

Yes	22	75.9%
No	7	24.1%

Can you tell us more about your medications and milk counselling? What type of counselling do you provide to parents regarding medication use during lactation? When is counselling given? What does counselling entail? How long are these sessions? Is this covered by healthcare insurance? (N=18)

1. "If a lactating patient asks me directly about medication risks during breastfeeding I can look up the medication in the LactMed database and read about the evidence for the safety of its use during breastfeeding and the concentration of the medication that accumulates in the breast milk."
2. "During appointments, I talk about always discussing with a healthcare provider before taking medication while breastfeeding"
3. "Often i counsel that the medication is SAFE while breastfeeding, despite what the pharmacist might say (I'm part of Dr. Milk- great resource)!"
4. "I look up medications on infant risk and try to prescribe only inpatient medications that are compatible with breastfeeding. I see surgical patients so counsel them pre op and make plans for pumping perioperatively. At discharge I counsel them on safe medications for pain as well."
5. "Counsel during visit when prescribing a med re: potential risks, recommendations and safety in lactation. "
6. "Review UpToDate and InfantRisk at time of prescription, usually spend <5 mins as most commonly rx'd meds in primary care seem to be generally safe. Sometimes have to call pharmacy or ask pt to speak to their prescribing specialist."
7. "I will review evidence (if available) with parents, have a discussion about risks/benefits. Depending on medication, parent comfort/anxiety can be lengthy (15-30 min) conversation. Not covered by insurance."
8. "Risk benefit discussion Consider parental values Informed decision making Maybe takes 10 min Covered by provincial billing as part of the visit"
9. "This is built into any prescribing I do for a breastfeeding patient. I generally discuss what we know, things to watch for with baby, and sometimes warn them that pharmacist etc. may tell them something different."
10. "I always review meds on infant risk."
11. "As a physician there is always counseling about starting new medications. I talk about it prior to prescribing. With breastfeeding parents this is usually a 5+ minute conversation."
12. "Usually, inhaled therapies but sometimes IV asthma medication; counselling given as part of medical appointment; it is covered by provincial medicare; follow-up appointments 15 min first appointment 45 min"

13. “Counseling around risk of starting psychotropic vs risk of untreated mental illness. Begin conversation before conception if I can, always during early pregnancy. Outline available data and ask about values and opinions. Try to give patient time to discuss with family or friends before coming to a decision.”
14. “On first meeting parents review maternal meds so I can review the literature if I am not familiar so give a proper opinion. I ask parents to update me if there are new meds. Length - depends on the meds Part of infant and child visit”
15. “Prenatal depending on meds, early postpartum and whenever health status of breastfeeding person changes”
16. “Counselling given anytime someone is chest feeding and I'm prescribing or recommending a medication. I counsel on known safety of medication during lactation and explain why I'm recommending this particular medication given the circumstances. No special billing codes. Often "free". Usually, short discussion to cover important points.”
17. “Depends on the medication and my familiarity with its safety profile in breastfeeding. Usually, counselling is done whenever I prescribe a new medication. Going over risks and benefits and what adverse events to look out for with regards to the baby. Depends but usually 5 min. The visit would be covered. I always implore patients to take counsel from the pharmacist as well if I'm uncertain or unable to answer specific medication questions.”
18. “Will discuss risks of medications and potential consequences. Patient makes informed decision whether to proceed with medication.”

Appendix 5.5 Impeding/facilitating factors for HCP to support parents' decision making

Factors making it difficult for healthcare providers to support parents' decision making (N=20)

1. "Lack of time to fully and fairly explore patient's fears and anxieties about medication use"
2. "N/a"
3. "lack of time to spend discussing medication"
4. "So much misinformation from health care providers!"
5. "Loss of easily accessible resources like motherrisk"
6. "Difficult to overcome societal/cultural norms and expectations"
7. "Hospital culture (lots of other people suggesting pump and dump)"
8. "Time pressure and dogmatic belief that mother shouldn't take meds while breastfeeding"
9. "Often they have read online or heard from friends information that does not go along with current evidence, and this makes them unwilling to engage in conversation surrounding shared decision making"
10. "Lack of really definitive information."
11. "Nothing"
12. "I see many patients under medicating themselves, especially for pain because they worry about how it will affect their babe despite being given adequate information about its safety."
13. "Lack of information and patient trusting internet research"
14. "Some patients can be quite angry about even getting information provided in a neutral judgement freeway. Generally, they perceive psycho education as a judgement of their decision and can become upset. It is difficult to avoid this but luckily small minority of patients"
15. "I would not consider this difficult. My role is to provide information based in available evidence and explain areas of uncertainty. Parents role is to make a decision."
16. "When they are getting very different info from other MDs"
17. "Too much "I didn't own research". They've come with bad info, and I often don't have the time or energy to discuss"
18. "Lack of knowledge on specific medications or if the literature is ambiguous with its recommendations"
19. "The unknown effects of medications -- lack of education of medications and lactation"
20. "Patient expectations and lack of definitive guidelines."

Factors making it easier for healthcare providers to support parents' decision making (N=19)

1. "Better access to peer reviewed evidence-based resources"
2. "N/a"
3. "Reliable resources"
4. "I think I help support them quite a bit."
5. "Online easily searchable up to date information"
6. "More patient resources/pamphlets that can be shared with parents and other family members"
7. "More education around medication safety perioperatively for my attendings and co-residents (and even pharmacists)"
8. "Tariff code for MD billing on med counselling.Better parent resources/handouts"
9. "Written information/ handout to help support a patient's self-reflection on their own values and also a centralized, reliable, readable, and trusted by patients guideline on safety of medications"
10. "Sources like LactMed and Infant Risk that state more clearly whether a medication is safe for use."
11. "Nothing"
12. "I really, really, really miss the MotherRisk phone line and website. They were really helpful in decision-making."
13. "Hospital funding infant risk app for staff."
14. "N/a"
15. "If more doctors were aware and didn't always say pump and dump"
16. "Safe, reliable, patient friendly online resource"
17. "A clear simple database of recommendations including safest period to restart breastfeeding based on half-life, adverse effects, alternative options"
18. "More education around medications and lactation"
19. "Comprehensive guide on safe medications to use during breast feeding."

Appendix 5.6 Healthcare providers confidence in providing counselling on specific mediations

Are there specific medications or classes of medication that you are not confident about when counselling a lactating parent? (N= 29)

Yes	15	51.7%
No	14	48.3%

Tell us more about specific drug(s) or scenarios where you aren't sure about providing advice on maternal or infant safety to a lactating parent (N= 14)

1. "Pain medications"
2. "Biologics, immunosuppressants, chemotherapy"
3. "Most medications!"
4. "Tylenol #3 and tramacet are always my two difficult meds- I know there are better options for breastfeeding, but we have a strong cultural preference for using it here as it doesn't need a triplicate prescription pad. I've had pharmacists in our hospitals give conflicting information on their safety in lactation."
5. "Immune suppressants (would defer to a specialist) Sedatives/hypnotics/narcotics"
6. "Antiretrovirals, some antibiotics"
7. "Any meds for bipolar/schizophrenia"
8. "Non-psychiatric medications"
9. "I look up areas of uncertainty."
10. "Antipsychotics Hypertension meds"
11. "Less commonly prescribed medications Biologics New medications that are outside of my scope of practice"
12. "Psychiatric drugs, poor second-choice alternatives, single time ER use"
13. "Antidepressants, blood pressure medications, antibiotics, cold medicine"
14. "unclear long term adverse effects to infants in regards to many medications."

CHAPTER 6. CONCLUSION/FUTURE DIRECTIONS- PILOT PROTOCOLS, DECISION-AID

The current thesis project examined the methodologies and tools needed to study medications in human milk.

The first study, a systematic review summarized the collection procedures and analytical techniques used to analyze 186 medications (belonging to 46 therapeutic categories) in human milk. The results from this review can help to identify a medication of interest and inform the development and validation of standardized protocols for milk sample collection and drug quantification in future prospective studies. The systematic review identified common medical conditions among participants in the included studies, depression (N=36) was presented the most followed by HIV (N=16), and post-partum pain (N=16). The top five medication therapeutic categories include antidepressants (N=58), anti-retroviral agents (N=43), antibiotics (N=16), NSAIDs (N=14) and opioids (N=14).

Manitoba has a unique opportunity to lead medication in human milk research in Canada with the development of the Manitoba Interdisciplinary Lactation Centre (MILC) funded by CFI (Canada Foundation for Innovation). MILC is led by Drs. Azad, Nickel and Kelly. MILC provides opportunities to conduct interdisciplinary research on the impact of policies on breastfeeding, the biology of human milk, the influence of social factors on breastfeeding biology and behaviours, the impact of breastfeeding and human milk on maternal, infant and child health, and healthcare spending. MILC will allow us to conduct new one-of-a-kind research by building a novel human milk biorepository to study breast milk linked with provincial administrative health data on infant feeding. Both have the potential to be linked to provide a wealth of data on health and social services.

The second study, a scoping review and survey on parent and healthcare providers' preferences, decision making and knowledge on medication use during lactation suggests that parents and healthcare providers would benefit from improved educational material and reliable sources for information on medication use during lactation.

Future studies could focus on assessing the decisional needs of commonly used medications by postpartum parents, these can include the five medication categories most used by postpartum parents (N=146) within six months which include pain medications (58.9%),

medications to treat gastrointestinal conditions (21.9%), allergies (19.2%), psychiatric conditions (17.1%) and infections (14.4%).

In addition, around half (51.7%) of healthcare providers in this survey answered that there are specific medications or medication classes that they are not confident in providing counselling to parents. Specific medications mentioned include pain medications, biologics, immunosuppressants, chemotherapy, sedatives, hypnotics, antiretrovirals, antibiotics, psychiatric medications, and newer medications. These medications should also be considered as priority medications to assess decisional needs as well for developing standardized protocols to quantify drug transmission to human milk.

Future versions of the survey should specifically target under representative groups to include participants from different demographics to better represent the Canadian population. This can include a version in French as well as translators for underrepresented communities.

Parents valued healthcare providers as a reliable source for information and trusted the advice given for their decision-making. Therefore, a shared decision-making tool that can facilitate better communication between parents and their healthcare providers could improve parents' decision qualities on medication use during lactation.

Knowledge gained from this study and our future work will better enable parents and healthcare providers to make evidence-based decisions about the risks of drug exposure and the benefits of human milk feeding for their children.

Knowledge translation

We plan to publish this research in an open-access journal and share our findings at national conferences related to pediatric health and breastfeeding. We have held community engagement events locally in Winnipeg to involve interested mothers, parents, and the public to have meaningful interactions and exchange of knowledge between researchers and members of the community.